東京大学ジェロントロジー研究

２０１１

２０１２年３月

東京大学 高齢社会総合研究機構
INSTITUTE OF GERONTOLOGY, The University of Tokyo

はじめに

東大ジェロントロジー研究の 2011 年版をお届けします。高齢社会総合研究機構設立から 3 年目となる 2011 年度は、東日本大震災直後の混乱の時期にスタートしましたが、被災地の復興支援のいくつかのプロジェクトが動き出しました。コミュニティケア型仮設住宅の提案と実現は高い評価を得て、宮内庁からの依頼で天皇皇后両陛下へのご説明の機会もありました。大槌をはじめとする地域での取り組みは、本格復興までの息の長い支援活動になっていくものと考えております。

2011 年 5 月には、念願の柏のジェロントロジー新棟（第 2 総合研究棟）が完成し、稼動を開始しました。研究拠点として様々な活動が始まっております。

柏と福井をフィールドとした長寿社会のまちづくりモデル構築に向けたプロジェクトも順調に推移し、柏の豊四季台団地へは、野田総理、前田国交大臣、宮島厚労省老健局長、丹呉前財務次官等が視察で訪れ、意見交換をいたしました。

このほか、産学連携では、前年度で一段落したジェロントロジーコンソーシアムの後継版として、ジェロントロジーネットワークが組織化され、50 社を超える企業の参加を得て、活発な活動を実施中ですし、国際連携では、第二回日瑞国際会議を 9 月にスウェーデン・ウプサラ大学で開催し、日本から 40 名を超える人数の訪問団で向かいました。

教育活動は横断講義を例年とおり実施しましたが、懸案の実習・演習の追加については残念ながら先送りになりました。

活動の広がりとともに、機構専任スタッフ数も増加し、スタート当初の 6 名から 4 倍以上の規模になっており、第 1 期 5 年の折り返し地点を全速力で通過している感じです。そろそろ第 2 期に向けての組織の設計を行う時期にあると思っております。

課題としては、専任以外のメンバの方々との交流もっと進めたいと思っていますが、なかなか時間の余裕が無く、できていません。教育活動の充実も、まだまだ着手できていません。可能なものから進めていきたいと考えております。

今後とも、よろしくご指導お願い申し上げます。

高齢社会総合研究機構長　鎌田　実

目次

１．機構の活動報告

1. 機構の活動報告

1.1 教育活動

1.1.1　学部横断型教育プログラム「ジェロントロジー」

高齢者や高齢社会の諸問題に関する学際的な知識を有する学生を育成するため、ジェロントロジーに関する学際的教育プログラムを 2008 年度より国内で初めて実施し 2011 年度も同様に継続実施した。受講対象者は、学部 3、4 年生（大学院生も受講可）である。

（1）プログラムの構成

本教育プログラム「ジェロントロジー」は、2 つの必修科目と、学内 8 学部に存在する約 50 の選択科目で構成されている。2 つの必修科目（各 2 単位、計 4 単位）と選択科目の中から 8 単位分以上を履修する。所定の単位を取得した者には、東京大学教育運営委員会より修了証を付与している。

（2）2011 年度の実績

2011 年度は、学内 9 学部 7 研究科から、必修科目 1 には約 50 名、必修科目 2 には約 120 名の受講があった。2011 年度は 9 名が修了証を取得し、累積で 27 名となる。


授業風景

（３）必修科目の講義一覧

必修科目１／加齢にともなう心身機能・生活の変化と適応

No	月日	担当者	所属	職位	テーマ
1	4|19	樋口　恵子 甲斐　一郎	高齢社会を良くする女性の会 医学系研究科	代　表 教　授	人生100年時代を生きる ガイダンス
2	4|26	跡見　順子	東京大学	名　誉 教　授	身体機能の変化と適応
3	5|10	大内　尉義	医学系研究科	教　授	老化の理論とアンチエイジング
4	5|17	秋山　弘子	高齢社会総合研究機構	特　任 教　授	ジェロントロジー：長寿社会を支える学際科学
5	5|24	秋下　雅弘	医学系研究科	准教授	疾病・障害とヘルスプロモーション
6	5|31	伊福部　達	先端科学技術研究センター	名　誉 教　授	身体機能を補う福祉工学機器
7	6|7	西村　宏子 （ゲスト）	新潟大学	教　授	老年病は胎生期に始まる
8	6|14	真田　弘美	医学系研究科	教　授	要介護高齢者の褥瘡ケア
9	6|21	甲斐　一郎	医学系研究科	教　授	高齢者の自立と依存（9～13回目の総論）
10	6|28	小林江里香 （ゲスト）	東京都健康長寿 医療センター研究所	主　任 研究員	高齢期の社会関係
11	7|5	牧野　篤	教育学研究科	教　授	シニア社会を支える担い手づくり
12	7|12	高山　緑 （ゲスト）	慶応義塾大学	准教授	知的機能の変化と適応
13	7|19	清水　哲郎	人文社会系研究科	特　任 教　授	死をめぐる諸問題

必修科目２／高齢社会の社会システムと生活環境

No	月日	担当者	所属	職位	テーマ
1	10|4	横石　知二 白波瀬佐和子	株式会社　いろどり 人文社会系研究科	特任研修 教　授	生涯現役社会をめざして ガイダンス
2	10|11	白波瀬佐和子	人文社会系研究科	教　授	高齢化の人口学
3	10|18	岩本　康志	経済学研究科	教　授	人口減少社会における年金と社会保障財政
4	10|25	清口祐一郎 （ゲスト）	労働政策研究・ 研修機構	統　括 研究員	年齢に基づく雇用システムと高齢者雇用
5	11|1	大方潤一郎	工学系研究科	教　授	超高齢社会の都市計画・まちづくり
6	11|8	大原　一興 （ゲスト）	横浜国立大学	教　授	高齢期のための住まい
7	11|15	鎌田　実	高齢社会総合研究機構	教　授	高齢者の移動を支える
8	11|22	樋口　範雄	法学政治学研究科	教　授	高齢者と法：自己決定と本人保護
9	11|29	上野谷加代子 （ゲスト）	同志社大学	教　授	超高齢社会のソーシャルワーク
10	12|6	井口　高志 （ゲスト）	信州大学	講　師	家族介護・施設介護の臨床：臨床を対象とする社会学
11	12|13	村嶋　幸代	医学系研究科	教　授	高齢者を地域で支える：地域包括ケア
12	1|10	辻　　哲夫	高齢社会総合研究機構	教　授	21世紀の医療・介護・福祉のかたちを考える
13	1|17	小泉　秀樹	工学系研究科	准教授	高齢社会のコミュニティを支える市民社会組織のまちづくり
14	1|24	総合討議			教員と学生とのディスカッション

1.2　主要な研究活動

1.2.1　千葉県柏市での取り組み

（1）豊四季台地域高齢社会総合研究会

「柏市豊四季台地域高齢社会総合研究会」は、柏市を舞台に超高齢社会に対応した地域づくりを検討、実践する場として、柏市、独立行政法人都市再生機構（以後、ＵＲ都市機構）と東京大学高齢社会総合研究機構の 3 者共同で立ち上げた研究会である（2009 年 6 月発足)。柏市内でも住民の高齢化が突出して進んでいる豊四季台団地とその周辺地域を中心に活動しており、2010 年 5 月に柏市、ＵＲ都市機構、東京大学高齢社会総合研究機構の 3 者協定を結び、協定締結後は定期的に「総合研究会」を開催するとともに、研究会の下に 3 つの委員会を設置し、各委員会ワーキンググループ（ＷＧ）に関係者、市民らに参加いただき、構想案および事業化について具体的に取り組んできた。

本年度は、各委員会、ワーキンググループで検討を重ねてきた構想をとりまとめ、4 月、5 月の「総合研究会」にて構想案を策定、6 月 28 日の平成 23 年度第 3 回総合研究会にて対外向けに構想を発表した。第 3 回総合研究会は柏市秋山市長、ＵＲ都市機構千葉地域支社宇佐美地域支社長、東京大学柏キャンパス共同学術経営委員会上田委員長の出席のもと、公開で開催した。また総合研究会に次いでマスコミ向けの質疑応答を開いた。

第 3 回総合研究会の様子

また、8 月より「柏市豊四季台地域高齢社会総合研究会」の公式ホームページを開設し、構想資料や各ワーキンググループの活動報告、問い合わせ窓口の設置などを行った。

http://kashiwa-toyoshikidai.org/
ホームページより抜粋

本年度後半は、2012 年 1 月に第 4 回総合研究会を開催し、各委員会活動の報告が行われたが、主に各委員会ＷＧを活動の中心の場として、構想を具体的な事業やシステム、研究活動に落とし込んでいく活動が中心となった。一方の「総合研究会」では、構想の公表により多くなった国内外からの視察・視察に対応する機会が多かった。主な視察・視察は以下のとおり。

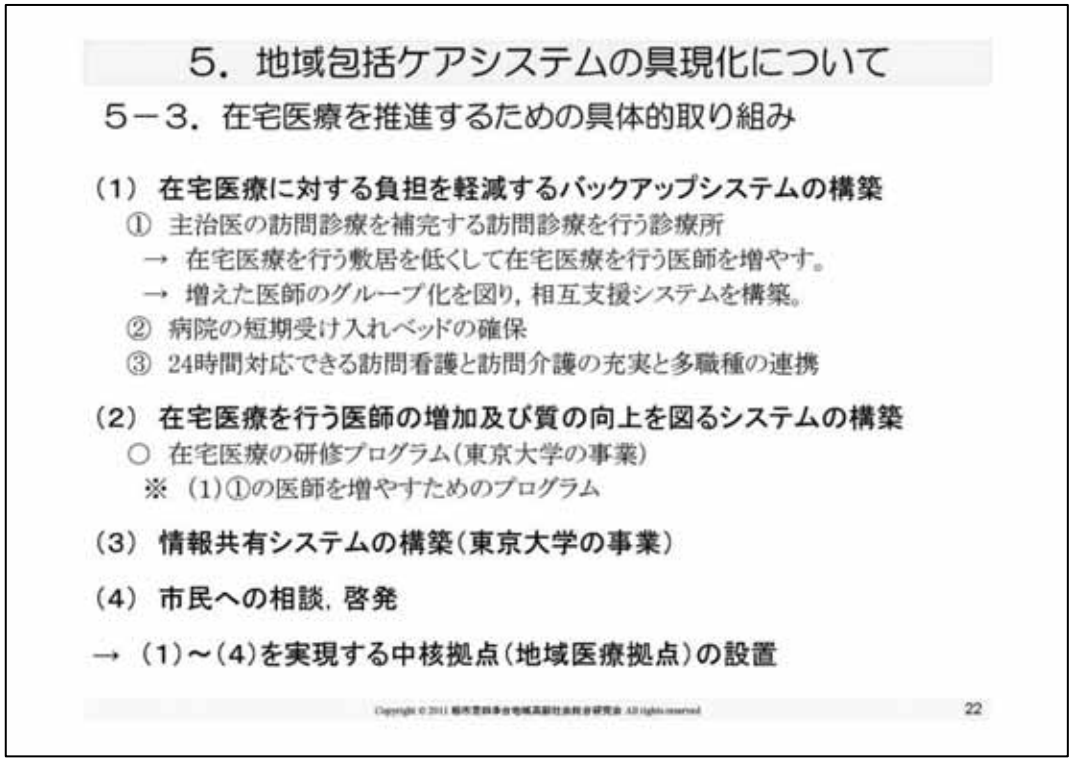
2011 年 8 月 10 日　カナダケベック州「La Presse」（取材）
2011 年 9 月　㈱プロトコーポレーション「介護のことがよくわかる本」（取材）
2011 年 9 月 29 日　内閣官房地域活性化統合事務局局長代理一行（視察）
2011 年 11 月　九州大学知財本部総合調整グループ（視察・ヒアリング）
不動産ジャーナリスト会議（視察・ヒアリング）
2012 年 2 月　ヒューマンヘルスケアシステム「シニアコミュニティ」（取材）
2012 年 2 月 11 日　野田総理大臣一行（視察・意見交換）
2012 年 3 月 2 日　前田国土交通大臣一行（視察・意見交換）

野田首相　豊四季台団地視察の際の意見交換の様子

（２）在宅医療の推進

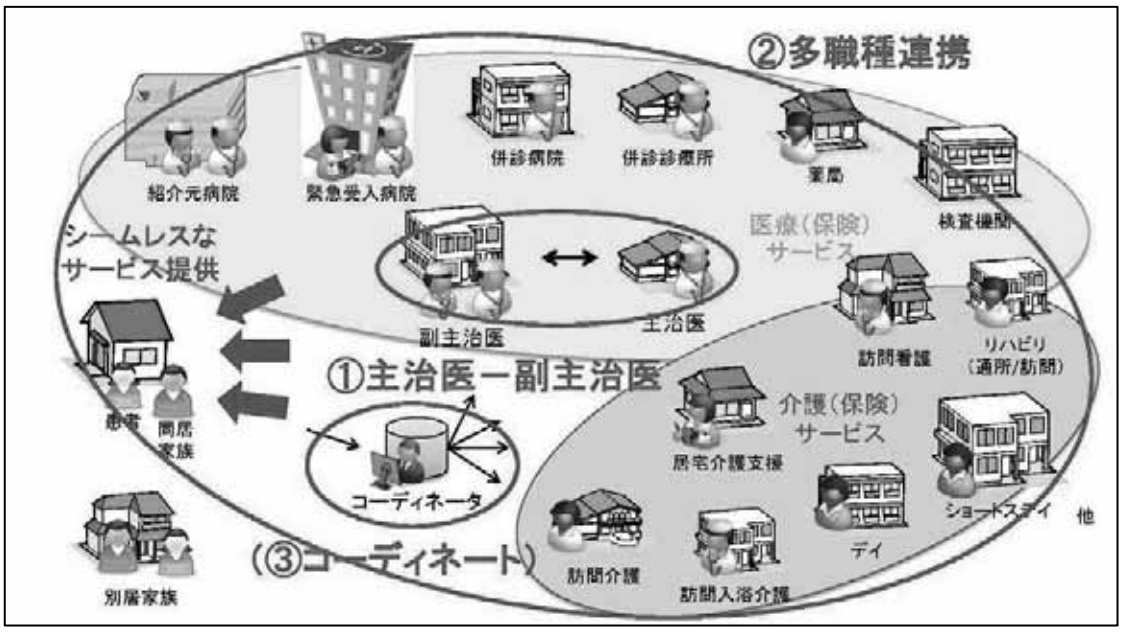
本年度は、6 月 28 日に総合研究会として発表した構想資料を基本として、地域包括ケアシステムの具現化を目指し、特に優先順位が高いと考えられる「在宅医療の推進」を中心に取り組みを継続した。在宅医療推進のための具体的取り組みとしては、以下の点を中心に進めているところである。

柏市豊四季台地域高齢社会総合研究会「長寿社会のまちづくり（平成 23 年 6 月 28 日版)」より
(http://kashiwa-toyoshikidai.org/uploading/110628_kashiwa-toyoshiki.pdf)



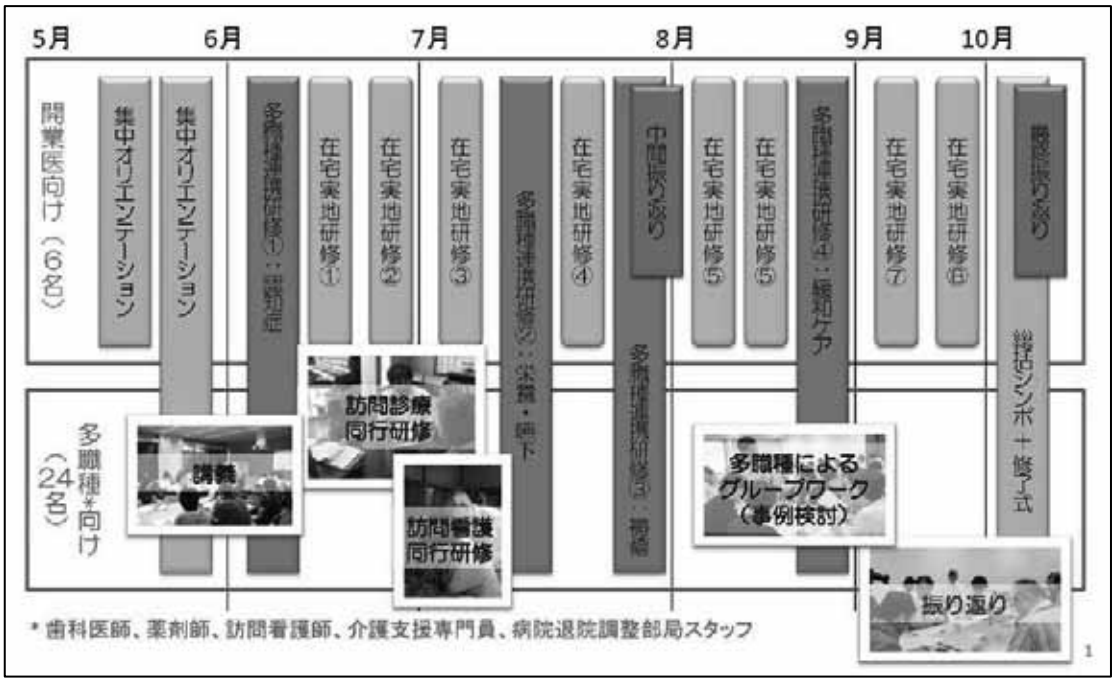
このうち、「（１）在宅医療に対する負担を軽減するバックアップシステムの構築」については、モデル的な在宅医療システムを導入するための実証実験を行うべく、柏市内の一部地域を対象とした「主治医－副主治医制と多職種連携を組み合わせた在宅医療推進モデル」に関するワーキンググループを、6 診療所、3 病院等を含む市内 27 事業者の協力を得て、平成 23 年 11 月に発足させた。このワーキンググループにおける実証の内容は、①主治医－副主治医制、②多職種連携（情報共有システムを用いたオンラインの連携と関係者が顔を合わせるオフラインの連携)、③主治医・副主治医・多職種のコーディネートの 3 点とし（発足当初)、限定症例における試行作業を、平成 25 年度にかけて実施する予定としている（イメージは右図参照)。ワーキンググループは平成 23 年度内に計 3 回開催され、試行で用いる情報端末ならびに情報共有システムの説明、個人情報の取り扱い方針等について説明、議論が行われているところである。平成 24 年 1 月以降は、実際の症例に基づく試行も開始された。

主治医－副主治医制と多職種連携を組み合わせた在宅医療推進モデルのイメージ（平成 23 年 11 月時点）



続いて「（２）在宅医療を行う医師の増加及び質の向上を図るシステムの構築」については、その最たる取り組みが、在宅医療に関する研修プログラムの開発並びに試行、評価である。まず、平成 22 年度より開発に着手した在宅医療に関する教育研修プログラムについて、第一弾となる「柏在宅医療研修試行プログラム」の作成を完了した（下図参照）。

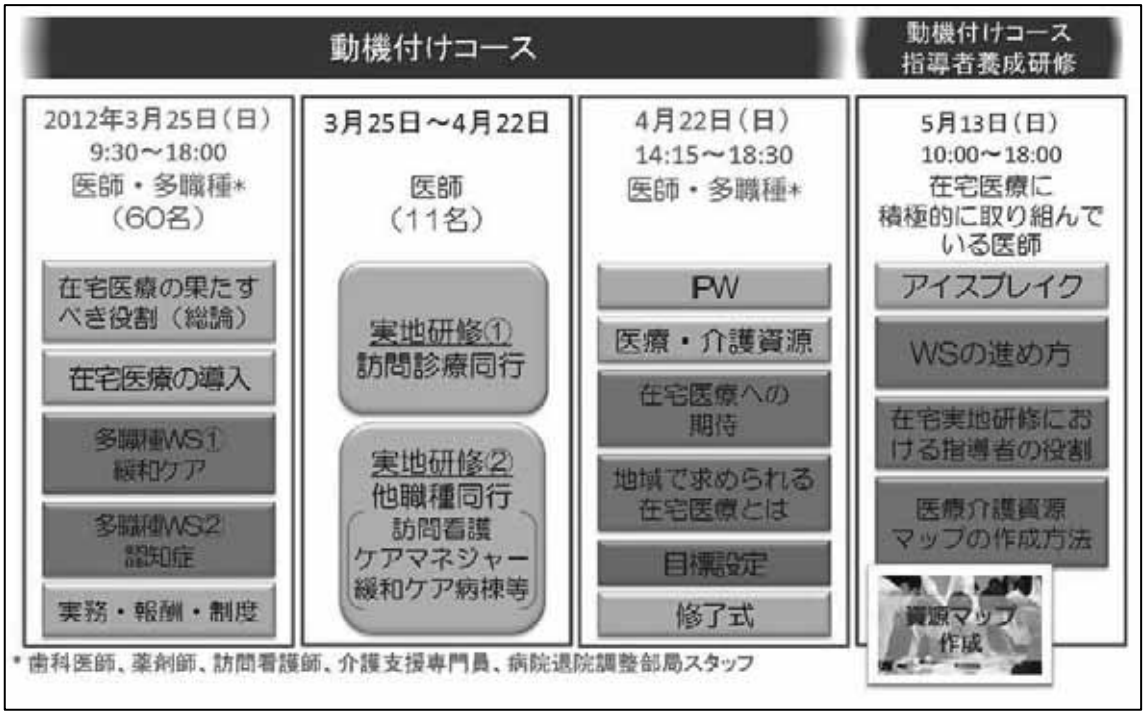
柏在宅医療研修試行プログラムの概要



柏在宅医療研修試行プログラムは､5 月 21 日～10 月 1 日にかけて､柏市内の開業医 6 名、多職種（歯科医師、薬剤師、訪問看護師、介護支援専門員、病院退院調整部局スタッフ等）24 名を対象に開講された。約 5 ヶ月間、延べ 8.0 日（開業医以外は 3.5 日）の構成となっている。プログラムの評価を行うため、受講前と受講直後にアンケート調査を実施し、意識や行動の変化を追跡した。また、開業医 6 名に対しては受講直後に個別のインタビュー調査を実施し、同プログラムを受講したことによる影響や、プログラムの改善点等について聴き取りを行った。

そして、このプログラム評価に基づき、在宅医療研修プログラム作成小委員会のメンバーにより、短縮版の研修プログラム「動機付けコース」と「動機付けコース指導者養成研修」を作成した。動機付けコースは、延べ 2.5 日（医師以外は 1.5 日）と、柏在宅医療研修試行プログラムを大幅に短縮した内容となっている。指導者養成研修は、延べ 1.0 日の構成となっている。動機付けコースは、3 月 25 日に初日を迎え、約 1 ヶ月の間に実地研修 2 回を経験し（医師のみ)、年度を超えた 4 月 22 日に最終日を迎える予定としている。受講者は、柏市内の医師 11 名、多職種（歯科医師、薬剤師、訪問看護師、介護支援専門員、病院退院調整部局スタッフ等）49 名を対象としている。また、平成 24 年度以降に柏市以外の市町村においても動機付けコースと同様の研修が開催され、各地域における在宅医療の推進に広く寄与することを目的とし、柏市を擁する二次医療圏である東葛北部保健医療圏の地区医師会在宅医療（または介護保険）担当理事、ならびに各市において積極的に在宅医療に取り組む医師に、研修へのオブザーバー参加を呼び掛けた。

動機付けコース／同指導者養成研修の概要



「（３）情報共有システムの構築」については、前述のとおり、（１）の試行を行う中で一体的に検討しているところである。「主治医－副主治医制と多職種連携を組み合わせた在宅医療推進モデル」に関するワーキンググループにおいて暫定版の情報システムを開発し、参加メンバーにタブレット端末を貸与して、掲示板やメッセージといった一部機能の試験的使用を開始した。

「（４）市民への相談、啓発」については、平成 23 年 10 月 21～22 日に行われた東京大学柏キャンパス一般公開において、個人の老化とそれを支える社会の仕組みあるいは課題を双六を通じて体感する「高齢社会双六（仮称）」の試作版を作成するなど、一般市民向け意識啓発用ツールの開発にも着手しつつある。平成 24 年 2 月 22 日および 29 日には、柏市民を対象として「在宅ケア柏市民集会」を開催し、柏市内の開業医、訪問看護師、介護支援専門員、在宅医療を受けている患者家族等が登壇した。

そして、「（１）～（４）を実現する中核拠点（地域医療拠点）の設置」に向けては、平成 24 年 3 月に、柏市医師会、柏歯科医師会、柏市薬剤師会、柏市、東京大学による「柏市地域医療拠点建設協議会」が設置され、平成 25 年度内の竣工を目指し、設計業者、建設業者の公募が計画されている。同拠点は、柏市医師会・柏歯科医師会・柏市薬剤師会が建築した後、柏市に寄附される予定となっており、その一部に、（２）で開発中の研修会や（４）の市民向け啓発イベントを開催することができる多目的ホールを設置する方針となっている。また、柏市が中心となって在宅医療の資源に関するコーディネートの機能を担うことも予定されており、その手順等については（１）の試行において検証を行っているところである。

（3）人と人のつながり委員会

人と人のつながり委員会のもとでは、本年度は「就労ワーキンググループ（WG）」が設置され活動した。

「就労WG」は JST - RISTEX（社会技術研究開発センター研究開発領域「コミュニティで創る新しい高齢社会のデザイン」）からの研究受託を受け、地域での活躍の場として「就労」という形で住民の地域参加を促し、地域の人のつながりのきっかけを生み出すプロジェクトに取り組み、「高齢者の生きがい就労の場の創成」「シニア住民と就労をつなぐシステム開発」「就労事業に参加することの、シニアへの効果検証」を主な目的として研究・実践活動を展開している。

本プロジェクトは、柏市内で支え手ニーズの高い領域である「農業」「食」「子育て支援」「生活支援」の 4 領域において事業を立ち上げ、ないしは発展させ、シニア層に支え手として事業に参加してもらうシステムの構築を目指している。本年度は、昨年度につづき各領域で事業主体となる企業や組織の支援を行った（柏市、UR、東大の 3 者による）。

（1）休耕地農園事業：柏市内の農家 7 名が参加するかたちで有限責任事業組合（ＬＬＰ）「柏農えん」を立ち上げ（2012 年 1 月登記完了）、当該組織が中心となって、柏市内の休耕地を利用した高齢者の生きがい就農を促進していくことになった。

（2）ミニ野菜工場事業：事業の担い手となる支援企業との交渉をすすめ、事業の担い手確保と計画策定に取り組んでいる。

（3）屋上農園事業・コミュニティ食堂事業・移動販売／配食事業：豊四季台団地商業区開発（平成 25 年度以降）の事業展開と連動するため、複数の企業と構想の具体化について検討を重ねている。

（4）子育て支援：「子育て支援センター」「高齢者の保育園への出前講座」については柏市内の学校法人くるみ学園が事業主体となり 4 月より事業開始、「学童保育兼学習塾」については柏市内で学習塾を展開している杉浦環境プロジェクト㈱が豊四季台団地近郊に新たな店舗を設置し、2012 年 3 月に開校し事業開始に至った。

本プロジェクトでは、「働く場」の開発と同時に、シニア層の就労支援のシステムづくり、および就労することがシニア当人および地域社会に与える効果を検証するためのデータ収集を実施している。

就労支援システムづくりに関しては、2011 年 11 月より東京大学高齢社会総合研究機構が主催、柏市、ＵＲ都市機構が共催、というかたちで「就労セミナー」を開始した。柏市に在住で「働く」ことに関心のある 60 歳以上を対象として参加者を公募し 50 名強の参加があった。2 月に第 2 回講座を開催、30 名強が参加した（「セミナー」は 2012 年度も継続開催されている）。参加者は全 4 回の講座を受講し、修了証を得るとともに、東京大学が行う各種調査や計測会への参加を呼びかけられる。また高齢者が働くということについての継続的な勉強会の案内や自主的な研究会を開催する機会などを提供される。また実際の仕事に関しては、先述の 4 領域の事業をはじめ「生きがい就労」プロジェクトに賛同し就労の場の提供と開発に協力を申し出た柏市内の事業者と意見交換を行う場が設定された。さらに各事業者は別途「就労セミナー」卒業者向けの説明会等を開催し、うまくマッチングが成立した人から各自雇用が開始されるという形をとることとなった。なお本セミナーや勉強会の開催等を企画、マネジメントする「オフィスセブン準備室」が東京大学高齢社会総合研究機構内に設置され、活動している。本準備室は JST -RISTEX の委託事業終了後には独立し「生きがい就労」推進の中心的組織となるべく、継続的な組織のありかたを検討中である。

就労プロジェクトがシニア当人および地域社会に与える効果の検証に関しては、2011 年 4 月に柏市内 5 地域に在住の 55 歳以上ランダムサンプル 2000 名への社会調査を実施し、地域社会への効果の「ベースライン」となるデータを収集した。また、シニア当人への効果に関しては、「就労セミナー」受講者を対象とした認知機能、身体機能の測定会、社会意識に関するアンケート調査等を実施し、データベースを構築中である。現在のところセミナー受講者のほぼ全員に協力いただき、3 月現在では 90 名程の「就労前」にあたるデータが収集されている。今後の計画では、同一人物に約半年に 1 回のペースで追跡データの収集を行う計画である。「セミナー」受講者がその後様々な仕事に就くことで、就労者と非就労者の比較、就労前と就労後の同一人物の比較により、働くことがシニア当人の健康や意識、行動にもたらす効果を検証する計画である。

（4）住まい・移動ワーキンググループ

住まい・移動ワーキンググループは、本年度次の 2 点の活動を行った。1 点目は豊四季台に新しくつくられる近隣公園（約 1ha）に対して、地元住民との勉強会を通し、これからの高齢社会に必要となる機能を検討することである。2 点目は地域循環居住である。従来の団地の問題は、一度に同世代が大挙しそのまま高齢化をしていくことである。豊四季台団地の建て替えに際して、多くの土地が民間に売却されることから、数十年後再び同じ問題が発生することが予見できる。これを事前に防ぐべく、地域内での住み替えを適切に行い多世代のソーシャルミックスを実現させる方法について検討する。

公園づくり勉強会は、今後豊四季台地域の近隣公園を最も利用する方の要望を事前に整理して、公園を設計するさいの条件に反映してもらうことを想定している。豊四季台団地自治会関係者、豊四季台地区民生委員、豊四季台周辺地域町会、豊四季台にお住いの一般住民の方らをメンバーに総勢 20 名の勉強会を発足させた。参加者は日々地域活動に忙しい中で、住民の声に接する方たちであり、日々の活動の中で公園等パブリックスペースへの要求や工夫を予め想定することで、現在のような高齢者があまり利用しない公園ではない、高齢社会を支えるコミュニティインフラについて検討を進めた。

第 1 回勉強会（2011 年 6 月）では東京都健康長寿医療センターの村山洋史氏に閉じこもりを防止し、なるべく外にでて、健康を維持することの重要性とそのポイントを教えていただき、これからの公園に求められる機能について話し合った。第 2 回勉強会（2011 年 7 月）では、参加する勉強会メンバーが、地域にお住いの前期、後期高齢者、子育て世代にインタビューを行った。第 3 回勉強会（2011 年 12 月）には、第 1 回、第 2 回の勉強会で出たニーズに対応するには、地域住民側にも公園で発生するだろう様々なトラブルをみなで解決する管理の仕組みづくりについて話し合いを行った。

1.3 産学連携活動

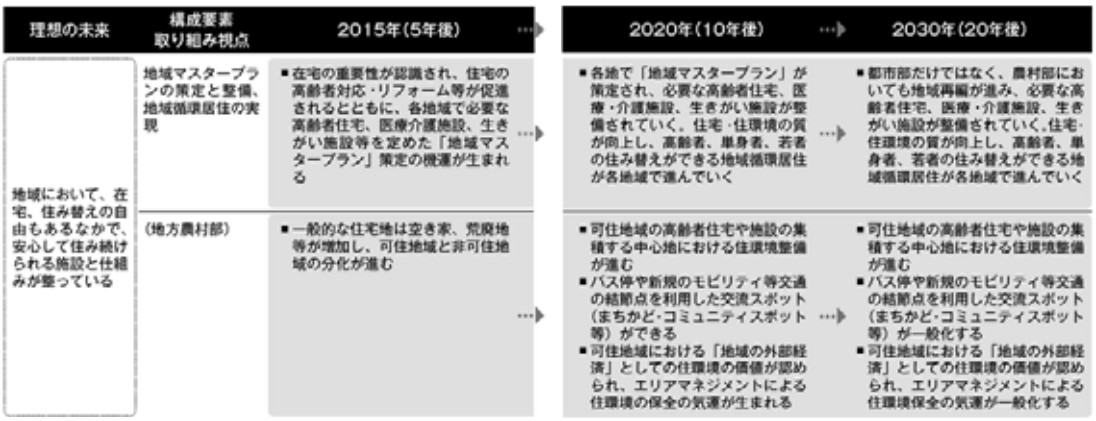
1.3.1　ジェロントロジー・ネットワーク

「Aging in Place～住み慣れた地域で最期まで自分らしく老いることができるまち～」を実現するためには、医療・介護システム、住環境、移動・交通システムそして生きがい就労など様々な領域が連動し、イノベーションを創出していくことが求められており、イノベーション創出のためには大学だけではなく、社会を支える産業界の取り組みが不可欠である。東京大学では 2009 年度より産業界と連携してジェロントロジー・コンソーシアムを組織し、超高齢社会における課題を明らかにするところから一緒に活動を開始した。東京大学の最先端のジェロントロジー研究の知見をベースにして正しい現状認識の上に立ち、幾度も議論を重ねながら課題を明確にして解決策を検討した。

この活動の成果として、3 人に 1 人が高齢者となる 2030 年に向けたロードマップが完成し、2011 年度に書籍「2030 年超高齢未来　破綻を防ぐ 10 のプラン」として公開することができた（下図）。2030 年のあるべき姿、そしてそれまでに何をすれば良いのかが明確になってきたことで、いくつかの企業は具体的なアクションを起こし、共同研究等を開始した。

書籍「2030 年超高齢未来　破綻を防ぐ 10 のプラン」　東洋経済新報社

ロードマップの例（住まい・住環境）



さて、2011 年度は、ジェロントロジー・コンソーシアム活動を引き継ぐものとして、産学連携ジェロントロジー・ネットワークを組織しており、約 50 社の企業が参加した。

ジェロントロジー・ネットワーク参加企業一覧（2012/3 最終）

NO.	業界区分	企業名
1	自動車・機械メーカー	㈱ジェイテクト
2		トヨタ自動車㈱
3		日産自動車㈱
4		八千代工業㈱
5		ヤマハ発動機㈱
6	電機・精密機器メーカー	沖電気㈱
7		GEヘルスケア・ジャパン㈱
8		日本電気㈱
9		パナソニック㈱
10		富士フイルム㈱
11		㈱日立製作所
12		シーメンス・ジャパン㈱
13	食品・生活用品メーカー	味の素㈱
14		花王㈱
15		サンスター㈱
16		サントリー食品インターナショナル㈱
17		サントリーピア＆スピリッツ㈱
18		㈱資生堂
19		㈱ニチレイフーズ
20		ネスレ日本㈱
21		ハウス食品㈱
22		ユニ・チャーム㈱
23		ライオン㈱
24	流通・外食・総合商社	住友商事㈱／㈱住友商事総合研究所
25		㈱ゼンショー
26		三井物産㈱

NO.	業界区分	企業名
27	建築・不動産・住空間	㈱荒井商店
28		オリックス不動産㈱
29		大和ハウス工業㈱
30		三井不動産㈱
31		㈱LIXIL
32	事務機器・家具	㈱イトーキ
33	IT・情報通信	㈱NTTドコモ
34		大日本印刷㈱
35		富士ソフト㈱
36		フランステレコム㈱
37	マスコミ・教育	㈱電通／電通総研
38	運輸	東京急行電鉄㈱
39	素材	㈱地球快適化インスティテュート
40	金融	西武信用金庫
41		㈱みずほ銀行
42	医療・福祉機関	㈱フレアス
43		ヘルスケアパートナーズ㈱
44		㈱ユメコム
45	マーケティング・コンサルティング	イーソリューションズ㈱
46		㈱テレマーケティングジャパン
47		㈱富士通総研
48		㈱メディシンク
49		㈱ユーディット
50		㈱リサーチ・アンド・ディベロプメント
51	寄付/支援企業	UR都市機構
52		㈱セコム
53		日本生命保険相互会社

本活動は、各企業が具体的なアクションを見出すためのインキュベーションの場と位置付けており、そのための議論や調査を行った。具体的には、住宅、モビリティ、ICT、ライフデザインなどの特定テーマに基づく分科会（ワーキンググループ）を設置し、情報の共有や議論を重ねながらフィールドテストや市場調査などを検討した。

ワーキンググループテーマ一覧

	WGテーマ	概　要
1	地域マスタープランの構築・展開	大都市、地方都市、田舎の将来変化を見据えた上で、これからの住環境、住居、移動システム、ＩＣＴ等を総合的にデザインする研究。これを通じたビジネス展開を検討。
2	ジェロントロジー住宅の開発	居住者の状態（身体・認知能力、世帯構造等）に応じてフレキシブルに最適な居住空間を提供する未来型住宅を追究（Aging in Placeを支える住宅設計）するとともに具体ビジネス展開を検討。
3	未来の交通システムの構築	大都市、地方都市、田舎の将来変化を見据えた上で、理想の移動システムのあり方を追究するとともに、具体ビジネス展開を検討。
4	未来のＩＣＴのあり方の追究	超高齢社会下におけるＩＣＴ技術のあり方を追究した上で、住環境、コミュニケーション場面等での新たな技術開発及びビジネス展開を検討。
5	高齢者支援プラットフォームの構築	地域の中で住民と行政、企業がwin-winで連携し、高齢者の生活を元気高齢者が支援する仕組み＝街の新しいインフラを構築することを通じた新たなソーシャルビジネスを展開。

	WGテーマ	概　要
6	人生100年時代のライフデザイン研究を通じた人生教育・コンサル事業	人生100年を前提としたライフデザインのあり方を追究し、ライフデザイン教育（ジェロントロジー教育）を核とした人生教育産業等の創造を目指す。国民のＱＯＬ、地域社会のＱＯＣ指標開発も視野に入れる。
7	高齢者と家族のニーズ顕在化研究	本人やその家族が漠然と感じている『不安』や『不便』を軸に調査研究を行い、潜在ニーズについての分析・理解を通じ、前期シニアをターゲットとする市場対応を進めるための方向性を明らかにする。

また、分科会活動の共有化のための全体会議や合宿、さらには、東日本大震災において、被災した高齢化が進む地域の支援のための活動も開始した。

■ジェロントロジー・ネットワーク全体会の開催

情報共有のための話題提供と議論・交流会を年３回、合宿（1泊2日の議論等で親睦を深める）を年１回開催。

6月15日　第1回全体会　　ＩOGの取り組み紹介、説明、交流会
10月5日　第2回全体会　　講演2件、ワーキンググループ（WG）報告、交流会
12月2,3日　合宿（１泊）　WG活動報告・議論他、交流会
3月２１日　第3回全体会　講演2件、WG報告、ＩOG報告、交流会

■被災地視察

東京大学高齢社会総合研究機構の被災地支援活動の成果であるコミュニティケア型仮設住宅を視察（2/26,27）。東京大学と包括協定を締結した大槌町の支援について、町長以下職員と意見交換。

このような取り組みがいずれ共同研究や事業化に発展することが期待され、そこから生まれるイノベーションは、日本だけでなく、これから超高齢社会を迎える海外の国々にも大いに貢献するものと考えられる。言い換えれば、日本で得られた知見・技術・ノウハウ等は、世界をリードできる可能性があり、学術界としても産業界としても最も注力すべき領域の一つであると考えられる。

1.4　イベント等の実施

1.4.1 一人暮らし高齢者とのふれあい会食会（２００人ワークショップ）

（2011 年 11 月 14 日；参加者：豊四季台団地に住む一人暮らしの高齢者約 200 名、豊四季台団地民生児童委員らとの共催）

柏市豊四季台団地で活躍する民生児童委員らが毎年開催している一人暮らしとの高齢者会食会を、昨年度に引き続き東京大学高齢社会総合研究機構、ジェロントロジー研究会と共催で実施した。当機構としても実際に１人暮らしをしている 200 人の高齢者の意見収集ができる機会であった。

プログラム内容としては、暮らしの困りごとや工夫していることについて、話を伺いながら、現在の生活状況（食事、つながり、情報源など）について 6 名を 1 テーブル、紙芝居方式で実施した。その後昼食をはさみ、地元ボランティアによるコミュニティ喫茶店、認知症予防講座、一人暮らしのための食の工夫講座を行った。また、今年度の試みとして、ジェロントロジー・ネットワーク企業の協力を得て、お化粧教室、パーソナルモビリティ試乗会も開催した。参加者アンケートでも今回プログラムの満足度が高く、楽しく過ごすことができたとの回答が多くみられた。

200 人ワークショップの風景

お化粧教室の様子

1.4.2　柏キャンパス一般公開（2011 年 10 月 21－22 日）

東京大学柏キャンパスに 2011 年 5 月に第二総合研究棟が竣工し、当機構も柏キャンパスの正式な仲間入りをしたことから、本年度はじめて柏キャンパス一般公開に参加した。

柏キャンパス一般公開はキャンパス周辺の住民やつくばエクスプレス沿線住民を中心に毎年多くの来場者があることから、キャンパス周辺の方々に機構の存在と研究内容を知っていただく好機ととらえ、来場者参加型の催しを中心に企画した。また、一般公開全体の企画である特別講演会で鎌田機構長が「ジェロントロジー（老年学）の拠点が柏に」という題目で講演をすることとなった。

機構が企画・実施したのは以下の 7 企画である。

＜展示＞
・ポスター掲示による機構の研究、活動紹介
　-高齢社会総合研究機構とは
　-柏市豊四季台地域での研究活動紹介
　-東日本大震災復興まちづくりの紹介
＜展示・見学・ツアー＞
・福祉用具、模擬住居の見学・体験
　（工学系研究科機械工学専攻　鎌田・小竹研究室による企画・実施）
＜参加・経験＞
・頭と体の健康チェック（21 日のみ）
・介護・医療よろず相談（21 日のみ）
・「高齢社会すごろく」（22 日のみ）
＜講座＞
・今日から出来る認知症予防（21 日のみ）
・バランストレーニングによる高齢者転倒予防講座（22 日のみ）
　（先端科学技研究センター　田中研究室による企画・実施）

柏キャンパスの一番奥まった場所に出来たばかりの建物であるという条件から、当日の来場者数がどこまで伸びるか未知数でやや心配したものの、徐々に来場者が増え、特に事前に柏市内等で参加者を募った講座型の企画では、友人や知人を誘い合って参加された方が少なからずみられた。最終的には機構には 350 名を超す来場者があったとみられる（パンフレット等の配布数より）。また、2 日目の午後に行われた鎌田機構長の特別講演会を聞いた方々が、閉場直前に駆け込みで見学にこられ、時間切れになるまで熱心に機構の活動について質問していくなどの様子も見られた。

自分自身が高齢者だから、という動機で機構に足を運んだ方もいれば、おじいちゃんおばあちゃんと暮らしているから、といいながら見学する家族連れ、高齢社会について学び研究する「ジェロントロジー」という学問の存在を初めて知ったという学生、新しい建物だからと入ってきて、模擬住居や福祉器具など、他の研究棟ではなかなか見られない展示に熱心に見入る方など、多様な方に来場していただいた。機構の存在や研究活動を、このように多様な方々に知っていただくことが出来たことは、一般公開に参加した何よりの収穫であった。

研究員の説明に耳を傾けるご家族

パネル展示による機構の紹介

1.5　国際連携

1.5.1 スウェーデン-日本　高齢社会シンポジウム（2011 年 9 月 21-23 日）

9 月 21 日（水）～23 日（金）の 3 日間、ウプサラ大学（スウェーデン　ウプサラ市）において、スウェーデンー日本　高齢社会シンポジウム「Conference on Aging Societies a Japanese-Swedish Research Cooperation」が開催された。本会議は 2009 年 10 月に本学において開催された日本－スウェーデン高齢社会シンポジウムを受けて開催された、第 2 回会議であり、今回の会議は主催がウプサラ大学と東京大学、共催者に日本学術振興会、後援に在日スウェーデン大使館の協力の下行われた。

本会議の目的は、高齢社会を共通のテーマとしてスウェーデン各研究機関の研究者と東京大学をはじめとする日本の研究者との共同研究、研究協力を推進することである。前回の第 1 回会議ではスウェーデンからはウプサラ大学をはじめ複数の大学、研究機関から 30 名近い研究者が来日し、安田講堂での公開シンポジウムを含め 3 日間の会議、高齢者施設や日本企業の見学を行った。今回は、その会議を受けて更なる研究者間の交流を進めること、また研究者のみならず高齢社会の課題に関心を持つ企業との産学連携活動を模索すること等をめざし、ウプサラ大学がホストとなって企画されたものである。今回日本からは、松本洋一郎東京大学理事（副学長）を筆頭に、東京大学所属の教員や大学院生を中心とした研究者、および東京大学高齢社会総合研究機構が主催する産学連携ネットワーク参加企業よりの参加者、計 43 名が訪瑞した。

日本からのたっての要望で、会議の開催前には、ウプサラ市内で高齢者福祉施設のサイトビジットが行われた。参加者は 2 班に分かれ、最新のテクノロジーが導入された高齢者施設の見学等を行った。午後から開始された会議では、Anders Hallberg ウプサラ大学総長、渡邊芳樹在スウェーデン特命全権大使、松本理事（副学長）、Eva Nillson-Bagennholm 氏（スウェーデン社会福祉省）、Peter Egardt ウプサラ市長、佐野浩日本学術振興会ストックホルム研究連絡センター長の挨拶に続き、Barbro Westerholm ウプサラ大学教授、辻哲夫本学高齢社会総合研究機構教授の基調講演が行われた。また夜にはレセプションが開かれた。会議 2 日目は、「社会保障と政策」、「生命医科学研究」、「テクノロジー」の 3 つの専門分野に分かれての両国関係者間でのワークショップ、及び日本から参加した研究者及び企業によるポスターセッションが開催された。3 日目は地域社会における実践型プロジェクトの紹介が行われた。各発表後には、両国関係者でディスカッションが行われ、高齢化に関する両国の現状や課題認識、政策、産官学連携の取組み、新たなテクノロジーの開発など、幅広い分野に渡って活発な意見交換と相互理解が深まり、非常に充実した内容となった。

3 日目の最後には、Lars Magnusson ウプサラ大学教授、鎌田実本学高齢社会総合研究機構長よりの挨拶があり、2 年後にはまた日本での第 3 回会議の開催を目指そうという提案が出され、閉会した。

1.6　その他の活動等

1.6.1　平成 23 年度老人保健健康増進等事業　「介護等を受けながら住み続けられる高齢者の住まいのあり方に関する調査研究事業」

（1）実施目的、検討体制

要介護状態における高齢者の住まい方は大きく分けて、在宅（自宅)、サービス付き高齢者向け住宅、施設サービスの 3 つがある。

都市部を中心に、急激な単身高齢者及び高齢者夫婦のみの世帯の増加が見込まれる中、重度の高齢者が在宅生活を続けることのできる仕組みを構築することは、「Aging in place」の観点から望ましいとともに、施設への移行を極力少なくすることは、介護保険財政の持続性を向上させることにも寄与するものと考えられる。

平成 22 年度の調査研究事業の検討成果を踏まえつつ、「24 時間在宅ケア」のサービスの合理的なありかたを考察するとともに、柏市をフィールドに現在の供給体制から「24 時間在宅ケア」への転換に必要な条件を明らかにする。

検討委員会　委員等名簿　（敬称略、五十音順）

氏　名	所　属
高橋　紘士(委員長)	国際医療福祉大学大学院　教授
石黒　暢	大阪大学　世界言語研究センター　准教授
石原　美智子	社会福祉法人新生会 理事長
大月　敏雄	東京大学　工学系研究科建築学専攻　准教授
小山　剛	社会福祉法人　長岡福祉協会 高齢者総合ケアセンターこぶし園　総合施設長
園田　眞理子	明治大学　理工学部建築学科　教授
堀田　聰子	独立行政法人 労働政策研究・研修機構　雇用戦略部門 研究員
村上　卓也	独立行政法人　都市再生機構　団地再生部 団地再生計画チーム チームリーダー
村嶋　幸代	東京大学　医学系研究科地域看護学分野　教授

事務局　東京大学　高齢社会総合研究機構

辻哲夫、廣瀬雄一、後藤純、瀬沼智洋、吉江悟

株式会社富士通総研　第一コンサルティング本部　金融・地域事業部

稲永和年、名取直美、湯川喬介

（2）実施内容

本調査事業は、以下 2 つの視点から実施した。

①「24 時間在宅ケア」の 2 タイプの抽出による具体的な形態の検討及び需要分析

以下 2 タイプのサービス形態を選び、各事業者の実態把握をするとともに、それをもとに 24 時間の在宅サービス形態のあり方を検討した。

・小規模多機能型居宅介護からのアプローチ（社会福祉法人長岡福祉協会）

・短時間巡回訪問介護サービスからのアプローチ（株式会社新生メディカル）

②「24 時間在宅ケア」へのシステム移行の検討

柏市の介護保険給付実績のデータ分析から、サービスの提供サイド、利用サイドの双方における実態分析を行い、「24 時間在宅ケア」システム展開への諸条件を確認した。

また、これらを統括する形で、検討委員会を実施したが、実施経過と連動するものなので、各回の検討委員会の議事内容説明をもって、経過報告とする。

第 1 回（8 月　東京大学）

１．調査研究の概要

２．24 時間在宅ケアの先駆的事例としてこぶし園と新生会の視点の共有

３．両者の取り組み、視点を踏まえた論点確認　及びディスカッション

第 2 回（10 月　東京大学）

１．定期巡回・随時対応サービスに対する議論

・「短時間巡回訪問介護サービス・岐阜県方式」～在宅生活の継続を支える～中間報告書

２．柏市介護保険給付データ整理進捗報告

第 3 回（11 月　東京大学）

１．厚労省にて議論されている「複合型」、「定期巡回型」の整理

２．柏市における対利用限度額 6 割以上利用者のサービス利用状況確認

柏市（都市計画課・高齢者支援課）を交えて分析データ読込み（3 回・12 月～1 月東京大学）

１．分析データにみられる特徴及びその背景の確認

２．今後の示唆に繋がるものの精査

第 4 回（1 月　東京大学）

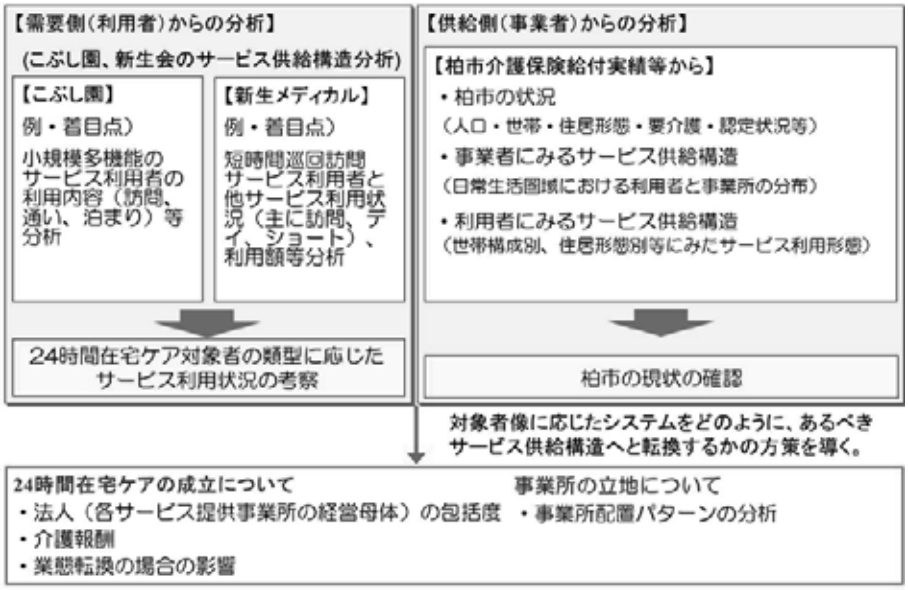
１．委員からの分析要望に対する追加分析結果報告及びデータ分析の方向性検討

２．報告書構成案に対する議論

第 5 回（3 月　東京大学）

１．報告書案に関するディスカッション

本調査研究のワークフロー



（3）実施結果

本研究においては、今後日常生活圏域（地域包括支援センター単位）で在宅サービスを確保する、あるいは在宅サービスの需給バランスを日常生活圏域内でとる、という方向性の下で、まちづくりとの関係性を考慮しながらサービスを構築すべき、という前提にたって提言するものである。

1. 今回の調査から見た在宅サービスの供給と利用の構造

(1) サービスの立地のばらつき

訪問系サービスを日常生活圏域で賄えるところはゼロのところが多くあり、訪問・通所いずれのサービスにおいても越境しているのが現状であった。事業者にとってそれは異常ではなく、市場原理に基づく行為として行われてきたものと考えられる。

(2) 世帯構成から見たサービスの利用状況

世帯構成でサービスの利用状況をみると、世帯の中に要介護者以外の同居家族がいる場合、利用の中心となるのは通所・短期入所サービスの利用であり、訪問系サービスはあまり利用されていないが、要介護度が高くなるにつれ、訪問系サービスの利用は増加する傾向があった。今後は核家族化の進行・高齢者のみ世帯の増加が予想されるが、その中で在宅生活を支えていくには訪問系サービスのニーズへの対応が必須であると考えられる。要介護度の低い者で利用率が高い傾向が見られたが、所得のある層についてはこの点でのニーズがサービス付き高齢者向け住宅に向かうことが推測される。

(3) サービス供給事業者の母体法人種別から見たサービスの利用状況

施設の設置主体であるか否かが、通所、短期入所に傾斜するか、訪問介護に傾斜するかの要因になっていることが推測され、設置主体であれば通所、短期入所に傾斜する傾向が窺えた。需要分析は定性的に、「通所と短期入所併用で支えてきたが家族が倒れたらダウン」、あるいは「通所で支えてきたが、本人の重度化に伴い訪問介護の利用にシフト」という大きく分けて 2 つのパターンに分けられた。前者は施設系ケアマネの場合にみられる傾向であり、そのまま入所というストーリーが窺われ、後者は営利法人系にみられる傾向である。これは、事業者側の事情がケアプラン作成に影響を与えており、母体法人の施設設置有無と提供サービス内容の傾斜傾向に結びついていると考えられる。

2. サービス付き高齢者向け住宅の位置づけ

サービス付き高齢者向け住宅における「サービス」とは、いわゆる見守りに代表される生活支援であり、現時点では、それに係る費用は自己負担すべきものとして整理されている。また、従来、特別養護老人ホームで対応していたニーズを「外付けの介護保険サービス」と「生活支援サービス付きの住まい」に分解するという政策に則るものである。

他方、建物として住宅を整備するには、新築の場合は相当程度の初期資本投下が必要であり、既存住宅を活用すれば、それを軽減することもできるが、良質な住宅、住環境が確保されるには、資本投下が適切に行われなければならない。しかし、現状では、地域で安定的に適切な規模の資本を集約する仕組みがない。例えば、大規模な株式会社の場合、株主への利益還元と間接経費等で建物等の環境整備に純粋に投下される資金が小さくなる、あるいは高額な価格になる懸念がある。高齢者住宅や居住施設及びサービス提供のための拠点施設等のインフラ整備に対して、従来のように公的資金を潤沢に投下し難い財政下にあっては、地域における負担と受益の関係をより直接的にするコミュニティファンドの構築といった手段を活用する場面も出てこよう。

以上のような適切かつ効果的な資本集約の仕組みも考慮に入れ、サービス付き高齢者向け住宅に係る家賃と生活支援費用、食費等を合わせた月額負担料と、中間所得層の負担可能額が擦り合うための工夫が一層必要と考えられる。また、生活支援費の自己負担が困難な経済階層の居住の場をどう確保するのかは早急に明らかにしなければならない重要課題である。

3. 訪問系サービスの重要性

高齢独居世帯、夫婦のみ世帯が今後増加し、施設整備が抑制的な政策がとられる中で、訪問系サービスの充実が必要であり、事業者における訪問系サービスの充実（特に施設系事業者）、利用者に対するサービスの組み立て方の見直しが求められるのではないか。24 時間対応の在宅サービスは今後、必ず訪問系サービスを組み込まなければならないことから、施設系事業者がいかに取り組むかが課題である。

4. 24 時間在宅ケアへの移行方策の提案

以上の状況を考慮すると、24 時間在宅ケアシステムを必要とする後期高齢者（世帯構成においては特に高齢者独居世帯、夫婦のみ世帯）が多い地域でこのシステムを導入し、「施設から 24 時間在宅ケアへ移行」という実証を先駆けて行い、サービスモデルとして他圏域へ波及という流れを作る必要がある。このような流れをつくるためには、複合型サービスや定期巡回・随時対応型訪問介護看護等への転換を促すよう、行政は事業者を積極的に誘導する必要がある。このためには、下記の点に留意する必要がある。

ⅰ.サービスの立地政策について、市行政は将来に渡る詳細なデータに基づく 24 時間型を組み込んだサービス展開のビジョン及びガイドラインを持つ必要であり、今後の方向性を踏まえると、事業者に対して転換すべきサービスをメッセージとして発することが必要である。

ⅱ.そのようなビジョンの下で、行政は介護事業者協議会やケアマネ連絡会等を通して担い手に新しいサービスのノウハウを学んでもらえる場を提供し、地域住民にも新しいサービスの位置づけを説明し、理解を求めるなどの姿勢が必要である。このような育成、啓発等の政策を持ちつつ、そのサービスの立地政策のガイドラインとセットでサービス付き高齢者向け住宅も誘致しなければ、地域包括ケア、Aging in Place の実現に向かえない可能性がある。市場がオープンである場合、粗悪な事業者等に対する退場規制をできるようにしておく等の対応も重要であろう。

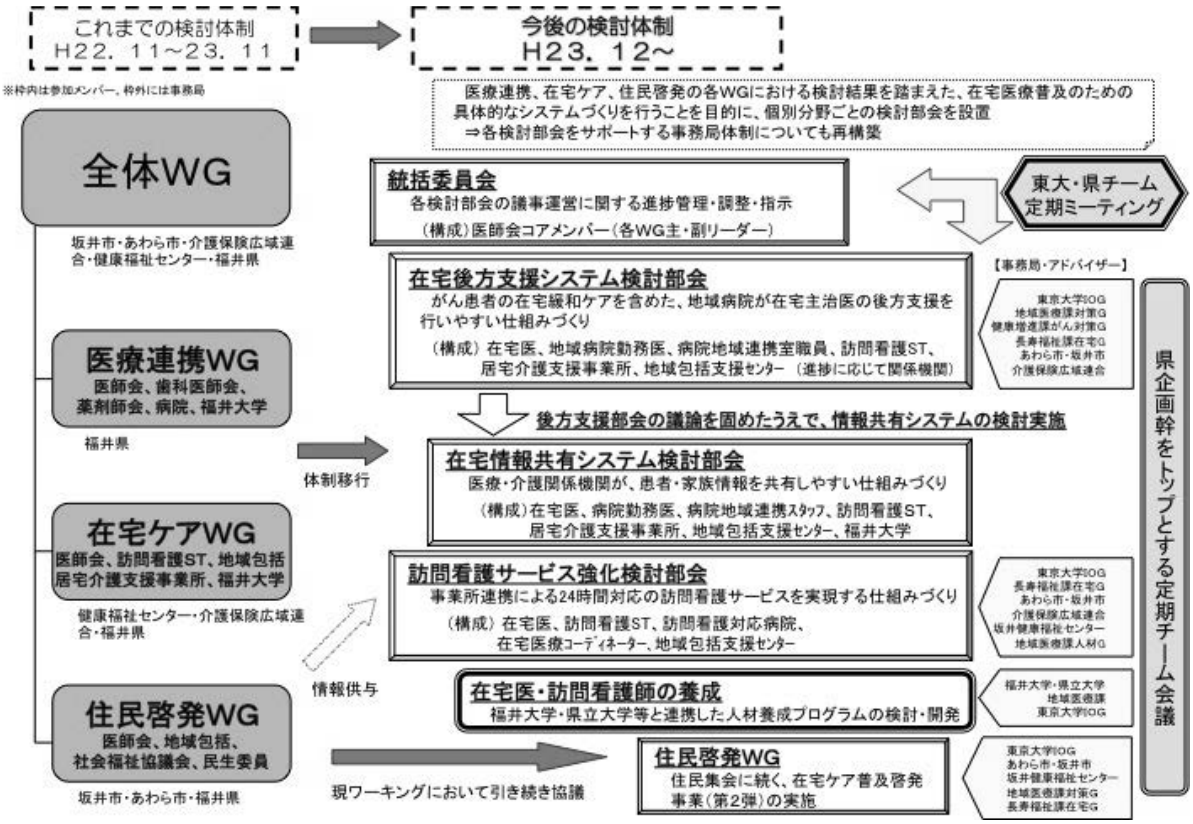
ⅲ.24 時間在宅ケアシステムの大前提は住まいの確保である。サービス付き高齢者向け住宅をはじめとする高齢者向けの住まいが日常生活圏域内で適切に立地するよう誘導する必要がある。従って、行政は 24 時間対応の在宅サービス事業者を公募する際には、例えば、日常生活圏域単位の市のビジョンを前提に、サービス付き高齢者向け住宅と組合せるなど、地域包括ケアの拠点となるよう全体構造を明示し、これを公募要件にすると共に、その拠点を中心に地域特性に応じて、様々な高齢者向けの住まいを配置する必要がある。

1.6.2 福井県との共同研究計画の実施（坂井地区における在宅医療福井型モデル）

（１）活動履歴と活動体制の変遷

今年度の 11 月までは、昨年度からの継続で、3 つの WG を中心に活動を進めてきた。特に医療連携 WG（医師会、病院等医師）と在宅ケア WG（多職種）においては、議論の内容が連動する場合も多く、議論の流れに応じて合同 WG として実施してきた。住民啓発 WG はできるだけ汎用性の高いイベントプログラムと説明ツールの作成をめざして、時には単独実施やイベント実施も含めて若干開催頻度を上げて実施してきた。

12 月以降は医療連携 WG と在宅ケア WG において委員会性主体の活動へとシフトした。WG 活動は一時休止とし、テーマをしぼった議論（下図参照）をこの場で実施することで、より議論の深堀を目指している。これらの委員会の進捗方針や議内の容検討やスケジューリング等の意思決定については、統括委員会（医師会コアメンバー＋各 WG 主・副リーダー＋県庁＋東大）を設け、県庁と東大とで実施する定期ミーティングの内容を踏まえた議事運営委員会的な位置づけで各委員会の進行管理を行う。



WG は、今年度に医療連携 WG と在宅ケア WG は 4 回実施（5 月、7 月、9 月、11 月／7 月、9 月は合同開催)、住民啓発 WG は 6 回実施（5 月、7 月、9 月、11 月、12 月、 1 月）をした。住民向けの活動としては、住民集会を坂井市とあわら市で 1 回ずつ（2011.9.4 の AM,PM で同日開催)、出前講座を 2 回、市民委員会を 1 回実施し、地元住民に在宅ケアとまちづくりの重要性、地元の体制や各種サービス（医療・介護）の利用方法について、考えて頂く機会とした。

（２）在宅医療を含めた在宅ケア実施体制の構築

医療連携 WG と在宅ケア WG では、以下内容が主要論点として収斂され、今後委員会で検討予定とされている。

・在宅後方支援システムとして、がん患者の在宅緩和ケアを含めた、地域病院が在宅主治

医の後方支援を行いやすい仕組みについて
・情報共有のシステムとして、医療・介護関係機関が、患者・家族情報を共有しやすい仕組みについて
・訪問看護サービスの強化という観点で、事業所連携による 24 時間対応の訪問看護サービスを実現する仕組みについて
・在宅医・訪問看護師の養成という観点で、福井大学・県立大学等と連携した人材養成プログラムの検討・開発について

また、厚生労働省にて平成 24 年度予算化が議論されている在宅医療連携拠点事業において、事業実施が確定すれば、坂井地区介護保険広域連合を中心に坂井地区医師会、福井県庁と連携しながら臨む予定でいるが、委員会運営とも連携しながら、以下のことに取り組んでいく。

・坂井地区内の在宅ケアに関する課題抽出・対策検討ワーキング
・医療・介護スタッフの顔の見える関係づくりを強化する地域ケア会議
・多職種傘下による学習会・症例検討会
・24 時間体制を構築するためのネットワーク化及び、情報共有システムの構築
・地域包括支援センターのワンストップ相談機能の強化
・訪問看護資源を効率的に提供する仕組みづくり
・住民目線での普及啓発事業の展開

（３）地域住民への普及啓発（在宅医療等関係者を巻き込んだ Aging in Place のイメージ共有）

住民啓発 WG では、9/4 に坂井・あわらで以下の構成でイベントを実施した。両市とも 100 人程度の参加者があり、特にあわら市では市長が感想を述べたり、質疑応答も活発になされたりするなど非常に盛り上がり、アンケートでは 50 代の方が、先のことを心配して参加していた例も見られ、住民が高齢期を過ごすための準備として考えるきっかけにしてもらえた。市民が自主的に自分の自治会でもこのような集会を開催できるようにするためのツール（DVD 等）や担い手の発掘を継続的に実施中である。なお、実施した普及啓発イベントのポイントは以下内容である。

・民生委員が住民代表として、疑問点を口にするところから始める
・東大から高齢社会に関するクイズ（PPK、在宅死の割合、今後の地元の高齢化率等）
・医師から在宅における本人、家族の満足度の高い看取りの実態
・医師会から坂井在宅ケアネットによる在宅医療の利用の仕方
・地域包括支援センターから介護保険による、介護サービスの利用の仕方
・東大から在宅ケアの拠点の大切さ、高齢期の住まい方の選択肢、健康づくりとまちづくりの重要性

9 月 4 日に実施した在宅ケアを考える住民集会
写真と紹介新聞記事

（３）地域住民への意識調査

地域住民に対しては、これまでに以下の 2 段階で意識調査を行った。

①「在宅ケアを考える住民集会」アンケート

□調査目的：普及啓発イベントの構成において理解が進まない部分を確認すること

□調査対象：平成 23 年 9 月 4 日実施の在宅ケアを考える住民集会の参加者

□調査項目

・基本属性（性別、年齢、居住地域）

・シンポジウムに参加したきっかけ、在宅ケアに関して解消されなかった疑問等

□回収数：あわら市…調査対象 111 名　回答者数 88 名　回答率 79%

坂井市…調査対象 109 名　回答者数 71 名　回答率 65%

②長寿社会の健康と医療・住まいに関するアンケート

□調査目的：医療・介護・住まいに対する考え方を広く聞き、在宅医療を含めた在宅ケアの導入に向けた議論の題材とする。

□調査対象：県下全域（無作為抽出 2000 件）＋坂井・あわら地区（無作為抽出 1000 件）

□調査時期と方法：平成 24 年 3 月に実施。郵送によるアンケート配布、回収。

□調査項目

・基本属性（性別、年齢、世帯構成、住居形態、介護経験、等）

・在宅での医療や介護、終末期に対しての知識・経験・希望

・住まいや地域への居住継続含め希望や考え方　　等

□予定：平成 24 年度前半を目処に各種クロス集計を実施予定。

※医用・介護・特定健診データ分析、高齢者の QOL・生きがいと医療費の関連要因、及び移動・運転に関するプロジェクトは本冊子の研究報告の項を参照

1.6.3 平成２３年度高齢者・障害者・子育て世帯居住安定化推進事業評価委員会事務局業務

（1） 概要

高齢者・障害者・子育て世帯居住安定化推進事業（以下「推進事業」という。）は、国土交通省・厚生労働省共管の補助事業である。高齢者や要介護者等の増加、障害者の地域生活への移行に対するニーズや待機児童等の増加に対応し、高齢者、障害者及び子育て世帯（以下「高齢者等」という。）が安心して生活できる住まい、住環境の整備を支援することにより、その居住の安定確保を推進するとともに、地域の活性化等を図ることを目的としている。当機構は平成23年度の推進事業の事務局業務を、株式会社福祉開発研究所と共に行った。

推進事業は、先導性の高い事業を対象とする「一般部門」と特定課題に対応した事業を対象とする「特定部門」に分けて公募を行った。「一般部門」については、学識経験者から構成される高齢者・障害者・子育て世帯居住安定化推進事業評価委員会（以下「評価委員会」という。）による一件ごとの審査により評価を行った。「特定部門」については、補助対象となる要件について事務局で確認し、評価委員会に報告を行った。「一般部門」、「特定部門」ともに、評価委員会の結果を踏まえ、国土交通省が補助対象となる事業を選定した。

公募は平成23年度で2回行われた。

・第1回公募期間：平成23年5月10日（火）～平成23年6月10日（金）

・第2回公募期間：平成23年8月22日（月）～平成23年9月16日（金）

評価結果等については、推進事業のホームページにて公表しているので、参照にされたい。（ http://iog-model.jp/ ）

平成 23 年度高齢者・障害者・子育て世帯居住安定化推進事業評価委員会名簿 （敬称略）

委 員 長	高橋　紘士	国際医療福祉大学大学院 医療福祉学研究科　教授
評価委員	浅見　泰司	東京大学 空間情報科学研究センター　教授
評価委員	井上　由起子	国立保健医療科学院 医療・福祉サービス研究部　上席主任研究官
評価委員	大月　敏雄	東京大学大学院 工学系研究科建築学専攻　准教授
評価委員	大塚　晃	上智大学 総合人間科学部社会福祉学科　教授

評価委員	定行　まり子	日本女子大学 家政学部住居学科　教授
評価委員	中川　雅之	日本大学大学院 経済学研究科　教授
評価委員	三浦　研	大阪市立大学大学院 生活科学研究科　准教授
専門委員	辻　哲夫	東京大学 高齢社会総合研究機構　特任教授

（２） 平成２１年度高齢者居住安定化モデル事業・平成２２年度高齢者等居住安定化推進事業のフォローアップ調査

推進事業の前身となる平成21年度高齢者居住安定化モデル事業、平成22年度高齢者等居住安定化推進事業において選定された案件のうち、評価委員会により選定された案件（平成23年11月現在で竣工・入居開始済み）について、現地訪問によるフォローアップ調査を実施した。

①　多様な法人の協同で誰もが安心して生活できる地域づくりを支える多機能拠点「（仮称）生活クラブいなげ風の村」（社会福祉法人生活クラブ　／　千葉県千葉市稲毛区園生町）

千葉市稲毛区のＵＲ園生団地において、地域拠点を整備するにあたり、地域に必要なサービスを地域の方と一緒に考えるため、開設前から団地自治会をはじめ地域住民と共に「地域懇談会」などを開催し、地域を知ることから始めている。高齢者専用賃貸住宅の他、介護保険居宅サービス、障害福祉サービス、医療サービス、生協店舗、地域交流スペース等の事業を実施。また、その他、ボランティアコーディネート機能、福祉相談窓口、子どもの一時預かり機能等も備える。

②　サービス付きホテルとサテライト住戸による団地再生支援計画
（財団法人健康・生きがい開発財団　／　東京都多摩市聖ヶ丘）

東京都多摩市のニュータウン内において、会員制のサービス付きホテルと在宅サービス拠点（小規模多機能、グループホーム、居宅支援、訪問看護、地域交流プラザ）を一体整備するとともに、サテライト型の高齢者住宅を供給するものである。在宅サービス拠点では、地域ケアシステムの拠点づくりを目指し、地元多摩市で高齢者医療に長年取り組んできた医療法人財団天翁会と連携し、誰もが自分らしく生き、そして自分らしい完成期を送ることができるような支援を目指している。

③　見守り安心ネット公田町プロジェクト
（独立行政法人都市再生機構　／　神奈川県横浜市栄区公田町）

ＵＲ賃貸住宅で、居住者による NPO 法人を運営主体とする見守りシステムを本格的に構築するという実験的な試みである。システムの仕組みは、センサーを各住戸内に設置し、そこから得られた「安否情報」を無線によって「安心センター」に届ける。「安心センター」では担当者が、1 日 2 回程度（例えば午前 9 時と午後 5 時）管理サーバをチェックすることで異常を見つけ、異常の表示がある場合には連絡等を行い、人による見守りに引き継いでいる。

④　農菜園と地域密着型高齢者共同住宅
（八城商事株式会社　／　新潟市南区大通黄金）

高齢者共同住宅では、60歳以上の女性で一人暮らしに不安のある人から介護が必要な人まで利用できる。支援や介護が必要な場合、提携先の訪問介護すずらんのヘルパーよりサービスを受けることができるので、安心して暮らすことができる。建物は、木造平屋建てでバリアフリー、居室は10室全個室である。共有スペースの食堂は、入居者とスタッフの団らんのバリアフリーとなっている。敷地内の農菜園で収穫できた野菜や地場産コシヒカリ・果物をふんだんに使った食事を提供している。

⑤　高齢者・障がい者等の住まい方を支援する小地域福祉活動拠点整備事業
（社会福祉法人半田市社会福祉協議会　／　愛知県半田市）

古民家の改修等により地域拠点を整備し、地域住民の交流並びに高齢者・障がい者が住み慣れたまちで生活し続けることができるように必要な支援事業を実施。市内に3ヵ所の施設を開設し、障がい者の在宅生活支援を目的とした「宿泊訓練施設」の運営、障がいの有無や世代を問わない「多世代交流サロン」の運営、学童保育等の事業を行う「こどものいえ」の運営を行っている。

⑥　行動援護対象者向けケアホーム等のバリアフリー改修事業
（特定非営利法人ふわり　／　愛知県半田市）

NPOの障害者福祉団体が、知的障がい者、発達障がい者、精神障がい者に対して既存住宅のコンバージョンによるケアホーム等を開設し、障がい特性に沿った設計及び個別支援計画策定のためのアセスメントの有効性を検証しようとするものである。発達障がい者の居住環境整備をアセスメントから開始する取組が独創的で、個別支援計画への反映、人材養成、成果発信なども体系的に実施している。

⑦　密集市街地における「まちづくりエンアパートメント」
（社会福祉法人ヒューマンライツ福祉協会　／　大阪府大阪市西成区）

木造住宅密集市街地で、地域福祉団体等とのネットワークを活かしながら、老朽住宅に居住する高齢者の住み替え先として、「しごとづくり」「あそびづくり」「安心づくり」をコンセプトにした高齢者向け住宅、認知症高齢者グループホーム等を整備。高齢者をサービスの受け手と捉えるだけでなく、高齢者の潜在能力（エンパワーメント）を引き出す住まいづくりをコンセプトに、高齢者に新しい社会的役割を担ってもらえるような「居場所」（しごとと遊び）付きアパートメント事業を行う。

⑧　泉北ほっとけないネットワーク・新近隣住区
（ＮＰＯ法人すまいるセンター　／　大阪府堺市）

泉北ニュータウンの高齢化が進む住区において、府営住宅や徒歩圏内の戸建て住宅の空き住戸を活用したサポート付改修共同住宅、近隣センター内の空き店舗を活用した地域共用施設、さらに、24時間の見守りや緊急対応を行う24時間支援センターを整備。見守りが必要な住宅の独居高齢者・虚弱高齢者・障害者などに対して、安心居住サポート（見守り・緊急時対応等）と、食健康サポート（配食サービス・共同レストラン等）の2つのサポートも行い、地域活動団体・福祉機関・行政の連携体制で「泉北ほっとけないネットワーク」を構築し、高齢社会の「新近隣住区」を目指している。

⑨　穏やかに暮らせる家（スマイルライフ萩）
（社会福祉法人　萩原会　／　和歌山県橋本市）

地域に住む軽介護度、もしくは自立した高齢者を入居対象として、安心して穏やかに暮らせるような住環境を整えている。菜園を設けることで、農作業ができなくなった方も再び農作業を行えるなど、生きがいを持った暮らしができるようサービスを提供している。社会福祉法人では、特別養護老人ホーム・短期入所・通所介護・居宅介護支援事業所も運営しており、安心して穏やかに暮らせるよう全体でサポートしている。入居者の健康管理（往診及び急な病気の対応を含む）も行っている。

⑩　中心市街地での医療・学術・地域協働による高齢者に優しい街づくり（仮称）
新きらら尾道プロジェクト（株式会社誠和　／　広島県尾道市）

中心市街地における既存の高齢者向け優良賃貸住宅と同一敷地内に地域交流を重点においた適合高齢者専用賃貸住宅、介護付き有料老人ホームを整備し、医療と地域の連携した尾道方式地域包括ケアシステムに加え、県立広島大学保健福祉学部の学術支援の協働によって施設利用者だけでなく、地域に住んでおられる方々を含めて充実した医療・保健・福祉の総合化による高齢者に優しい街づくりに取り組んでいる。

⑪　セントラルビレッジを核にした真和志地区医療福祉循環構想
（セントラルビレッジセンターによる『あんしん』の仕組みづくり）
（医療法人 寿仁会　／　沖縄県那覇市）

那覇市において、高齢者賃貸住宅（130 戸、うちグループホーム 9 戸）、デイサービスセンター、地域交流センター、保育施設、診療所等を併設した複合型施設を整備。65 歳以上による会員の組織化を図り、シニアライフコーディネーターを配備してさまざまな相談に応じる。高齢者に対する居住安定化はもとより、関わる従業員の「あんしん」につながる就業環境も創出。

1.6.4　震災復興支援

（1） はじめに

2011 年 3 月 11 日に発生した東日本大震災をうけて、一日も早い被災地の回復と復興にむけ、当機構は各領域の専門家を結集して、被災地における支援及び復興に対して仮設まちづくり支援、震災復興支援プロジェクトを立ち上げてきた。震災以前から当機構が取り組んでいたのは、「住まい」と「在宅ケア」が一体となった、高齢者が安心して最期まで暮らし続けられるまちづくりである。特に震災復興においては、日本の将来を見据えつつ、地元住民の生活(コミュニティ）を最優先することが重要である。多くの被災地は高齢化率が全国平均を超えており、一部では既に高齢化率が 35%を超えていた。復興に際して重要なことは、経済面での復興はもとより、高齢者が孤立することなく、安心してコミュニティ内での役割をもち暮らし続ける試みを実現することである。機構ではこれまで Aging in Place をキーワードに掲げていたが、今回の津波にでは多くの Place が流されてしまった。被災地のすべての人が将来に向けて安心して過ごせる超高齢社会のコミュニティづくりを進めることが復興の第一歩と考える。当機構では、震災前に住まいとケアの一体的整備について研究を進めていた後藤、廣瀬、瀬沼特任研究員を中心に、日頃から連携している都市工学、建築学、看護学の教員・学生らと、震災対応のために、ケアタウン構想を提案し、この構想を土台にした上で、被災地の活力ある再建についての提言を行った。

（2） 仮設住宅の課題

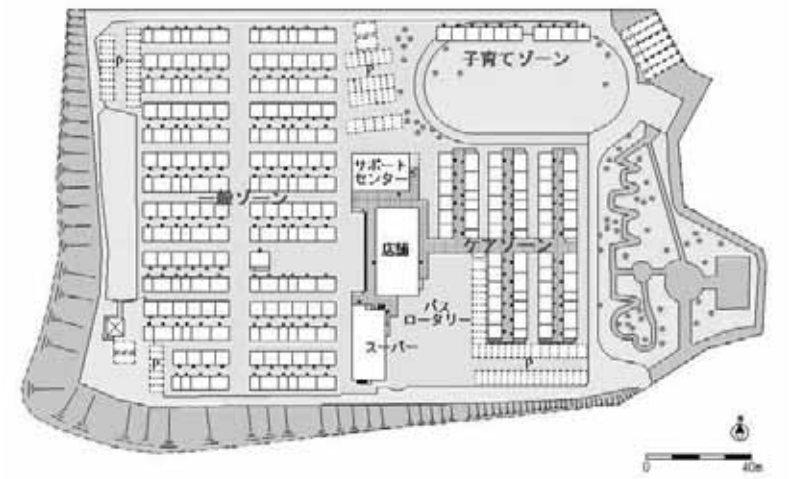
三陸地方のある避難所を訪れた際、避難されている高齢者の方が、「私たちは 2 度流される。1 度目は津波で、2 度目は復興の波だ。」とつぶやいた。震災直後の 5 月、仮設住宅建設のめどなども立ち始め、被災地にもようやく復興への希望が見えてきたときである。今回の津波被害の甚大さと、三陸地方特有の地形により仮設住宅の建設用地が少なく、小規模の用地に仮設住宅が転々と都市的生活基盤の薄い地域に建てられた。他方、避難所は定期的にボランティアの医師が訪問し、1 日 3 食の食事が提供され、自衛隊による銭湯の提供があるなど、プライバシーさえ我慢すれば、い（医療、介護などのケア）・しょく（食、職、生きがいづくりなどのコミュニティ活動）・じゅう（バリアフリーの住宅）が満たされた環境である。自家用車などを持たない単身高齢者、夫婦のみ高齢者世帯からすれば、仮設住宅への入居を切望しつつも、日常生活への不安が大きい状態であった。

（3） コミュニティケア型仮設住宅

ケアタウン構想の核となるのが、このような課題に応えるコミュニティケア型仮設住宅である。過去の震災の経験として、阪神淡路大震災ではコミュニティを維持することの重要が明らかになっていた。また中越地震では長岡福祉協会が自主的に行った、サポートセンターの設置による高齢者・障害者・子育て世代へ包括的ケアの提供といった、高齢者・

障害者・子育て世代が暮らしやすい仮設住宅の姿は考えられてきていた。2011 年 4 月の段階では、応急仮設住宅については、量とスピードが最優先されており、これまでの経験は全く活かされていなかった。当機構は過去の経験を踏まえ、被災地の仮設生活を改善すべくコミュニティケア型仮設住宅を開発した。これは緊急避難、応急措置として大至急住居を与えるのではなく、家を流され、家族や友人を失った被災者が閉じこもることなく、再び生きがいを見つけ、元の生活を取り戻せるような住まいとケアそして生活に必要な機能が一体的に整備された、少子高齢化社会に対応した仮設の「まち」である。

その特徴次の 5 点である。1 点目は仮設住宅地内にケアゾーンを設定することにより、独居高齢者や障害者などに集住してもらい、より支援が行き届きやすくした。2 点目はウッドデッキを設けバリアフリー化を図ると共に、玄関を向い合せにして路地をつくり天井に屋根をかけ路地を住民交流の場をつくった。3 点目は設計段階から関係機関と連携することにより、高齢者の生活を支援する拠点として厚生労働省が設置するサポートセンターや診療所、子育て支援拠点を併設した。4点目は被災した地元商店を再生した仮設店舗を併設、市内と仮設住宅を結ぶ路線バスの停留所を設け通院、通学の利便性を向上させ日常生活機能を充実させた。そして5点目はコミュニティの包摂力を向上させるために、住民自治組織の立ち上げ支援を行い、東京大学、地元自治体、自治会等の代表者が参画するまちづくり協議会を設置し、仮設住宅地で発生する様々な課題の話し合いなどのコミュニティ・マネジメントを実施した。



岩手県釜石市平田地区コミュニティケア型仮設住宅団地

（4） 建設までの経緯

4 月上旬から、鎌田機構長、辻教授、大月准教授、小泉准教授らとコンセプトを固めて提言をまとめてきた。提言の実現に向けた予算を取るべく社会技術研究開発センターの社会技術研究開発事業「研究開発成果実装支援プログラム」に応募をした。この際、実装のフィールドを確保する必要があり、東京大学海洋研究所（岩手県大槌町）との関係で被災地支援の拠点形成を行っていた遠野市を中心に、三陸沿岸地域に提言活動を行った。

仮設住宅の建設は「スピードと量」が第一命題であり、長期に暮らすことは全く念頭に置かれていなかった。国土交通省の担当者、厚生労働省の担当者などの話を聞いても、理念としては理解していただいたものの、実装については現地の判断に任せるとのことであった。そこで、震災以前からの在宅医療に関連して辻教授と交流のあった岩手県釜石市、小泉准教授と関係の深かった陸前高田市、村嶋教授が保健師活動として支援していた上閉伊郡大槌町、東大の拠点がある遠野市に対して、5 月 1 日～5 月 3 日に鎌田機構長、辻教授、小泉准教授、大月准教授と後藤研究員の 5 名で自治体を訪問しコミュニティケア型仮設住宅の提言を行った。

釜石市への訪問時に野田武則市長に会いコミュニティケア型仮設住宅地を提言した。市長から釜石市で最後に建設する平田総合運動公園（市内 6km ほど離れた土地）での建設を打診された。仮設住宅の建設の許可は、岩手県が出すため、岩手県保健福祉部、県土整備部を訪問し、担当部長、課長らと意見交換をし、地元の意向を尊重してコミュニティケア型仮設住宅の建設を認めていただいた。その後、遠野市でも遠野市長が即断して、後方支援型として岩手県遠野市穀町の遠野駅から徒歩 10 分といった街中の好立地に 40 戸建設することとなった。陸前高田市、大槌町では仮設住宅建設の目処は立ってしまい、新しい提案を受け入れるのは難しいとのことであった。

（５） 各自治体での展開

① 岩手県釜石市：市長によるトップダウンでの決断を受けて、仮設住宅の建設を行っていた都市計画課、中小企業庁の仮設店舗を建設予定の商工労政課、サポートセンターの適地を探していた高齢介護福祉課、バスを管理する市民課ら関係者が被災後初めて一堂に会し、意見交換を行った。各者とも独自に用地確保を検討しており、釜石平田で協力して取り組むことになった。この一連の取り組みをコーディネートしてくださったのが、釜石市医療特命部長の高橋昌克医師である。小泉准教授を中心にプロジェクトが進み、同年 8 月にサポートセンターが完成し、公募により株式会社ジャパンケアが運営を行うこととなった。ついで仮設住宅も完成し、続々と入居が開始された。釜石平田は釜石市でも一番最後の仮設住宅で入居者は、2 次募集に漏れた方たちであった。この間、行政、ジャパンケア、診療所、当機構が協議会の準備会を設置し、定期的な意見交換を行う。同年 11 月に第 5 仮設、第 6 仮設の自治会を立ち上げ、自治会を中心とした仮設まちづくり協議会を設置した。同年 12 月に商店街が完成し、ウッドデッキが全体につながり、釜石平田のコミュニティケア型仮設住宅が完成した。

② 岩手県遠野市：遠野市では 5 月の訪問直後からプロジェクトが動き出し、市役所職員のための駐車場を仮設住宅の建設用地とした。こちらも関係部署があつまり、大月准教授と遠野市に常駐した建築学科博士課程の冨安亮輔氏を中心にプロジェクトが進められた。現地の株式会社リンデンバウム遠野の絶大な協力を受けて、地場散財を活かし建設した。遠野市のまちなかの利便性の高いエリアにあり、遠野市では住宅とサポートセンターを設置し、そのほかの機能は街の機能を取り入れることとした。本仮設住宅では間取りを工夫することができた。同年 7 月に完成し、40 戸入居した。

③ 岩手県三陸地方全体：沿岸広域振興局の高橋浩進課長（現大槌町副町長）と連携をし、被災した三陸自治体に対する情報提供活動を、日本財団 ROAD プロジェクトの活動助成金を獲得し実施した。6 月に中越地震でサポートセンターを自力設置した長岡こぶし園の小山氏によるサポートセンターの運営方法に関する情報提供。7 月に小泉秀樹准教授による仮設コミュニティづくりの勉強会。8 月に大月准教授らによる仮設住宅を住みこなすコツの勉強会。12 月にコミュニティでの見守りの在り方について。翌年 2 月に流通科学大学・特任教授・金子幸雄氏、都岐沙羅（つきさら）パートナーズセンター・理事・事務局長・斉藤主税氏らによるコミュニティビジネス講座を行った。この活動を機に、三陸沿岸部で自治会の立ち上げや見守り体制の見直しなど少なからず、被災地への支援を行うことができた。

（６） 岩手県上閉伊郡大槌町での展開

① 大槌町の被災状況：このような取組のなか、大槌町は町長以下幹部職員を失い、被災状況も大きく仮設住宅の建設用地がないために休耕田などに小規模な仮設住宅が点在するように建てられ、事前にコミュニティケア型の仮設住宅を建設することができなかった。今回、大槌町では約 2000 戸強の仮設住宅が建設されている。しかし被災した従来の中心市街地から 4km 以内に設置された仮設住宅は、約半数の 1000 戸にとどまり、残りの約 1000 戸は、既存の中心市街地から 4km 以上離れた遠隔地に立地している。斜面地や農地などを造成して確保した小規模の仮設住宅地が市内に約 50 か所点在しており、コミュニティケア型仮設住宅のようなサポートセンターと住宅を一体的につくることが難しい状態であった。

② チーム形成：村嶋教授ら当機構とは別に、保健師活動として流されてしまった住民基本台帳を取り戻すべく大槌町住民の悉皆調査を行っていた。これを手伝った後藤研究員、小泉准教授らが大方教授と意見交換をし、大槌町の被災状況の大きさから、後付によるコミュニティケア型のまちづくりを検討した。まず大方教授を中心に、大月准教授、小泉准教授、村嶋教授らと仮設まちづくり支援チームを立ち上げた。活動費として RISTEX コミュニティで創る新しい高齢社会のデザインのファンドを獲得した。

③ 仮設コミュニティづくり；まず 7 月下旬、仮設住宅への入居が始まると同時に仮設コミュニティづくりの工程表というものを作成し、大槌町に提言した。現在約 50 ある仮設住宅地で自治会が立ち上がりつつある。住民ひとりの不満は行政への「苦情」でしかないが、自治組織としてまとめれば、それは立派な「提言」となる。そして月に一度、仮設住宅自治会の代表者が集まる代表者会議を行い、様々な課題について大槌町と代表者同士で意見交換をできるようにした。ここでは地区の課題だけでなく、地区が行う独自の工夫なども紹介される。このように、空間の基盤づくりのまえにコミュニティの基盤をつくることから始めることにした。

④ コミュニティ住環境点検活動：具体的な自治会活動の端緒として、コミュニティ住環境点検活動を、地元自治会と協働で実施した。仮設住宅の周辺について街歩きを行い日頃の不満や課題を住民どうして話し合う機会である。ハードだけではなく日々の生活についての不満も語り合った。この中で、仮設住宅全体に共通することで県や町にお願いすべきこと、ある仮設住宅特有の課題で早急に解決してほしいこと、住民同士の共助活動として解決すべきことという役割を整理した。前2者については仮設代表者会議や町への直接提言を行い、住民同士の活動については BBQ 大会や新年会での餅つきなど住民発意の企画として支援を行った。住民はこのリストをもとに、独自に NGO や NPO などの支援団体と連携するなど、自主的な環境改善活動を実施した。

（7） おわりに

2012 年 3 月 11 日、震災から 1 年が経過した。被災地の復興はまさにこれから始まるところである。今回の津波被害の大きさから、おそらく防潮堤等が完成し、安心した土地基盤の整備が済むまで 5 年程度の期間が必要となる。仮設住宅から災害公営住宅へと移り住むのも、平均して 4～5 年かかると予測できる。本年度は、仮設住宅での生活をいかに安心して暮らせるのかを絞り支援を行ってきた。復興は現在の仮設生活の延長線上にあり、環境移行をいかにスムース図に行うかが重要である。次年度以降は少しずつ復興に向けた取組を増やしていくが、土地区画整理事業などのハードの復興だけではなく、ソフトの復興とともに、住民一人一人の生活像が立体的に見えるまちづくりを考えていきたい。

1.6.5 東京大学ジェロントロジー 医療・介護＆予防プロジェクト －東大ジェロントロジー・コンソーシアム Healthcare Innovation Project（略称 HIP）

（1）プロジェクトの概要

東京大学ジェロントロジー・コンソーシアムでの2年間の研究成果を元に、東京大学と企業12社（以下4. に述べる）は、来るべき超高齢社会に向けた最先端の情報・知見・ネットワークの集積と実証を行うため、2011年7月から2年間の共同研究プロジェクト：東大ジェロントロジー・コンソーシアムHealthcare Innovation Project（HIP）を立ち上げた。

（2）HIPのVISION

共同研究を通じて、超高齢社会に向けてあるべき方向性を共有し、企業の新しい役割を見出しながら、新事業を生み出す共通基盤（Platform）の構築を目指す。共同研究活動だ

けに終わらず、新しい研究事業の企画と推進、及び新たな社会システム創造（＝まちづくり）に向けた応用展開を目指す。

（３）共同研究の内容

超高齢社会における高齢者QOLのマキシマム化と社会コスト増のミニマム化両立の観点から、「高齢になっても出来る限り元気で自立して、弱っても生活の場で自分らしく最後まで」(Aging in Place)の実現のために、医療、介護、予防の連携から生活モデルへのシフトを目指し、「予防」、「在宅ケア」と、それを支える「ICT / 機器開発」の三本柱で共同研究を行う。

（４）プロジェクトの組織と参加企業

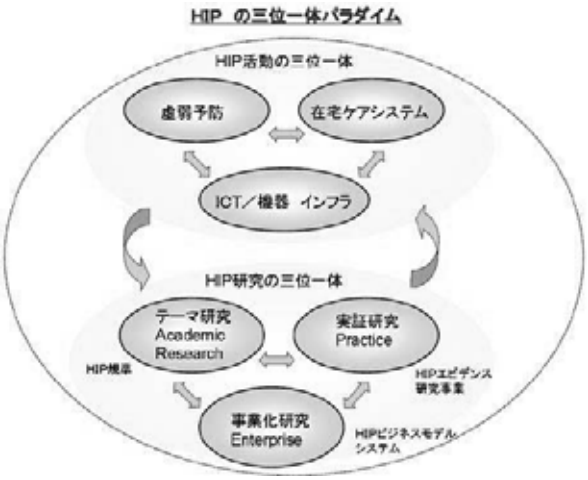
①HIP組織

１）プロジェクトリーダー　　辻 哲夫教授（東京大学　高齢社会総合研究機構）
２）プロジェクト事務局長　　辻 哲（ヘルスケアパートナーズ株式会社）
３）予防チームリーダー　　土屋 秀一（花王株式会社）
４）在宅ケアチームリーダー　　椎名 一博（三井不動産株式会社）
５）ICT / 機器チームリーダー　山田 隆（富士フィルム株式会社）

②HIP参加企業

１）予防チーム：花王株式会社、サンスター株式会社、イーエヌ大塚製薬株式会社、
株式会社ニチレイフーズ
２）在宅ケアチーム：　三井物産株式会社、ヘルスケアパートナーズ株式会社、
三井不動産株式会社、株式会社スギ薬局

３）ICT / 機器チーム：富士フィルム株式会社、GEヘルスケアジャパン株式会社、
株式会社カナミックネットワーク、日本アイ・ビー・エム株式会社
（参加各社は、各チームに属しながら、三位一体での研究活動を行う）



（５）2011年度HIPプロジェクトの活動

① HIPプロジェクトの設立と発足

2011年7月、東大ジェロントロジー・コンソーシアム Healthcare Innovation Project（HIP）を9社で設立し、その後3社が加わり、計12社体制下で、予防チーム、在宅ケアチーム、ICT / 機器チームの活動を開始した。

② 高齢社会に向けた課題の理解と先端的な知見、技術の習得と活用

高齢者研究において第一線の研究者、先進的な方法で介護事業を展開している事業者、並びに機器開発、ICネットワーク技術の分野での先端技術の研究者から、日本の高齢社会の有している課題や研究成果のご教示を仰ぎ、多くの重要で意義深い知見を学んだ。

１）予防チーム；

口腔衛生、誤嚥問題、咀嚼の重要性、公衆衛生学的なアプローチからの健理学、高齢者栄養とNST、胃ろう問題、整形

外科領域に於ける運動器障害（ロコモーティブシンドローム）の取り組み、高齢者の虚弱化と予防の重要性、健康経営による社員の健康管理等のテーマ研究

２）在宅ケアチーム；

多職種連携による在宅訪問ケアの実践と今後の課題、24時間在宅ケアシステム、被災地高齢者対策、地域サポートセンターを核にした新しい在宅ケアシステム等のテーマ研究

３）ICT / 機器チーム；

高齢者福祉機器の開発、医療（通信）ネットワーク、国民ID化とその課題、スマートウエルネスシティ等のテーマ研究

４）その他　高齢者研究学会、フォーラムへの参加と意見交換

医療経済研究機構、柏在宅医療研修シンポジウム、東大公共政策大学院ERESセミナー、健康生きがい開発財団学会、つくばウエルネスネスリサーチ10周年記念シンポジウム、2011 Aging Forum 等への参加と高齢者の健康、医療、介護問題への意見交換

③ 高齢者関係諸団体との意見交換

健康生きがい財団様、健寿の駅プロジェクト様、WHO（Age Friendly City）様、つくばウエルネスリサーチ株式会社様、HCCヘルスケアコミッティ様との意見交換会を通して、HIPとの連携の可能性も踏まえながら、高齢社会が抱える諸問題に協働して取り組む方向を検討した。

1.6.6　株式会社日立製作所デザイン本部との共同研究
「高齢者における経験価値の構造化研究」

高齢者の態度や行動等に関する意思決定は、長年培かわれた経験や価値観、現在の置かれた環境等、様々な要素が複雑に関連し合い、そのプロセスを構造的に把握することは非常に難しい。本研究ではそのプロセス解明を試みる目的で、高齢者の生活を取り巻く重要な課題である「ヘルスケア」をテーマに設定し、如何なる要素が高齢者の態度・行動を規定し経験価値に繋がるか、その構造をモデル化し可視化することを目指した。具体的にはデスクリサーチに基づく事前検討、フィールドリサーチによる仮説構築と検証、それらを分析することによりヘルスケアのあるべき未来提案をまとめた。

先行研究の概観やディスカッションから、まず虚弱化の一次予防としてのヘルスケア行動を研究の対象とし、基本的には自立した高齢者全般を対象に、若い人も含めた（若いときからの）長期的な予防対策として「ヘルスケア」をとらえることとした。また第二に、医療や筋トレ、サプリメント、等の直接的な健康行動に矮小化せず、生活構造全体を俯瞰し、生活環境および生活習慣として「虚弱化の一次予防」をとらえることとした。すなわち健康の維持増進の目的に特化した行動や意識のみならず、日常生活の中で自然と習慣化する行動や意識、楽しく快適に生活することが予防につながるようなヘルスケアのありかたを目指す必要があるとの認識にいたった。具体的に日常生活の中でのヘルスケアを追及する領域として、生活習慣としては「栄養」「体力（身体)」「社会との関わり」の３領域を設置し、それぞれ個人の行動と地域社会のありかた（＝まちづくり）の両者にわたって、本研究でいう「ヘルスケア」を調査することとした。

以上の視点から従来ある「ヘルスケア」関連のサービスや「健康長寿（を実現するため）のまちづくり」等の取り組みをレビュー、分析し、キーワードを取り出した。健康に関わる個人の行動の背景要因としては、健康に関心を持つきっかけ、行動を促すインセンティブ、行動の継続困難・離脱原因となる要因が検討された。また個人の行動および地域社会のありかたの両方に共通して、国民全体そして特に高齢者が持つ「自立」および「健康」についての価値観が果たす役割について検討した。

内部議論を踏まえて実施したフィールドリサーチでは、地域のまちづくりを通して地域住民（特に高齢者）の健康づくりに先駆的に取り組む富山市を視察し、キーパーソンへのヒアリング、事業や施設の見学、住民へのインタビューを実施した。

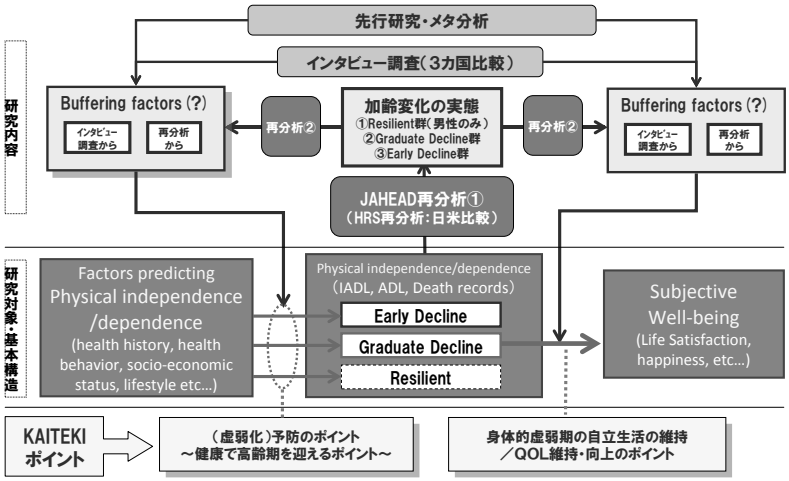
また、高齢者自身の「ヘルスケア」に関する意識と行動の把握を目的に、横浜市栄区及び青葉区にて高齢者 30 名を対象としたフォーカスグループインタビュー（計 4 回）を実施した。

最後に、これまでの内部議論と富山視察、高齢者インタビューを経て得られた知見・情報を踏まえて高齢者のヘルスケアニーズを掘り下げて検討するワークショップを開催した。

以上の研究内容は報告書（内部資料）としてまとめられた。

1.6.7　株式会社地球快適化 Institute との共同研究
「長寿社会における人生第４期の KAITEKI 生活研究」

高齢化課題先進国として世界の先頭を歩む日本であるにも関わらず、高齢者の加齢に伴う様々な生活・意識の変化の実態は不透明なままである。本研究プロジェクトは、高齢者の最大の関心事と言える「健康」面に焦点を当てながら、豊かな高齢期を迎えるための予防方策、及び身体的な自立度が低下の渦中にあっても高齢者のニーズを満たした生活を維持する方策を探るため、高齢期における個人の生活自立度および主観的 well-being の変化、およびその規定因を明らかにし、高齢期（特に人生第 4 期）における「快適(KAITEKI)」の構成要素を明らかにすることを目的とした。具体的には、①日本および米国で収集された高齢者の全国サンプルを対象としたパネル調査データの二次分析による、日常生活自立度の変化と主観的 well-being に関する研究、②高齢者の心身の健康や主観的 well-being に関する先行研究のレビュー、③日欧米 3 地域での 75 歳以上高齢者を対象としたインタビュー調査、を実施し、以上 3 つの結果をあわせて豊かな KAITEKI 生活実現の方策を追究した。なお、本研究を補完する位置づけで「快適な社会生活」の未来予測も行った。



研究フレームワーク

（１）　高齢者の日常生活自立度の加齢変化の実態：パネル調査二次分析より

身体、認知機能の低下は日常生活を自らの力で自立して送ることを困難にさせるが、自立度は生活の質を左右する大きな要因であることがこれまでも指摘されてきた。日常生活の自立度は総じて高齢ほど低下すると言えるが、そこには大きな個人差がある。そこで、日常生活の自立度が加齢によりどのように変化するのか、またその軌跡にはどのようなパ

ターンが存在し、何かパターンを規定しているのか。それらの課題を定量的に可視化して把握する試みとして、定量的な解析を行った。

用いたデータは、日本全国高齢者パネル調査（東京都健康長寿医療センター研究所（旧東京都老人総合研究所）、ミシガン大学、東京大学）および米国 Health and Retirement Study (HRS)である。それぞれのデータで ADL (Activity of Daily Living, 日常生活動作)、IADL(Instrumental Activity of Daily Living, 手段的日常生活動作)、死亡データを合成した「自立度変数」を作成し、調査対象者の 60 代前半から 80 代後半までの経年変化を分析した。

得られた結果はおおむね日米で共通しており、外出、移動に関する自立度から低下が始まり、ほぼ全ての人が自立している 60 代前半から、70 代半ばでは自立度の個人差が大きくなり、大多数が非自立または死亡になる 80 代後半に向けた推移が明らかとなった。潜在クラス分析の結果、日米および男女に共通して（さらに米国データでは白人、黒人ともに)、比較的早期に自立度が低下し死亡に至るパターンと、70 代半ばまで自立を維持し、その後自立度が低下していくパターンの 2 つが見出された。加えて日本人男性データにおいてのみ、80 代後半まで自立度を維持するパターンが見られた。早期に自立度が低下するパターンは脳卒中後遺症、心臓病などの疾患を有する人が多く、徐々に自立度が低下するパターンは高血圧、慢性の腰痛など慢性疾患を有する人が多かった。加えて生活習慣（運動習慣、喫煙習慣など）にも差がみられた。さらに日本データのみで自立度と主観的な評価（生活満足感、人生満足感）との関連およびその緩衝要因の分析を行い、自立度の低下が主観的評価の低下と連動する相関関係がみられた一方で、自立度の低下という事実以上に、そのことで「生きがいとしていた活動が制限される」ことが問題であり、主観的な生活満足度を大きく低下させる可能性が高いことが示唆された。

（２） 健康や寿命に関する先行研究のレビュー

健康や寿命に関する研究成果は国内外に膨大に蓄積されているわけであるが、国内外の本課題追究に関する論文等のリサーチを行った。生活習慣や生活環境と寿命及び生命予後との関係を示した社会医学的、疫学的な研究成果を中心にその知見を抽出すると、健康寿命の延伸に資する要因として「健康習慣」「社会や他者との関わり」「意欲や自律などの心理的な要因」にまとめることが出来た。規則正しい生活やバランスの良い食事、また適度な運動といったことは、健康の維持増進の基本認識と言えることであるが、「Ｉ」の分析から示唆されたように、高齢期の心身の健康維持は日々の活動や他者との関係、またそのことから生じる気持ちの持ち方（意識）といったことまで、健康や寿命に影響する要因であると考えられた。これは WHO-ICF が示した、個々人が有する個人・環境因子（生活習慣・環境等）と、心身機能と社会的な活動と参加の実態が相互に作用し合って健康がかたちづくられている、という定義に集約される。

（３）高齢者のヘルスケアニーズの探究：日欧米 3 地域でのインタビュー調査より

高齢期における自立度とその関連要因についてみてきたが、豊かな高齢期とは何か、どうすれば迎えることができるか、また身体的自立度低下の渦中にあっても高齢者のニーズを満たした生活を維持できるか、を探究するために、次の定性的な調査研究を行った。

日本（東京近郊）・デンマーク（コペンハーゲン近郊）・米国（ロサンゼルス近郊）の 3 地域で計 7 回、計 44 名の 75 歳以上高齢者を対象にフォーカスグループインタビューを行った。主な質問項目は、①健康で高齢期を迎えるための予防策、②理想の晩年生活及び「自立」に対する考え方、③自立生活を維持する方法、④日常生活の楽しみ、⑤日常生活の困りごとと将来不安、についてである。なお、デンマークと米国については、日本との比較という観点から、高福祉高負担、低福祉低負担の代表的な国として選択した。

いずれもインタビューに参加した方々は経済的に恵まれ、社会への関心が高い人々に偏った点は留意すべきであるが、共通してみられたのは①健康に対する高い関心　②自立した生活の「継続」が目標　③他人に迷惑をかけることへの躊躇が強く自立度を失うことへの大きな不安を抱えている　ということである。デンマークでのインタビューでみられたように、例え医療費・介護費の心配がない社会制度が確立していても、制度利用のための手続き等で誰かの助けを受けざるを得なく、その不安は変わらず存在していた。

以上の 3 つの研究から得られた知見を踏まえ、プロジェクトメンバにより高齢者のヘルスケアに関連したニーズの洗い出しを行った。ニーズは生活全般に渡り、自立した生活を継続していく中でいかに起こりうる喪失を防ぎ、また喪失を補い、または喪失に適応していくか、という連続した課題が洗い出された。それぞれのフェーズ、生活場面における細かいニーズに対応していくうえでは社会制度の改善、技術の開発、サービスや商品の開発が必要であり、超高齢・長寿社会において目指すべき「快適な社会」の実現に向けて、企業として、また社会として取り組むべき課題が確認された。

以上の研究成果は報告書（内部資料）としてまとめられた。

1.7　啓発・広報

1.7.1　産学連携による取り組みについての視察

（2011 年 6 月 15 日 : 出席者　内閣官房国家戦略室平野達男副大臣他 7 名、ジェロネット各代表、機構より鎌田実機構長ほか）

内閣官房国家戦略室より平野達男副大臣が来校し、ジェロネット各代表と機構より鎌田実機構長による産学連携による取り組みについての説明を、本学列品館大会議室にて行った。機構の取り組みやジェロネット AP8 グループの各代表からアクションプランの内容について説明。平野達男副大臣からは「大変意義のある取り組みで参考になった。」とのコメントを頂き、機構の柏での取り組みについても情報提供してほしいとの要望があった。

平野達男副大臣を囲み意見交換を行う

1.7.2　柏の葉キャンパスシティに関する共同記者会見で IOG の活動を紹介

（2011 年 7 月 12 日）

7 月 12 日、柏市・千葉県・東京大学・千葉大学・三井不動産の５者で、柏の葉キャンパスシティのまちづくりを通じて世界に社会的課題の解決モデルを提示していくとした共同記者会見が開催された。本学からは濱田純一総長が出席し、本学の取り組みの 1 つとして IOG の活動が選ばれ、柏に第２総合研究棟の完成、豊四季台等での取り組み、そしてジェロントロジーコンソーシアムでの取り組みについての説明がなされた。会場には 400 名近くの報道関係者が集まり、熱気に包まれた共同記者会見となった。

1.7.3　柏キャンパス第２総合研究棟のお披露目

（2011 年 8 月 1 日　柏キャンパス、第２総合研究棟）

本学第 2 総合研究棟に入居する 4 組織合同による学内向けの竣工見学会と懇親会が、8 月 1 日、柏キャンパス第 2 総合研究棟で開かれた。今回は柏キャンパス内の他部局等の関係者に、第 2 総合研究棟及びその入居組織の活動を知ってもらおうと企画されたもの。1 時間の見学会の後に懇親会が開かれた。機構の占有部である 1 階の医療機器や、2 階の模擬住居については多くの来場者の関心を集めた。

柏第 2 総合研究棟　事務室

２．研究現況

後期高齢者のＱＯＬに関する評価尺度開発に関する研究

秋山弘子、前田展弘、菅原育子（高齢社会総合研究機構）

個人のＱＯＬについては、1940 年代以降、医学、保健学、心理学、老年学等の諸分野で国内外に数多くの研究成果が蓄積されてきており、特定集団を対象としたＱＯＬ指標も数多く開発されてきた。一方で、我が国で急増しているいわゆる「後期高齢者」一般を対象としたＱＯＬに関する研究は僅少である。本研究ではこれまで QOL 概念および測定に関する文献研究及び後期高齢者本人やその家族、民生委員等を対象としたインタビュー調査をもとに概念整理を行い、9 項目からなる自己回答式の質問項目を作成した。在宅医療サービスを提供している民間企業の協力を得て、全国のサービス利用者を対象とした調査を実施し、1273 名の回答（要支援 1 または 2、要介護 1 または 2、要介護 3 以上、がそれぞれ約 3 割ずつ）を得た。既存の QOL 尺度や関連変数と新しく作成した 9 項目の相関関係の検討、要介護度別の解析等を実施し、新規作成した尺度の妥当性や利用可能性について検討を行った。また、同調査で収集した自由回答の分析から、要支援または要介護認定を受け自宅で生活をしている高齢者にとっての、生活上の喜びや困難と QOL についての更なる検討を行っている。

経年に伴う要介護度、認知症の重度化及び看取りに対する高齢者向け賃貸住宅における計画要件の整理
－ 高齢者等居住安定化推進事業における採択事例フォローアップ調査から －

廣瀬雄一、瀬沼智洋、後藤純（高齢社会総合研究機構）
大月敏雄（工学系研究科建築学専攻）

既に団塊世代が定年を迎え始めている日本のこれからの高齢化は 75 歳以上の後期高齢者の増加が特に著しく、併せて「要介護高齢者」も増加し、介護・医療ニーズが急増する中、自宅への継続居住、高齢者向け住宅への住み替え等も含め、住み慣れた地域で最期まで住み続けることの重要性が増している。

地域で住み続けるための選択肢の一つとしてサービス付き高齢者向け住宅（以後、サ付き）がある。これまでの調査研究から、高齢者居住安定化モデル事業における高専賃をとりあげることで、自立期から看取りまで時系列的に、空間、マネジメントの観点から計画要件を整理したが、認知症への対応や地域資源の活用に関しては十分に言及できておらず、今後の課題として残った。この部分を踏まえて、本研究においては Aging in Place を実践しうる要介護度、認知症の重度化対応策及び看取り対応策について知見を充実、整理することで、今後のサ付きに対する知見とされたい。

高齢者・障害者転倒予防用感覚刺激型立位・歩行支援システム開発

田中敏明（先端科学技術研究センター）、泉隆（東海大学）、敦賀健志（北海道工業大学）
三谷篤史（札幌市立大学）、和田親宗（九州工業大学）
武田秀勝（札幌医科大学）、伊福部達（先端科学技術研究センター）

高齢者の転倒による外傷・骨折は日常生活活動能力を著しく低下させることから保健・医療・福祉行政において大きな問題となっている。高齢者の転倒の原因として加齢に伴うバランス能力の低下が大きな因子となっている。高齢者のバランス能力低下は、筋力などの運動機能の衰えだけでなく、感覚機能の衰えによる姿勢制御への影響が指摘されている。しかしながら、現状では、運動と感覚の両機能からのバランストレーニングアプローチは確立しておらず、本件のごとく体性感覚刺激を利用したバランストレーニングおよび立位・歩行など動的条件下でのバランス支援機器の開発研究は皆無である。

そこで本研究は、立位バランスに重要な立位荷重時の高齢者の足趾・足底感覚を新型感覚検査機器で評価し、その評価に基づきバランス能力を改善するための最適な立位・歩行時の重心移動を足底へ振動感覚刺激で呈示する方法を確立し、加えて、転倒の危険を回避する注意喚起可能な感覚刺激内蔵型靴の開発研究を実施した。平成 22 年度は振動装置による足底感覚評価および動的バランス能力評価のための床振動装置の製作を実施した。平成 23 年度は試作機器を用いて若年者および高齢者を被験者として実験を実施した。

視覚認知障害のための移動支援用３次元視覚バリアフリー機器開発

田中敏明（先端科学技術研究センター）、泉隆（東海大学）
宮坂智哉（植草学園大学）、伊福部達（先端科学技術研究センター）

脳卒中などによる脳障害では、空間の認知が困難になる半側空間無視（Unilateral Spatial Neglect: USN）などの視空間障害が起こり、患者の日常生活活動（ADL）を著しく後退せしめる原因でもあり、早急に解決すべき重要課題である。半側空間無視とは視空間の認知障害の一つで麻痺側に十分な注意が払えなくなった無視状態である。この半側空間無視を改善する方法として、従来のリハビリテーションは患者の無視側へ注意を喚起する方法が行われていたが持続的効果は明らかではなく、重度であれば無視しているという認識を持たない状況であるため抜本的な解決には至らず、歩行可能な患者も監視が必要となり、車いす生活を余儀なくされていた。研究代表者は視空間認知障害を代償可能とする画像呈示方法を開発した。しかしながら、これは机上での静的な姿勢でのリハビリテーションへの評価訓練機器開発であった。本件では、歩行動作および車いす操作など、より動的条件での3 次元視覚情報バリアフリー機器開発のための基礎研究を行う。平成２２年度は車いす移動・歩行などでのHMD により注意喚起を促すため、車いす移動時に磁気センサ、

電気角度計、加速度計による車いすのタイヤ、座面などの移動およびヒトの重心移動、関節運動をセンシングしながら、HMD と同期して無視領域に注意を喚起する車いす用HMD 支援システムを構築した。平成23年度は試作機器を用いて若年者を被験者として多様な歩行を実施し本システムでの歩行分析に関し検証し臨床応用を検討した。

視覚認知障害支援を目的とした視覚情報バリアフリー機器開発

田中敏明（先端科学技術研究センター）、泉隆（東海大学）
伊福部達（先端科学技術研究センター）

脳卒中などによる脳障害では、高次脳機能障害を合併する場合があり、リハビリテーションの大きな阻害因子となる。このなかで半側空間無視（USN）など視空間の認知障害がある。これは、麻痺側に十分な注意が払えなくなった無視状態である。この半側空間無視を改善する方法として、従来のリハビリテーションでは、患者の無視側へ注意を喚起する方法等が行われていたが、抜本的な解決策はなく、歩行可能な患者も監視が必要となり、車いす生活を余儀なくされていた。本研究では脳卒中後遺症の一つである半側空間無視等の視覚認知障害を解決する福祉機器として、小型 CCD カメラ付きＨＭＤ（ヘッドマウンテッドディスプレイ）システム開発研究を実施している。成果としては、通常の空間無視検査に加え本機器を使用することにより、空間における障害をより正確に評価し、リハビリテーションを効率良く行える可能性が示唆された。また、支援機器として視覚障害の少ない片眼もしくは両眼視野領域に正常な視覚情報を与え、かつ、視覚障害部へ注意喚起を促す機能を有し、高齢者および視覚認知障害者の安全かつ安定した日常生活活動（ADL）の自立向上を支援する 3 次元ＨＭＤ機器開発を実施した。現在、高齢者および弱視者用の視覚情報拡大化呈示用 HMD の試作機器を開発中である。平成 23 年度は拡大 HMD を試作し弱視者にモニターを実施した。

高齢認知障害者のための複合感覚刺激を利用した日常生活支援注意喚起システム開発

田中敏明（先端科学技術研究センター）、泉隆（東海大学）
宮坂智哉（植草学園大学保健医療学部）、中島康博（北海道立工業試験場）

高次脳機能障害のうち、半側空間無視および認知症を有する患者・障害者の日常生活支援のための注意喚起システム開発を目的とする。脳血管障害合併症である半側空間無視および認知症患者の車いす操作に関する動作分析を行い、車いす操作時の操作ミスを患者データから把握した。そのなかで、認知障害のなかで日常生活、特に移動動作に重大な障害を来す半側空間無視および認知症に関して、各々の複合感覚刺激（視覚、体性感覚、聴覚）

を用いた注意喚起システムを移動支援機器、特に車いす操作支援用として開発する。平成21年度は半側空間無視者の車いす操作に関するＨＭＤ（ヘッドマウンテッドディスプレイ）による（視覚・体性感覚刺激）注意喚起システムを開発した。平成22年度以降は認知症患者への車いす操作に関する注意喚起システム（視覚・聴覚・体性感覚刺激）および臨床においてその効果を検討し最終型注意喚起システムを開発する。平成23年度は平成21，22年度で開発されたシステムに振動感覚刺激を加えたシステムを構築し、本統合システムの臨床においての効果を検討し、最終型注意喚起システムを開発製作し、本機器を用いて患者10数名に関して本システムの効果を検証した。

高齢者・障碍者の移動支援用小型軽量トランスファ・スツールの開発

田中敏明（先端科学技術研究センター）
中島康博（北海道立工業試験場）、株式会社プラウシップ

日本の介護労働需要は非常に高いが、その一方で現場の労働環境は劣悪であり、介護従事者の7割以上が腰痛を経験する程である。中でも移乗作業は特に負担が大きく、持ち上げ移乗によって介護従事者の大半が腰にダメージを受けるとされている。このような重作業が、介護従事者の年間離職率21%の一要因になっている。

これまで、移乗作業の負担軽減のため、トランスファボードや移乗リフトなどの移乗補助装置が製品化されてきたが、様々な普及努力にも関わらず現場の運用事例は少ない。その一因として、これらの機器が（現状の）日本の現場環境に適していないことが挙げられる。日本の病院や介護施設が保有する車いすはアームレストが外れない標準型が圧倒的多数を占めるが、先に挙げた移乗補助装置はアームレストが外れることを前提に開発されているため、運用できる場所は極めて限定されている。日本の現状では、標準型車いすでも適用可能な、安全で低コストな移乗補助装置のニーズが極めて高いと考えられる。

そこで本開発グループは、標準型車いすでの座位移乗を簡易に実現できる装置として、小型スツールとトランスファボードを組み合わせた「トランスファ・スツール」を開発し、介護現場の負担軽減を図り、同時に要介護者にとっても安心感のある座位移乗を実現する。本スツールは小型イスの上にトランスファボードが結合した構造の移乗補助装置で、ベッドー車いす間にセットすることで座位移乗を行え、従来標準型車いすでは困難であったトランスファボード移乗が実現可能となる。本開発によって、高齢者・障碍者のADL（日常生活活動）の自立および介護・介助者の負担軽減を目指す。平成23年度は長期的、継続的に患者および医療従事者に本機器の使用してもらいモニター調査を実施した。

東京大学先端科学技術研究センター・東大高齢社会総合研究機構共催
足・腰振動刺激付きバランス機器による高齢者転倒予防連続講座（４回）
―バランストレーニングで健やかな老後を―

平成23年12月より平成24年3月まで4回連続での高齢者転倒予防講座を高齢社会総合研究機構にて実施した。田中研究室スタッフは、田中特任教授、前田研究員、および4名の協力研究員であった。

4回連続講座参加総数69名であった。 講座内容は以下の通りである。特に研究室で開発した振動付きバランス検査訓練機器を用いて各高齢者のバランス能力および身体能力を評価した。

1回目は、高齢者の転倒やバランス能力に関する講義を実施した。その後、各参加者のバランス能力を評価するため、重心動揺計によるバランス評価、足底面に対する感覚検査、筋力測定、臨床バランス検査（Timed Up and Go Test およびFunctional Reach Test）、形態計測、関節可動域検査を実施した。これらの評価結果をもとに個人用トレーニングプログラムを作成した。2回目には、1回目に実施した評価結果を参加者個人に提示し、それぞれの現状を説明した。その後、個人用トレーニングプログラムを実演し、自宅にて週3回以上実践するよう指導した。3回目は、1か月間のトレーニングプログラム実施の効果を判定するため、1回目と同様の項目で再評価を行った。さらに、田中研究室監修のもと企業が開発した座位バランス訓練ツールを紹介し、実技指導を行った。4回目は、再評価結果を参加者に提示し、重点的にトレーニングすべき項目について説明した。さらに、上記内容をもとに再作成された個人用トレーニングプログラムを実演し、今後も継続してもらうように指導した。

高齢者や軽度認知症者を対象とした対話型コミュニケーションシステムの開発

二瓶美里、小竹元基（工学系研究科機械工学専攻）、鎌田実（高齢社会総合研究機構）
井上剛伸（国立障害者リハビリテーションセンター研究所）

独居高齢者や軽度認知症高齢者は増加傾向にあるため、介助者や家族のように必要なタイミングで必要な量の情報を支援することで自立生活維持をサポートするシステムが求められている。本研究では、軽度認知症者やもの忘れのある高齢者の特性に合わせて日時の把握、スケジュール管理、行動支援までの一連の活動を支援する情報支援パートナーシステムを開発することを目的とする。現在、人対人の対話による支援のコミュニケーション構造を基に、対話型インタラクションを用いた情報支援パートナーロボットのプロトタイプを開発し、認知症者や高齢者への介入評価実験を行っている。

認知症者を対象とした近時の成功経験の想起を促す電子日記帳の開発

二瓶美里（工学系研究科機械工学専攻）、鎌田実（高齢社会総合研究機構）
武澤友宏、石渡利奈、井上剛伸（国立障害者リハビリテーションセンター研究所）

特に認知症初期においては病気の自覚や受容が難しく、心理的なストレスとそれに伴う活動意欲低下がおこる可能性がある。本研究では、複数の日記の中から成功経験（自分で設定した目標を達成した経験や他者との絆を感じた経験）を記した日記を抽出・呈示する電子日記システムを開発し、「認知症発症後の自分にできること」へ注意を誘導し、活動への意欲を高める方策を提案する。従来の福祉工学は心身機能の補完等による活動支援を中心に発展してきており、活動意欲への働きかけは活動達成による二次的なものであった。心理的要因への働きかけは、高齢者の機器開発の重要な要素であると同時に、精神障害者など従来になかった支援の実現への応用が考えられる。

高齢者施設で生活する高齢者を対象とした自立支援機器に関する研究

二瓶美里（工学系研究科機械工学専攻）、鎌田実（高齢社会総合研究機構）
井上剛伸（国立障害者リハビリテーションセンター研究所）

施設入所者が誰の心配もかけずに自由に行動することが可能な移動支援機器や環境の提供は、高齢者が自尊心を保ちながら自立した生活をする上で重要である。本研究では、介護施設に入所する高齢者の自立移動に着目し、高齢者やその介護に関与する者に対する移動に関する意識調査、導入における阻害要因の分析、計測用電動車いすを用いた介入実験を行うことで、実生活に適応した移動支援機器の設計要件や利用環境への要件を明らかにすることを目的とする。将来的には、福祉機器開発の一つの手法として、本研究で実施する実生活における介入実験の方法論を提案することを目指す。

手動車いす自動ブレーキ装置の臨床評価と評価手法に関する研究

二瓶美里（工学系研究科機械工学専攻）
石渡利奈，井上剛伸（国立障害者リハビリテーションセンター研究所）
出口弦舞（国際医療福祉大学）

車いすのブレーキかけ忘れは、転倒やそれに伴う怪我、骨折などの原因となり、施設内で起こる事故の主要な原因といわれている。本研究では、車いす利用者の失念、認知機能

低下に伴う失認等によるブレーキかけ忘れを起因とした、車いす移乗時の転倒リスクを軽減・回避する装置の臨床評価を行うことで、装置の有効性を評価することを第一の目標とている。また、本研究では車いす自動ブレーキ装置をケーススタディとして、新しい機器の有効性を検証するための臨床場面における機器の評価手法の構築を目指す。

高齢者の安全安心な移動のためのパーソナルモビリティの安全戦略

小竹元基（工学系研究科）、鎌田実（高齢社会総合研究機構）

高齢者が安全にかつ安心して外出できる移動手段の開発を行っている。安全な移動の実現のため、運転支援や自律移動（自動運転）の安全戦略の構築を目指し、衝突リスクの定量化、危険回避のストラテジーの構築はもちろん，ユーザの受容性，危険感まで考慮した、安全戦略について検討を行っている。

高齢者の安全安心な外出支援のための
階段昇降可能なパーソナルモビリティの開発

小竹元基（工学系研究科）、鎌田実（高齢社会総合研究機構）、友國伸保（近畿大学）

高齢者の外出支援のため、階段が登れるパーソナルモビリティの開発を行っている。脚車輪とスライダを用いた機構と制御の検討を行い、乗り心地と走破性の向上を目指している。本年度は、その実現性について、シミュレーションでの確認を行うとともに実験機の設計を行っている。

高齢ドライバの不安全行動の抽出とその行動に基づく支援・教育に関する研究

小竹元基、二瓶美里（工学系研究科）、鎌田実（高齢社会総合研究機構）

高齢者の自動車による安全な外出を実現するため、運転時の不安全行動の抽出と各運転者がもつ心身・生活特性の関係から必要とされる運転能力を定義し、その運転能力の低下に伴いどのような対策を行えばよいかを検討している。体系的に整理するための評価法の構築、その評価法に基づく教育方法、支援方策に関して検討を行っている。

高齢者のハンドル形電動車いす使用時の問題に関する研究

小竹元基（工学系研究科）、鎌田実（高齢社会総合研究機構）

現在、高齢者の移動手段として電動車いすが普及しているが、事故の報告も数多い。本研究では、事故防止を目指して、常時記録形ドライブレコーダを用いて実環境における不安全行動の抽出を行うとともに、それを引き起こす高齢者の身体特性や運転能力に関して検討を行っている。

高齢運転者の能力低下による運転断念と代替交通手段に関する研究

鎌田実（高齢社会総合研究機構）、二瓶美里、小竹元基（工学系研究科）

高齢運転者の安全なモビリティ確保に向けて、高齢者講習のデータを収集し、またアンケートやインタビュー調査を行い、運転断念に関する諸々の検討をおこなっている。福井県福井市・坂井市の 6 地区および千葉県柏市の 10 地区を対象に実施している。

長寿社会における健康格差と地域環境についての実証研究　第 1 報
－ 地域力調査：地域環境要因の把握 －

斎藤民、涌井智子、甲斐一郎（医学系研究科公共健康医学専攻）

近年、地域の防災活動や子育て支援、高齢者の孤独死など、地域が抱えるさまざまな課題を解決するための新たな方策として地域の役割が期待されている。既に、地域住民同士のネットワーク、支え合いや問題解決能力が地域住民の健康に影響を及ぼすことは欧米で実証されており、サポートを必要とする高齢者や、在宅で介護を担う家族介護者の健康には、特に、地域の役割が重要と考えられる。そこで、本研究プロジェクトでは、地域環境要因と、高齢者および介護者の健康との関連を明らかにすることを目的として、福井県全域（17 市町）において、地域住民、高齢者、介護者を対象に自記式の質問紙調査を行った。

まず、地域住民を対象とした地域力調査では、福井県の 20 歳以上一般住民 11,447 名を対象に、住民同士のネットワーク、ソーシャルサポート、地域活動への参加、その他の住民間の支え合いに関する実態を測定する横断調査を実施した（回収率 43%）。

対象者の平均年齢は 57 歳、男性が 42%であった。年齢によって地域活動参加の度合いが異なること等が明らかになっている。今後は、第 2 報、第 3 報にて紹介する高齢者・介護者調査データと結合し、高齢者と介護者の健康に影響を与える地域環境要因を解明する予定である。

長寿社会における健康格差と地域環境についての実証研究　第 2 報
－ 高齢者の健康および在宅生活の継続と地域環境 －

斎藤民、涌井智子、甲斐一郎（医学系研究科公共健康医学専攻）

本研究では、高齢者の健康増進・介護予防や住み慣れた地域での生活継続を支援するうえで、地域住民間の支え合いや、サービスへのアクセシビリティ、および社会人口学的・社会経済的環境が果たす役割を定量的に把握することを目的とした。縦断的調査デザインに基づき、同じ対象者に 2 度の調査を実施した。初回調査は、2010 年 5～6 月、65 歳以上男女 5684 名への質問紙調査により実施した（有効回収率 62%）。第 2 回調査は、2012 年 2 月、初回調査の有効回答者のうち、死亡・施設入所ケースを除く 3387 名を対象に実施した。現在、データクリーニング等、分析準備中である。以上の調査を通じて、今後、生活機能、健康度自己評価、主観的幸福感など、追跡期間中の健康度の変化および在宅生活継続状況について把握するとともに、これらと地域力調査や公的統計などにより得られた地域環境指標との関連を分析する予定である。

長寿社会における健康格差と地域環境についての実証研究　第 3 報
－ 在宅介護の継続と地域環境 －

斎藤民、涌井智子、甲斐一郎（医学系研究科公共健康医学専攻）

今後、介護を要する高齢者数が増加することが見込まれており、誰がどのように介護を担うかということは我が国の課題である。女性の社会進出、少子化や晩婚化といった背景は「女性による在宅での介護」という従来の介護形態を変えつつあり、公的介護保険サービスに加えて、地域社会全体で介護を支える仕組みが重要であろう。そこで本研究では、地域ごとの介護継続状況の違いを把握し、介護継続状況と地域環境要因との関連を明らかにすることを目的とした。

無作為抽出された要介護高齢者の介護者を対象に、郵送による自記式の質問紙による縦断調査を実施した。初回調査時は、5639 名の要介護高齢者の家族宛てに、介護状況、介護保険サービスの利用状況、介護負担感および抑うつの程度を測定した。2011 年の 2 回目調査では、介護継続の状況、精神的健康度の変化を把握するため、第 1 回調査に回答した者で、要介護高齢者の施設入所や死亡などの理由で介護を継続していない者を除外した 1769 名に調査を実施した（回収率 75%）。現在は、地域環境と在宅介護継続との関連解明に努めており、本研究によって介護継続に寄与する地域の在り方について示唆を得ることが期待される。

有料老人ホームにおける看取りの実現に関連する要因と看取りが職員に与える心理的影響

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本研究では、有料老人ホームに焦点を当て、そこでの看取りの実態を把握した上で、看取りの実現に関連する要因を明らかにすること、さらに、看取りという多大な感情投入を伴う業務が職員に与える心理的影響についてもあわせて検討を行うことを目的として、ヒヤリング調査およびアンケート調査を実施した。結果、過去 1 年間に 7 割以上の施設において看取りが行なわれている実態や、看取りを支える体制が少しずつ整備されてきていることが明らかとなった。ただし、その体制は医療の充実を目指すものではなく、入居者の意思を基本に据えてそれを支えていく体制であると考えられる。また、看取りが有料老人ホーム職員に与える心理的影響としては、中長期的には業務に対する充実感といった正の影響を与えることができる可能性が示唆されたが、そのためには、個々の看取り体験に対して、それを承認する同僚や上司等の関わりが重要と考えられた。

患者等の意思決定を支援する看護師等の役割に関する研究

吉江悟（高齢社会総合研究機構）、水木麻衣子（医学系研究科医療安全管理学講座）

本研究では、患者やその家族が行う医療に関連した意思決定およびそのプロセスの質を高める支援を看護師等が行う上で必要な資質等について、その概念整理を行うことを目的として、既存資料の分析と看護師を対象としたインタビューを行った。結果、看護のみならず、ソーシャルワーク、認知心理学等の領域においても意思決定に関する記述が多く確認された。またインタビューを通じ、よい決定を構成する要素や意思決定を支援する上で重要と考える態度等が見出されつつある。例えば、意思決定を支援する上で重要と考える医療者の態度については、「中立的である」「患者の自律を尊重する」「患者に関心をもつ」等があげられ、チームに関連した態度としては「チームとしての一貫性を保つ」「他のスタッフを巻き込む」などがあげられた。また、EBM 等の考え方とも通じるところがあると考えられる「根拠に基づく対応」や「適切な情報提供」を行うことがよい決定のために重要という指摘がある一方、「合理的であっても納得していなければよい決定とは言えない」という発言もみられた。看護における意思決定支援機能の担い方については、その機能をその他の看護業務と分離して（専門的なコーディネーターとして）担う立場、分離せず（例えばプライマリナース等が）担う立場の双方がみられた。

３．研究報告

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ORIGINAL ARTICLE

Indications and practice for tube feeding in Japanese geriatricians: Implications of multidisciplinary team approach

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Aim: The aim of this study was to examine how geriatricians decide the indication of tube feeding in the elderly with eating difficulty as a result of several disorders, and to determine the factors associated with their decision making and interventions for dysphagia.

Methods: The design was a cross-sectional study. All board-certified geriatricians in the Japan Geriatrics Society were recruited to this study in September 2010. We sent questionnaires to 1469 geriatricians. Among them, 629 agreed to participate. The survey consisted of self-administered questionnaires regarding demographic information, indications of tube feeding and interventions for dysphagia before tube feeding.

Results: We analyzed the remaining 555 questionnaires after excluding incomplete ones. Over 90% of geriatricians answered that "neurological disorder" and "stroke" are indications, whereas 46.8% of them answered that "dementia" is an indication for tube feeding. Geriatricians who organize a multidisciplinary team conference tended to carry out more "interventions for dysphagia before the prescription of tube feeding" compared with the reference group (odds ratio 2.1–8.7) after multivariate adjustment.

Conclusions: The results show that approximately half of the geriatricians prescribe tube feeding when the patient has dementia with loss of appetite or apraxia for eating. There is no consensus among Japanese geriatricians about the indication of tube feeding for demented people. We suggest that guidelines for tube feeding in the elderly should be established. Furthermore, a multidisciplinary approach would be desirable for decision making for tube feeding. **Geriatr Gerontol Int 2012; ••: ••–••.**

Keywords: elderly, geriatrician, multidisciplinary team, percutaneous endoscopic gastrostomy, tube feeding.

Introduction

Many older patients have nutritional problems caused by eating difficulties as a result of stroke, cancer, dementia and other conditions. When the patients have a functional gastrointestinal tract and they cannot take sufficient nutrition orally, tube feeding is an option. Percutaneous endoscopic gastrostomy (PEG) is the preferential route when enteral nutrition is expected to last for a longer period of time, because it is associated with better nutritional status and a lower incidence of aspiration than nasogastric tube (NGT).[1] PEG was originally developed for pediatric use by Gauderer in 1980.[2] However, thereafter PEG has become the most common way to supply artificial enteral nutrition in the elderly, including dementia patients. The number of people on PEG is increasing because of the improved simplicity and safety. Approximately 5–30% of the advanced dementia patients in nursing homes are on tube feeding in Europe and the USA; whereas, in Japan, approximately 50% of those are on tube feeding.[3–6] Thus, the percentage of tube feeding including PEG for dementia patients is higher in Japan than that in Western countries. However, recent studies have questioned the appropriateness of tube feeding in these patients. The decision of the practice or the withholding of tube feeding in patients with dementia is a difficult challenge among geriatricians and many other health-care professionals, as they need to make a decision with clinical ethical dilemmas. Furthermore, the quality of life (QOL) in the elderly with tube feeding and its effect on long-term survival have not yet been clarified,[7–13] and neither has a guideline for tube feeding in the elderly, especially in dementia patients. Accordingly, tube feeding is the focus of some extremely complex legal and ethical questions. Therefore, it is important to study the current situation of tube feeding for the elderly in Japan.

When we make a decision on tube feeding, comprehensive assessment of the patient, such as nutrition, cognition and swallowing function, is important and the assessment should be based on a multidisciplinary team approach. Previous studies showed the effectiveness of inpatient geriatric evaluation and management; that is, comprehensive geriatric assessment (CGA).[14] A multidisciplinary approach might be required for medical and nursing care of elderly patients, especially when we need to make a complicated decision, such as that of tube feeding. However, it is unknown whether the team approach can affect the decision making for tube feeding and interventions for dysphagia.

Therefore, the aim of the present study was to examine how geriatricians decide on the indication of tube feeding in the elderly with eating difficulty as a result of various disorders, and to determine whether the team approach can affect their decision making and interventions for dysphagia.

Methods

The design was a cross-sectional study. All board-certified geriatricians in the Japan Geriatrics Society were recruited to the present study in September 2010. We separately sent self-administered questionnaires to 1469 geriatricians by post and collected them from October to December 2010. These geriatricians were chosen because of their experience in taking care of patients who require tube feeding, and carry out CGA by organizing multidisciplinary team conferences. The present study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (no. E984, 2010).

The questionnaires included demographic information, such as age, sex, place of employment, and clinical experience, reference guidelines for tube feeding, aims and indications of tube feeding in geriatrics, interventions for dysphagia before tube feeding, and multidisciplinary team approach if tube feeding is indicated. It was explained in the questionnaires that the term "elderly" was defined as people over the age of 75 years and those who require nursing care, and tube feeding included NGT, PEG and enterostomy tube.

We carried out descriptive analyses for each item in the questionnaire. The χ^2-test or t-test was used to compare the differences of place of employment and clinical experience. Logistic regression analyses were carried out to evaluate the differences of the frequencies and conference members according to the indication for tube feeding, and the interventions for dysphagia before tube feeding. Each item in the indication for tube feeding or interventions for swallowing disorder was adjusted for sex, working place and clinical experience of geriatricians. The frequency and number of members in a multidisciplinary conference were divided into five categories: not at all, occasional and less than five different health-care professionals, occasionally and ≧5 different health-care professionals, every time and less than five different health-care professionals, and every time and ≧5 different health-care professionals. The Statistical Package for Social Sciences version 18.0J (SPSS Japan, Tokyo, Japan) was used for statistical analysis. All probability values were two-tailed with a significant level of $P < 0.05$, and all confidence intervals were estimated at the 95% level.

Results

We sent a questionnaire to 1469 board-certified geriatricians, and 51 were returned as a result of being undeliverable because of wrong address. Among the rest, 629 agreed to participate in the present study. The response rate was 44.4%. After excluding the questionnaires with missing data, we analyzed the remaining 555 questionnaires. The prevalence of doctors aged over 60 years and male doctors was 34.6% and 89.2%, respectively. We found that 43.8% of the geriatricians had a clinical experience of more than 30 years, and 63.7% were working in acute hospitals, 30.7% in a clinic and 3.9% in long-term care facilities.

Table 1 shows the percentage of geriatricians who follow the guidelines and the purpose for tube feeding according to the geriatrician's place of employment and clinical experience. A total of 68% of geriatricians did not use any guideline for tube feeding. Among geriatricians following guidelines for tube feeding, 137 used "Guideline of Parenteral and Enteral Nutrition (EN) in

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Table 1 Use of guidelines and the aims of tube feeding according to place of employment and clinical experience

Questions	Characteristics of geriatricians							Total
	Place of employment				Clinical experience			
	Hospital $n = 360$	Clinic $n = 166$	Long-term care $n = 20$	Other† $n = 9$	P-value	<30 years $n = 317$	≧30 years $n = 238$	P-value	$n = 555$
Do you use any guidelines for TF in geriatrics?‡									
Guideline of Parenteral and EN in Japan*1	84 (23.3)	48 (28.9)	4 (20.0)	1 (11.1)	ND	87 (27.4)	50 (21.0)	0.082	137 (24.7)
Guideline of PEG in Japan*2	51 (14.2)	21 (12.7)	4 (20.0)	1 (11.1)	ND	41 (12.9)	36 (15.1)	0.460	77 (13.9)
Guideline of Parenteral and EN in America*3	13 (3.6)	11 (6.6)	0 (0.0)	0 (0.0)	ND	11 (3.5)	13 (5.5)	0.253	24 (4.3)
Guideline of Parenteral and EN for elderly in Europe*4	9 (2.5)	11 (6.6)	0 (0.0)	1 (1.1)	ND	9 (2.8)	12 (5.0)	0.178	21 (3.8)
Not using guideline for TF	253 (70.3)	106 (63.9)	10 (50.0)	7 (77.8)	ND	209 (65.9)	167 (70.2)	0.291	376 (67.7)
What are the aims of TF in geriatrics?§									
Improvement of survival	63 (17.5)	29 (17.5)	6 (30.0)	0 (0.0)	ND	54 (17.0)	44 (18.5)	ND	98 (17.7)
Improvement of general condition and prevention of complications	201 (55.8)	93 (56.0)	12 (60.0)	3 (33.3)	–	163 (51.4)	146 (61.3)	–	309 (55.7)
Improvement of activities of daily living	17 (4.7)	9 (5.4)	0 (0.0)	1 (11.1)	–	22 (6.9)	5 (2.1)	–	27 (4.9)
Improvement of quality of life	24 (6.7)	9 (5.4)	2 (10.0)	2 (22.2)	–	24 (7.6)	13 (5.5)	–	37 (6.7)
Satisfaction of patient	15 (4.2)	13 (7.8)	0 (0.0)	2 (22.2)	–	19 (6.0)	11 (4.6)	–	30 (5.4)
Burden of caregiver	5 (1.4)	9 (5.4)	0 (0.0)	0 (0.0)	–	6 (1.9)	8 (3.4)	–	14 (2.5)
Length of hospital stay	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	–	3 (0.9)	0 (0.0)	–	3 (0.5)
Living will	27 (7.5)	3 (1.8)	0 (0.0)	1 (11.1)	–	20 (6.3)	11 (4.6)	–	31 (5.6)
Other	5 (1.4)	1 (0.6)	0 (0.0)	0 (0.0)	–	6 (1.9)	0 (0.0)	–	6 (1.1)

Number (%). P-values were tested by χ^2-test. †Other included part-time doctors, retired doctors, researchers and so on. ‡Multiple answers were allowed. §Simple answer was allowed for nine items. *1 From Japanese Society for Parenteral and Enteral Nutrition *2 From Japan Gastroenterological Endoscopy Society *3 From American Society for Parenteral and Enteral Nutrition *4 From European Society for Gastroenterological Endoscopy Society. EN, enteral nutrition; ND, not determined; PEG, percutaneous endoscopic gastrostomy; TF, tube feeding.

Japan" from the Japanese Society for Parenteral and EN. For the purpose for tube feeding, more than half of the geriatricians chose "improvement of general condition or prevention of complications." However, a few geriatricians chose "improvement of QOL," "satisfaction of patient" or "living will." The working place or clinical experience did not affect the aims of tube feeding placement.

Table 2 shows the indication for tube feeding and the interventions for dysphagia before tube feeding according to place of employment and clinical experience. Among the seven target indications for tube feeding in the elderly, over 90% of the geriatricians answered that "neurological disorders other than dementia" and "stroke" are indications for tube feeding. Over 80% of the geriatricians answered that "head injury or facial trauma" and "oropharyngeal malignancy" are also an indication. In contrast, 46.8% of the geriatricians answered that "dementia" is an indication for tube feeding, and 65.9% of the geriatricians answered that "aspiration-prone frail elderly without comorbidities" is an indication. The place of employment was not associated with the judgment for the indication. The percentage of geriatricians who answered that "head injury or facial trauma" and "neurological disorders other than dementia" were an indication for tube feeding was significantly higher in those with less than 30 years of clinical experience than in those with more than 30 years of clinical experience" (head injury or facial trauma; $P = 0.012$, neurological disorder; $P = 0.049$). However, following guideline for tube feeding did not affect the decision making of tube feeding for these disorders (data not shown). We also asked about the life expectancy of the patient after PEG placement, and 79.5% answered that at least more than 12 weeks were expected.

Next, we asked how many interventions they carried out for swallowing disorder before tube feeding. The mean number of interventions was 6.22, and geriatricians with less than 30 years of experience carried out significantly more interventions than those with more than 30 years (6.49 ± 3.2 *vs* 5.86 ± 2.8, $P = 0.015$). The number of interventions was not significantly different between geriatricians working in an acute hospital and those working in a clinic. Among 15 items of interventions for swallowing disorder, over 70% of geriatricians answered that "thickening agent" and "using semi-solid and liquid foods" were afforded to patients with swallowing disorder.

Figure 1 shows the percentage of geriatricians organizing a multidisciplinary conference for tube feeding. A total of 63% of geriatricians discussed with other health-care professionals every time or occasionally. They also answered that physicians including themselves (95.4%), primary nurses (84.9%), dieticians (49.7%) and speech therapists (42.0%) were the members of the conference. The place of employment was not associated with the number of conference members (Table 3).

Table 4 shows the multiple logistic regression analysis for the frequencies and conference members according to the indication for tube feeding and interventions for dysphagia before tube feeding. More "interventions for dysphagia before introducing tube feeding" were carried out in geriatricians organizing a multidisciplinary team conference than the reference group after multivariate adjustment (odds ratio 2.1–8.7). We also found that geriatricians who always organize a conference with many types of health-care professionals (multidisciplinary) carried out more tests for the assessment of swallowing function and interventions for dysphagia before introducing tube feeding, such as oral ice massage, than the reference group. However, the indications for tube feeding were not affected by a multidisciplinary conference.

Discussion

In the present study, we found that approximately 70 % of board-certified geriatricians did not use any guidelines for tube feeding in their practice. We also noted that the use of guidelines was not associated with the decision making for tube feeding in the elderly, because "Guideline of Parenteral and EN in Japan" or "Guideline of PEG in Japan" does not describe the indications for tube feeding in elderly patients, especially in dementia patients.[15,16] Furthermore, more than half of the geriatricians consider that the purpose of tube feeding is to improve the general condition or to prevent complications in the elderly with eating problems. In contrast, only a few geriatricians selected living will or patient satisfaction. Decision making of geriatricians for tube feeding did not seem to be related to their working place or clinical experiences. Although the guideline describes that "respecting the wishes of the family or living will of the patient when nutrition therapy is needed for the elderly at the terminal stage or with dementia,"[15] most geriatricians who decide the indication of tube feeding might not have a chance to care for patients' living will. Although there is an ideal description in the guideline, it might be difficult for doctors to obtain a patient's living will beforehand, even if they understand the importance of respecting the living will of the patient. Therefore, comprehensive approaches not only from the field of nutrition and gastroenterology, but also from the experience and know-how from the professionals involved in medicine, nursing and care for the elderly, such as geriatricians, nurses, speech therapists, caregivers and care managers, would be expected to make a new guideline for tube feeding in the elderly.

Several studies have shown that there is no survival benefit in dementia patients who receive artificial

Table 2 Indications for tube feeding and interventions for dysphagia before introducing tube feeding according to place of employment and clinical experiences

Questions	Characteristics of geriatricians: Place of employment: Hospital $n = 360$	Clinic $n = 166$	Long-term care $n = 20$	Other† $n = 9$	*P*-value	Clinical experience: <30 years $n = 317$	≧30 years $n = 238$	*P*-value	Total $n = 555$
Is the following disorder an indication for TF?‡									
Head injury or facial trauma	313 (86.9)	144 (86.7)	8 (40.0)	7 (77.8)	ND	208 (88.3)	192 (80.7)	0.012	472 (85.0)
Oropharyngeal malignancy	286 (79.4)	143 (86.1)	13 (65.0)	7 (77.8)	ND	258 (81.4)	191 (80.3)	0.736	449 (80.9)
Neurological disorder	328 (91.1)	155 (93.4)	15 (75.0)	7 (77.8)	ND	295 (93.1)	210 (88.2)	0.049	505 (91.0)
Stroke	334 (92.8)	147 (88.6)	18 (90.0)	8 (88.9)	ND	290 (91.5)	217 (91.2)	0.899	507 (91.4)
Dementia	177 (49.2)	66 (39.8)	13 (65.0)	4 (44.4)	ND	1156 (49.2)	104 (43.7)	0.198	260 (46.8)
Aspiration-prone frail elderly without comorbidity	238 (66.1)	108 (65.1)	15 (75.0)	5 (55.6)	ND	216 (68.1)	150 (63.0)	0.208	366 (65.9)
Malnutrition in frail elderly without comorbidity	115 (31.9)	58 (34.9)	9 (45.0)	5 (55.6)	ND	115 (36.3)	72 (30.3)	0.137	187 (33.7)
How long does a patient need to survive after PEG placement?§									
2 weeks	3 (0.8)	2 (1.2)	0 (0.0)	0 (0.0)	ND	3 (0.9)	2 (0.8)	ND	5 (0.9)
4 weeks	19 (5.3)	16 (9.6)	1 (5.0)	2 (22.2)	–	18 (5.7)	20 (8.4)	–	38 (6.8)
6 weeks	4 (1.1)	2 (1.2)	1 (5.0)	1 (11.1)	–	7 (2.2)	1 (0.4)	–	8 (1.4)
8 weeks	39 (10.8)	21 (12.7)	3 (15.0)	0 (0.0)	–	37 (11.7)	26 (10.9)	–	63 (11.4)
12 weeks	295 (81.9)	125 (75.3)	15 (75.0)	6 (66.7)	–	252 (79.5)	189 (79.4)	–	441 (79.5)
Interventions for swallowing disorder before introducing TF									
No. Intervention; mean ± standard deviation (total 15 items)	6.44 ± 3.12¶	5.83 ± 2.93	6.70 ± 2.00	3.67 ± 3.32*		6.49 ± 3.20	5.84 ± 2.82	0.015	6.22 ± 3.06
No. interventions, ≧6 items¶	211 (58.6)	84 (50.6)	14 (70.0)	2 (22.2)	ND	188 (59.3)	123 (51.7)	0.073	311 (56.0)
Consultation									
To otolaryngologist	131 (36.4)	60 (36.1)	3 (15.0)	4 (44.4)	ND	123 (38.8)	75 (31.5)	0.076	198 (35.7)
To speech therapist	166 (46.1)	31 (16.7)	7 (35.0)	1 (11.1)	ND	131 (41.3)	74 (31.1)	0.013	205 (36.9)
To certified nurse of dysphagia nursing	77 (21.4)	25 (15.1)	4 (20.0)	2 (22.2)	ND	67 (21.1)	41 (17.2)	0.250	108 (19.5)
Test									
Repetitive saliva swallowing test	111 (30.8)	63 (38.0)	4 (20.0)	2 (22.2)	ND	109 (34.4)	71 (29.8)	0.257	180 (32.4)
Water swallowing test	243 (67.5)	104 (62.7)	13 (65.0)	5 (55.6)	ND	210 (66.2)	155 (65.1)	0.783	365 (65.8)
Video endoscopy	55 (15.3)	26 (15.7)	1 (5.0)	0 (0.0)	ND	50 (15.8)	32 (13.4)	0.444	82 (14.8)
Video fluorography	163 (45.3)	47 (28.3)	4 (20.0)	2 (22.2)	ND	140 (64.8)	76 (31.9)	0.003	216 (61.1)
Practice and education									
Oral ice-massage	102 (28.3)	23 (13.9)	5 (25.0)	0 (0.0)	ND	86 (27.1)	44 (18.5)	0.017	130 (23.4)
Swallowing exercise	72 (20.0)	40 (24.1)	5 (25.0)	0 (0.0)	ND	70 (22.1)	47 (19.7)	0.505	117 (21.1)
Vocalization exercise	50 (13.9)	20 (12.0)	1 (5.0)	0 (0.0)	ND	44 (13.9)	27 (11.3)	0.376	71 (12.8)
Using semi-solid and liquid foods	267 (74.2)	120 (72.3)	18 (90.0)	3 (33.3)	ND	236 (74.4)	172 (72.3)	0.565	408 (73.5)
Thickening agent	308 (85.6)	131 (78.9)	20 (100.0)	3 (33.3)	ND	267 (84.2)	195 (81.9)	0.474	462 (83.2)
Positioning	235 (65.3)	106 (63.9)	17 (85.0)	4 (44.4)	ND	215 (67.8)	147 (61.8)	0.138	362 (65.2)
Appropriate approach for swallowing	161 (44.7)	80 (48.2)	12 (60.0)	2 (22.2)	ND	153 (48.3)	102 (42.9)	0.206	255 (45.9)
Ways of coping with aspiration	161 (44.7)	85 (51.2)	17 (85.0)	4 (44.4)	ND	142 (44.8)	125 (52.5)	0.071	267 (48.1)

Number (%). *P*-values were tested by χ^2-test and Student's *t*-test. †Other included part-time doctors, retired doctors, researchers and so on. ‡Single answer was allowed for five items, and the other questions were allowed to select more than one. §*P*-values were tested by ANOVA. ¶$P < 0.05$ by Bonferroni. ¶Number of intervention items were divided into two groups, which used median value (≧6 ≧6 <6). ND, not determined; PEG, percutaneous endoscopic gastrostomy; TF; tube feeding.

feeding by PEG.[7,8,10,12] In addition, "Guideline of parenteral and EN for elderly in Europe" does not recommend enteral nutrition to persons with severe dementia as a result of more risks than benefits for persons with severe dementia, and occasionally in early and moderate dementia to ensure energy and nutrient supply and to prevent undernutrition.[17,18] In the present study, we found that approximately 45% of the geriatricians considered that dementia patients with loss of appetite or apraxia for eating should be on tube feeding and that 65% of the geriatricians considered that aspiration-prone frail elderly without comorbidities should also be on tube feeding, which is a relatively high percentage. In a previous study, approximately 60% of physicians in the USA answered that aspiration pneumonia was the indication for PEG placement, and was the most common medical indication.[19] The present finding are consistent with other results; therefore the medical situation in Japan might be quite similar to that in the USA. Indeed, PEG placement to the elderly with repeating aspiration pneumonia or not eating voluntarily with cerebrovascular disease or dementia is indicated in "Guideline of PEG in Japan."[7,8] In the present study, the questions did not specify the stage of disorders or the level of conditions; therefore our results should be interpreted with caution. However, it is certain that there is no consensus among Japanese geriatricians about tube feeding for the elderly with advanced dementia and there is an urgent need to develop guidelines to decide the risk/benefit ratio in the individual patient to optimize the timing and route of nutritional support. Thus, the indication for tube feeding in the elderly should be widely discussed in the future and hence a guideline should be established to describe the indication of tube feeding in more detail.

"Guideline of parenteral and EN for elderly in Europe" indicates PEG placement if EN is anticipated for longer than 4 weeks.[17,18] In contrast, the present study showed that approximately 80% of the geriatricians consider that survival more than 12 weeks should be expected for PEG placement. PEG is better than NGT for swallowing rehabilitation, and PEG placement

Figure 1 Do you organize a multidisciplinary conference before introducing tube feeding?

Table 3 Conference members for decision making of tube feeding according to place of employment

	Place of employment of geriatricians: Hospital $n = 249$	Clinic $n = 80$	Long-term care $n = 17$	Other† $n = 3$	*P*-value	Total $n = 350$
No. conference members; mean ± standard deviation (total 12 occupations)	4.4 ± 2.0	4.2 ± 1.8	4.3 ± 1.5	4.8 ± 4.2	0.864	4.31 ± 1.9
Conference members						
Attending physician	238 (95.2)	75 (92.6)	17 (100)	3 (100)	–	334 (95.4)
Primary nurse	224 (89.6)	54 (66.7)	15 (88)	3 (100)	–	297 (94.9)
Otolaryngologist	27 (10.8)	10 (12.3)	0 (0)	0 (0.0)	–	37 (10.6)
Certified nurse of dysphagia nursing	42 (16.8)	18 (22.2)	3 (18)	0 (0.0)	–	63 (18.0)
Physical therapist	55 (22.0)	12 (14.8)	4 (24)	1 (33.3)	–	72 (20.6)
Occupational therapist	37 (14.8)	8 (9.9)	4 (24)	1 (33.3)	–	50 (14.3)
Speech therapist	118 (47.2)	23 (28.4)	5 (29)	1 (33.3)	–	147 (42.0)
Dietician	126 (50.4)	37 (45.7)	9 (53)	2 (66.7)	–	174 (49.7)
Pharmacist	37 (14.8)	12 (14.8)	1 (5.9)	1 (33.3)	–	51 (14.6)
Discharge planning coordinator‡	26 (10.4)	14 (17.3)	2 (12)	1 (33.3)	–	43 (12.3)
Medical social worker	89 (35.6)	24 (29.6)	4 (24)	2 (66.7)	–	119 (34.0)
Care manager	46 (18.4)	39 (48.1)	5 (29)	1 (33.3)	–	91 (26.0)

Number (%), *P*-values were tested by ANOVA. *$P < 0.05$ by Bonferroni. Of the 555 geriatricians, 350 (63.1%) carried out a conference at least once. Respectively, hospital: 249 (69.2%), clinic: 80 (48.2%), long-term care: 17 (85.0%), other: 3 (33.3%). †Multiple answers were allowed. ‡Other included part-time doctors, retired doctors, researchers and so on. ‡They are a registered nurse and work for discharge planning and coordination in the hospital.

Table 4 Multivariate-adjusted odds ratios and 95% confidence intervals for frequency and the conference members according to the indication for tube feeding and interventions for dysphagia before using tube feeding

	Conference				
	Non	Occasional		Every time	
		Participating occupation		Participating occupation	
		Few	Multidisciplinary	Few	Multidisciplinary
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Is the following disorder an indication for TF?					
Head injury or facial trauma	Ref	1.02 (0.55–1.89)	1.15 (0.52–2.57)	0.80 (0.36–1.78)	1.52 (0.62–3.77)
Oropharyngeal malignancy	Ref	0.96 (0.56–1.66)	0.78 (0.41–1.52)	1.05 (0.48–2.31)	1.02 (0.48–2.16)
Neurological disorder	Ref	0.72 (0.34–1.52)	0.56 (0.23–1.34)	1.69 (0.46–6.16)	1.17 (0.39–3.53)
Stroke	Ref	1.41 (0.68–2.90)	1.84 (0.66–5.13)	2.35 (0.68–8.15)	4.03 (0.90–18.05)
Dementia	Ref	0.83 (0.54–1.28)	0.82 (0.48–1.42)	1.86 (1.00–3.44)	1.01 (0.56–1.83)
Aspiration-prone frail elderly without comorbidity	Ref	0.99 (0.63–1.55)	1.23 (0.69–2.19)	1.31 (0.68–2.52)	0.80 (0.44–1.46)
Malnutrition in frail elderly without comorbidity	Ref	0.77 (0.49–1.22)	0.98 (0.56–1.74)	1.30 (0.70–2.42)	1.18 (0.64–2.18)
How long does a patient need to survive after PEG placement? ≧12 weeks[†]	Ref	0.85 (0.50–1.43)	0.89 (0.46–1.74)	0.80 (0.39–1.63)	1.44 (0.64–3.21)
Intervention for swallowing disorder before using TF					
No. intervention items, ≧ 6 items[‡]	Ref	2.07 (1.33–3.20)	3.24 (1.81–5.78)	2.60 (1.39–4.85)	8.71 (3.99–19.00)
Consultation					
To otolaryngologist	Ref	1.13 (0.72–1.77)	1.36 (0.78–2.38)	0.94 (0.49–1.80)	1.48 (0.80–2.72)
To speech therapist	Ref	1.51 (0.93–2.46)	4.57 (2.52–8.29)	2.47 (1.28–4.76)	3.82 (2.01–7.27)
To certified nurse of dysphagia nursing	Ref	1.18 (0.65–2.14)	2.16 (1.11–4.23)	1.65 (0.76–3.61)	4.75 (2.43–9.32)
Test					
Repetitive saliva swallowing test	Ref	1.62 (0.98–2.66)	3.89 (2.16–6.99)	3.91 (2.05–7.44)	4.48 (2.37–8.46)
Water swallowing test	Ref	2.08 (1.32–3.28)	1.63 (0.93–2.87)	1.82 (0.96–3.44)	2.95 (1.49–5.88)
Video endoscopy	Ref	1.53 (0.83–2.82)	1.30 (0.59–2.86)	0.97 (0.37–2.53)	2.89 (1.37–6.09)
Video fluorography	Ref	1.62 (1.03–2.56)	2.08 (1.19–3.66)	3.07 (1.64–5.76)	2.28 (1.23–4.22)
Practice and education					
Oral ice-massage	Ref	1.19 (0.67–2.10)	2.19 (1.16–4.14)	2.34 (1.14–4.79)	3.59 (1.82–7.06)
Swallowing exercise	Ref	1.81 (0.97–3.39)	3.47 (1.74–6.91)	4.86 (2.34–10.09)	6.63 (3.27–13.45)
Vocalization exercise	Ref	1.55 (0.71–3.41)	2.96 (1.28–6.83)	2.70 (1.04–7.00)	6.84 (3.02–15.50)
Using semi-solid and liquid foods	Ref	1.83 (1.13–2.96)	2.12 (1.11–4.06)	1.71 (0.86–3.38)	5.96 (2.24–15.84)
Thickening agent	Ref	1.26 (0.73–2.21)	1.93 (0.85–4.39)	1.18 (0.54–2.59)	4.68 (1.36–16.12)
Positioning	Ref	1.46 (0.94–2.26)	2.36 (1.29–4.31)	1.75 (0.93–3.30)	7.22 (2.94–17.71)
Appropriate approach for swallowing	Ref	2.48 (1.59–3.88)	2.82 (1.62–4.92)	2.13 (1.15–3.95)	5.60 (2.94–10.65)
Ways to coping when the aspiration	Ref	1.48 (0.95–2.29)	2.86 (1.63–5.01)	1.24 (0.67–2.29)	5.31 (2.69–10.48)

Dependent variables: the indication for tube feeding and interventions for dysphagia before introducing tube feeding. Independent variables: frequency and the conference members (ref, non conference; 1, occasional and less than five different health-care professionals; 2, occasional and ≧5 different health care professionals; 3, every time and less than five different health-care professionals; 4, every time and ≧5 different health-care professional. Adjusted for sex, place of employment and clinical experience. [†]The period expected to survive after PEG was divided into two groups. (1: ≧12 weeks, 0: <12 weeks). [‡]Number of intervention items were divided into two groups, which was used median value into 15 items. (1: ≧6 items, 0: <6 items). CI, confidence interval; OR, odds ratio; TF, Tube Feeding.

in patients with stroke and oropharynegeal malignancy was associated with better prognosis; therefore PEG placement is recommended for these disorders by the European guideline.[20] We did not investigate how long PEG is placed in each condition. Thus, knowledge of geriatricians for tube feeding or PEG placement was not sufficiently explored in the present study; however, a period of PEG placement should be considered in each condition.

In Japan, requests for PEG to facilitate care are prevalent, because the staff in nursing homes tend to prefer PEG to time-consuming oral feeding. A multicenter study in the USA showed that feeding tube insertion is independently associated with both clinical characteristics of residents and fiscal, organizational and demographic features of nursing homes.[4] Therefore, these situations might have affected the decision making of geriatricians for tube feeding. Unfortunately, we did not include the question whether or not the request from nursing homes might have affected the decision making for tube feeding in dementia patients. Therefore, we should ask this question next time.

Regarding interventions for swallowing disorder, the mean number of interventions for swallowing disorder before introducing tube feeding was six items, which are not so many. Among the 15 items of interventions before introducing tube feeding, over 70% of the geriatricians answered that "Thickening agent" and "Using semi-solid and liquid foods" were afforded to patients with swallowing disorder. In contrast, consultation with other specialists was not frequently carried out, and care to improve swallowing dysfunction, such as "oral ice-massage," "swallowing exercise" and "vocalization exercise" was not usually carried out either. Therefore, from these data, we think that more interventions would be necessary to care for patients with dysphagia by consulting specialists and multidisciplinary approach.

It is interesting to note the relationship between multidisciplinary conference and knowledge and practice for tube feeding for the elderly. In the present study, we showed that those who have a multidisciplinary team conference for a patient indicated for tube feeding tended to carry out more "interventions for dysphagia before tube feeding" compared with the reference group after multivariate adjustment. Furthermore, the data showed that geriatricians who organize a conference with different health-care professionals carried out more interventions for dysphagia before tube feeding, irrespective of the frequencies of conference. The present study also showed that although there were no differences in the number of conference members and interventions between the geriatricians working in an acute hospital and those in a clinic before introducing tube feeding, the percentage of geriatricians who organized a multidisciplinary conference before introducing tube feeding was higher in the hospital than in the clinic. Therefore, the characteristics of facilities, not doctors themselves, might have affected this outcome. A previous study reported that multidisciplinary CGA is effective for the care of frail older persons admitted to the hospital, because evaluation and management by a multidisciplinary team during hospitalization documented a lower rate of institutionalization after 1 year.[14] Furthermore, decision making for treatment strategy should be discussed in a multidisciplinary team. The multidisciplinary conference would provide a better answer for each elderly patient who requires tube feeding, because they tend to have a complicated background.

Several potential limitations should be considered when interpreting these results. First, a cross-sectional study does not prove any causal relationship. Second, the practice rate of tube feeding in geriatricians was not clearly determined, because the present study was carried out by self-administered questionnaires. Third, the subjects were limited to geriatricians certified by the Japan Geriatrics Society, and also the response rate was not so high. Therefore, selection bias might have occurred. Finally, we did not investigate the number of beds in their place of employment; therefore these results were not completely adjusted by hospital size.

In conclusion, the present data showed that more than half of the board-certified geriatricians consider that the purpose of tube feeding is to improve the general condition or to prevent complications in the elderly with eating problems. Furthermore, regardless of their clinical experience, approximately 40% of the Japanese geriatricians consider that demented elderly with loss of appetite or apraxia for eating should be on tube feeding. At this moment, there is no consensus among Japanese geriatricians about tube feeding for advanced demented people, and hence the guideline should be established for tube feeding in the elderly. Furthermore, a multidisciplinary team approach is expected to find a better answer for each elderly patient with eating difficulty.

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LETTERS TO THE EDITOR

Gastrointestinal hemorrhage and antithrombotic drug use in geriatric patients

Dear Editor,

Recent guidelines recommend the aggressive use of antithrombotic medications in patients at high risk of thrombotic events. Although the risk of thrombosis increases with age, critical bleeding related to antithrombotic drug use is frequently seen in older patients.[1] Thus, guideline-directed use of antithrombotic medications might cause more harm than benefits among older patients with multiple comorbid conditions.[2,3] To increase the benefit-to-harm ratio, geriatricians might take care to stratify the risks and totally manage the patients. We hypothesized that such geriatricians' approaches lead to harmless use of antithrombotic medications. For this purpose, we carried out a case–control study to investigate the association between gastrointestinal hemorrhage and antithrombotic drug use.

We analyzed the inpatient registry of the Department of Geriatric Medicine, University of Tokyo Hospital between 1996 and 2007 (2249 patients) to identify patients ≥60 years-of-age who were admitted to the department as a result of gastrointestinal hemorrhage. The database was searched using the keywords of gastrointestinal hemorrhage, melena, hematemesis and anemia. Then, medical records of the extracted patients were reviewed. Finally, a total of 47 patients were defined to fulfil the criteria. Next, using risk-set sampling, we selected four controls per case matched for age, sex and the timing of hospitalization from the same inpatient registry. The data were obtained on prescriptions of antithrombotic drugs (aspirin, warfarin, cilostazol and ticlopidine) and anti-ulcer drugs (proton pump inhibitors and H2 blockers), and comorbid conditions.

Among the cases, causes of gastrointestinal hemorrhage were ulcer (48.9%), cancer (8.5%), ischemic colitis (6.3%), colon diverticulum (4.2%), Mallory–Weiss syndrome (4.2%) and hemorrhoid (2.1%), and 21.2% remained uncertain. As shown in Table 1, 17 cases and 71 controls were taking antithrombotic drugs. Of them, aspirin was most frequently prescribed both in case and control groups. There was no significant difference between case and control groups in the prescription rate of antithrombotic drugs ($\chi^2 = 0.20$, $P = 0.65$) and that of aspirin ($\chi^2 = 0.43$, $P = 0.51$). Furthermore, unadjusted logistic regression analyses showed that antithrombotic drug use and antiulcer drug use was not associated with gastrointestinal hemorrhage. The odds ratio of antithrombotic drug use for gastrointestinal hemorrhage was 0.91 (95% CI 0.46–1.81) after adjustment by age, sex and anti-ulcer drug use. Exclusion of the patients with cancer-related hemorrhage did not fundamentally influence the analytical results (data not shown).

This small case–control study showed no association of admission as a result of gastrointestinal hemorrhage with the use of antithrombotic drugs or aspirin among older patients. As most of the patients were managed by geriatricians in our department, the finding might be limited to the particular facility or cohort, but might not be extended to the general population. It is suggested, however, that geriatricians can make an appropriate decision on the indication and management of antithrombotic drugs for older patients. Although no studies have shown comparable findings in terms of gastrointestinal bleeding, geriatric evaluation and management has been reported to be effective to reduce serious adverse drug events.[4] A recent review on the management of antiplatelet agents[5] also recommended comprehensive strategies to reduce the risk of hemorrhagic complications. Prospective studies with a large sample size are required to confirm this issue. Nevertheless, it is certain that the use of antithrombotic medi cations should be carefully determined by considering the risk/benefit balance of each patient.

Table 1 Age, sex and medication use in case and control subjects, and unadjusted odds ratios for gastrointestinal hemorrhage

	Cases ($n = 47$)	Controls ($n = 189$)	Odds ratio (95% CI)
Age (years)	78 ± 10	77 ± 9	1.02 (0.98–1.06)
Men (women = 0, men = 1)	29 (61.7%)	120 (63.5%)	0.93 (0.48–1.79)
Antithrombotic drugs (no = 0, yes = 1)	16 (34.0)	71 (37.5)	0.86 (0.44–1.68)
Aspirin (no = 0, yes = 1)	10 (21.3)	49 (25.9)	0.77 (0.36–1.67)
Anti-ulcer drugs (no = 0, yes = 1)	18 (38.2)	45 (23.8)	0.67 (0.35–1.29)

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Pituitary insufficiency: A cause of hypoglycemia in an elderly diabetic patient

Dear Editor,

Hypoglycemia most likely occurs in the elderly as a result of poor glucose tolerance. The most common cause of hypoglycemia in elderly patients is antidiabetic drugs. Adrenal insufficiency, insulinoma and pituitary insufficiency are rare causes of hypoglycemia in older age.[1] Particularly in old patients, non-specific findings, such as weakness, fatigue and loss of appetite caused by pituitary insufficiency, might be attributed to aging.[2] Here, we reported an elderly patient with diabetes mellitus and hypopituitarism, presenting with refractory hypoglycemia and acute renal failure under therapy with oral antidiabetic drugs.

A 67-year-old woman was referred to geriatric clinic with symptoms of confusion, irritability, slowness of speech and movements, loss of appetite, nausea, and vomiting. A physical examination of her vital signs showed blood pressure 80/50 mmHg, pulse rate 104/min, body temperature 37.7°C and respiration 24/min. The patient was lethargic with incomplete cooperation (Karnofsky performance score of 30%). She had been taking metformin 2000 mg/day and gliclazide 30 mg/day with the diagnosis of diabetes for 2 years. In the biochemical examination, blood glucose, blood urea-nitrogen, creatinine, sodium and potassium were 32 mg/dL, 60 mg/dL, 3.2 mg/dL, 132 mmol/L and 4.9 mmol/L, respectively. After she was admitted to the geriatric clinic, her glucose infusion was given. Our initial evaluation of the clinical and laboratory parameters suggested that it could be acute renal failure as a result of dehydration and hypoglycaemia, which were the consequence of the prolonged effect of gliclazide. For this reason, oral antidiabetic drugs were discontinued, and glucose infusion was carried out. During her clinical follow up, we realized that her kidney functions had substantially increased. However, hypoglycemia persisted. Afterwards, all of the persistent hypoglycemia, hyponatremia and hypotension were evaluated, and the results were considered to be hypocortisolemia. The patient's other laboratory results, which were obtained during a hypoglycemia period, are presented in the Table 1. The basal serum cortisol (1.38 μg/dL) and adrenocorticototropic hormone levels (less than 0.3 U/L) showed strong evidence of cortisol deficiency. Due to these results, pituitary insufficiency was diagnosed. However, magnetic resonance imaging and magnetic resonance angiography did not show any structural or vascular abnormalities in the hypophysis and brain. Once prednisolone (7.5 mg/day) treatment

Table 1 Endocrinological laboratory results

Parameters		Normal range
Blood cortisol	1.38 ug/dL	6.2–19.4 ug/dL
TSH	0.055 uIU/mL	0.4–4.2 uIU/mL
Free T4	13.24 pmol/L	10.3–23.2 pmol/L
IGF-1	1.00 mg/L	1.73–5.11 mg/L
GH	<3 μg/L	
PRL	0.57 ng/mL	3–20 ng/mL
FSH	2.02 mIU/mL	25.8–134.8 mIU/mL
LH	1.36 mIU/mL	7.7–58.5 mIU/mL
Estradiol	27.96 pg/mL	5–54.7 pg/mL
C peptide	1.02 ng/mL	0.9–7.1 ng/mL
Insuline	2.83 μU/mL	3–28 μU/mL

All the laboratory results were measured between 08.00 hours and 09.00 hours, and confirmed by a second determination.
FSH, follicule stimulating hormone; GH, growth hormone; IGF1, insulin-like growth factor-1; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid stimulating hormone; T4, thyroxine.

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REVIEW SERIES

Hormonal effects on blood vessels

Masahiro Akishita[1] and Jing Yu[2]

The incidence of cardiovascular disease (CVD) is lower in younger women than in men of the same age, but it increases after menopause, implicating the atheroprotective action of endogenous estrogen. Although observational studies have suggested the efficacy of estrogen therapy in postmenopausal women, placebo-controlled, randomized trials, such as the Women's Health Initiative, have not confirmed effects of estrogen therapy on CVD. Conversely, basic, experimental research has progressed and provided mechanistic insight into estrogen's action on blood vessels. By contrast, the vascular effects of androgens remain poorly understood and have been controversial for a long time. In recent years, an increasing body of evidence has suggested that androgens may exert protective effects against the development of atherosclerosis, at least in elderly men. Epidemiological studies have shown that the incidence of and mortality due to CVD were increased in elderly men with low testosterone levels, although the efficacy of androgen therapy remains unknown. Furthermore, recent experimental studies have demonstrated the direct action of androgens on the vasculature. In this review, we illustrate the effects of sex steroids on the cardiovascular system, focusing on the action of testosterone on the blood vessels.
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Keywords: cardiovascular disease; endothelium; estrogen; testosterone; vascular smooth muscle

INTRODUCTION

Since the 1940s, it has been recognized that sex steroids have important roles in the cardiovascular system.[1,2] A number of epidemiological studies have shown that sex differences are apparent in the incidence of atherosclerotic disease. The incidence of cardiovascular diseases (CVDs), such as hypertension and coronary artery disease, is lower in younger women than in men of the same age.[3–5] However, it rises after menopause and, with age, catches up to that among men. These phenomena have been explained by the atheroprotective action of endogenous estrogen and its deprivation in postmenopausal women. In the past 20–30 years, many studies have suggested the efficacy of hormone replacement therapy (HRT) in postmenopausal women for the prevention of CVD and the putative vasoprotective effects of estrogen. However, reports from the Heart and Estrogen-Progestin Replacement Study (HERS)[6] and the Women's Health Initiative (WHI)[7] denied the efficacy of estrogen therapy in CVD.

By contrast, the actions of androgens on the cardiovascular system remain unclear. In the process of atherosclerosis, androgens may exert complex effects on vessel walls. Both beneficial and detrimental effects have been reported. For many years, it was widely believed that androgens have unfavorable roles in the development of atherosclerosis. Recently, however, the link between androgen deficiency and atherosclerosis has been demonstrated in a number of studies.[8–10] Various epidemiological and experimental studies have also demonstrated that androgens exert beneficial influences on CVD via the direct and indirect action of androgens on the blood vessels.

As the effects of estrogen on the cardiovascular system have been extensively studied and reviewed,[11–14] we allocated a small portion of our research to estrogen, highlighting recent developments. A larger part of this review focuses on androgens, particularly testosterone, to discuss the biological role of testosterone in vascular physiology and pathology in aging men.

ACTION OF ESTROGEN ON THE CARDIOVASCULAR SYSTEM

Effects of estrogen on cardiovascular risk factors

A number of studies have reported that estrogen therapy in postmenopausal women decreases the serum levels of both total and low-density lipoprotein cholesterol while raising high-density cholesterol and triglycerides, primarily by influencing the expression of hepatic apoprotein genes.[11,15] Also, estrogen inhibits the lipid peroxidation of low-density lipoprotein *in vitro* and *in vivo*.[16,17] Furthermore, estrogen can modulate glucose metabolism and prevent other risk factors for CVD, such as obesity (Table 1).[18,19]

Direct vascular action of estrogen

Two estrogen receptor (ER) subtypes, ERα and ERβ, have been identified and are expressed in the vasculature, and experimental studies have demonstrated the vasodilator effects of estrogen/ER through their action on the endothelium, smooth muscle and extracellular matrix. Estrogen enhances endothelium-dependent vasorelaxation via increased release of nitric oxide (NO),[20–22] endothelium-derived hyperpolarizing factor[23] and PGI_2[24,25] and decreased production of endothelin-1 (Table 1).[26] Several studies have demonstrated that estrogen inhibits calcium influx[27,28] and stimulates calcium efflux[29] in vascular smooth muscle cells (VSMCs), leading to endothelium-independent vasodilation. Moreover, estrogen inhibits neointima formation in response to balloon injury[30,31] and perivascular cuff placement.[32] Endothelial regeneration,[33] inhibition of endothelial apoptosis[34] and inhibition of VSMC migration and proliferation[32] may account for the inhibitory effects of estrogen on neointima formation. Analyses of knockout mice for ERα and ERβ have provided more information regarding the molecular mechanism of estrogen's action on the blood vessels.[5] Recent progress in nuclear receptor research has also clarified the non-genomic action of estrogen on the vasculature,[14] such as the direct interaction of ERα with the regulatory subunit of phosphatidylinositol-3-OH kinase.[35]

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Table 1 Anti-atherosclerotic effects of estrogen

Risk factors	*Vascular action*
Lipid metabolism	Endothelium-dependent vasorelaxation
HDL cholesterol↑	Nitric oxide↑
LDL cholesterol↓	Endothelin-1↓
Lp (a)↓	EDHF↑
Anti-oxidant	PGI_2↑
Glucose metabolism	Inhibition of EC apoptosis
Anti-obese	Endothelium-independent vasorelaxation
	Calcium antagonistic
	Inhibition of VSMC migration/proliferation

Abbreviations: EC, endothelial cell; EDHF, endothelium-derived hyperpolarizing factor; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VSMC, vascular smooth muscle cell.

Role of the novel ER G protein coupled receptor 30 (GPR30) in the cardiovascular system

In addition to the two classical ER subtypes, ERα and ERβ, a third membrane-bound and G-protein-coupled ER, GPR30, has been identified in human vascular endothelial cells (ECs) and smooth muscle cells.[36–38] Haas *et al.*[37] reported that G-1, a selective stimulator of GPR30, acutely blocked vasoconstrictor-induced changes in intracellular calcium concentrations and vascular tone, resulting in lowering of blood pressure in normotensive rats. Similar vasodilator effects of GPR30 have been confirmed in other studies.[39–41] It has also been reported that stimulation of GPR30 blocks VSMC proliferation.[37,42]

The vasodilator action of G-1 may be mediated by NO-independent[40] and NO-dependent[37,39,40] pathways; the latter involves GPR30-induced endothelial NO synthase (eNOS) phosphorylation.[43] Also, G-1 decreases nicotinamide adenine dinucleotide phosphate-stimulated superoxide production by the carotid and intracranial arteries, indicating the scavenging effects of GPR30 on superoxide anions.[39] In the heart, G-1 reduces ischemia/reperfusion injury and preserves cardiac function through the phosphatidylinositol 3-kinase/Akt and extracellular signal-regulated kinase pathways and by eNOS phosphorylation.[44,45] Treatment with G-1 for 2 weeks reduced the expression of angiotensin II type 1 receptor and angiotensin-converting enzyme.[40] The non-selective ER antagonist ICI 182780 and selective ER modulators, such as tamoxifen and raloxifene, have been shown to act as GPR30 ligands.[46] Moreover, both GPR30 and ER are required for estrogen action in some situations, whereas GPR30 can act alone in the absence of ER,[46,47] suggesting a complex network between GPR30 and ER.

HRT and CVD

Observational studies have suggested that HRT decreases the risk of CVD in postmenopausal women.[48,49] However, large-scale, placebo-controlled, randomized trials, such as the HERS[6] and the WHI,[7] did not confirm the findings of the observational studies. In the WHI, HRT with conjugated equine estrogen plus medroxyprogesterone acetate increased the incidence of CVD instead, particularly in women older than 60 years of age, although women who started HRT soon after menopause tended to have a decreased risk for coronary heart disease.[50]

Additional data from other studies have supported the concept that the vasoprotective effects of estrogen are evident only when hormone therapy is initiated soon after the onset of menopause and before the development of atherosclerosis. In a meta-analysis of hormone therapy, CVD mortality was lower in younger women on hormone therapy (mean age of 55 years old) than in age-matched controls.[51] Women aged 50–59 years who were enrolled in the conjugated equine estrogen trial of the WHI had significantly lower scores for coronary artery calcification 8.7 years after randomization than with placebo.[52]

Two ongoing clinical trials, the Kronos Early Estrogen Prevention Study[53] and the Early Versus Late Intervention Trial with Estradiol Study (available at http://clinicaltrials.gov/ct2/show/NCT00114517; accessed 16 November 2011), were designed to examine the timing, dosage, route and limited duration of administration on patients' cardiovascular outcomes and to prove the benefits of HRT in atherosclerosis when HRT is initiated soon after menopause. In the near future, these trials will provide additional insight into HRT and cardiovascular health in younger postmenopausal women.

ASSOCIATION OF LOW TESTOSTERONE LEVELS WITH CVD

Plasma testosterone levels decrease with aging, and >20% of healthy men older than 60 years of age have testosterone levels below the standard range in young men aged 20–30 years.[54,55] Lower testosterone levels are associated with cognitive dysfunction, muscle weakness, anemia, osteoporosis, mood disturbances and impaired general and sexual health in aging men.[56,57] Recently, many studies have demonstrated the relationship of testosterone with CVD, indicating a consistent inverse relationship between endogenous testosterone and adverse cardiovascular events.

A case–control study among 117 Indian men aged 30–60 years with old myocardial infarction showed that testosterone concentrations were significantly lower in the patients with myocardial infarction than in the control subjects.[58] Similar results were reported in men with acute myocardial infarction.[59] Cross-sectional results from the Massachusetts Male Aging Study (1709 men aged 40–70 years) showed that serum total and free testosterone levels bear an inverse relationship with CVD, independent of cardiovascular risk factors.[60] Recently, epidemiological studies have found that low testosterone levels are a predictor of all-cause and cardiovascular mortality in elderly men.[61,62] These findings were followed by studies investigating the incidence of CVD and testosterone levels.[63,64] According to these observations, endogenous testosterone appears to exert beneficial effects on the cardiovascular system.

ASSOCIATION OF LOW TESTOSTERONE WITH SURROGATE MARKERS OF ATHEROSCLEROSIS

The mechanisms underlying the epidemiological associations of low testosterone with CVD are complex and poorly understood. However, it is assumed that endogenous testosterone has physiological effects on the blood vessels and exerts atheroprotective effects. Actually, an increasing body of evidence has shown that low levels of endogenous

androgens are associated with atherosclerosis progression in elderly men. Carotid artery intima-media thickness, a common marker of clinical and subclinical atherosclerosis, has been shown to be correlated inversely with testosterone levels.[65–67] Demirbag *et al.*[68] reported a similar finding by examining the intima thickness of the thoracic aorta in older men. Similarly, in the Rotterdam Study population, Hak *et al.*[69] demonstrated that both bioavailable and total testosterone levels were negatively associated with calcified deposits in the abdominal aorta in men older than 55 years of age.

Arterial stiffness, measured as pulse wave velocity or augmentation index, is a predictor of cardiovascular events.[70] Yaron *et al.*[71] reported that age- and blood pressure-adjusted pulse wave velocity was significantly higher in hypogonadal men. Similarly, low testosterone levels in male hemodialysis patients were associated with increases in pulse wave velocity and CVD mortality.[72] Clinical and preclinical evidence exists linking endothelial dysfunction to androgen deficiency. In 187 Japanese men aged 47 ± 15 (s.d.) years, flow-mediated dilatation of the brachial artery, a reliable marker of endothelial function, was positively correlated with plasma testosterone levels, independent of other atherosclerosis risk factors.[73] Comparable results were reported from Europe[74] and specifically from Turkey.[75]

CLINICAL EFFECTS OF ANDROGEN REPLACEMENT THERAPY

As early as the 1940s, Lesser[2] demonstrated that testosterone administration alleviates symptoms and ECG abnormalities in men with angina. Subsequent studies have shown that short-term testosterone administration in men with coronary artery disease results in coronary artery dilation and resistance to ischemia. Indeed, testosterone infusion into the coronary arteries induces vasodilation,[76] and intravenous administration of testosterone reduces the exercise-induced ischemic response in men with stable angina.[77,78] Furthermore, acute administration of testosterone in men with chronic heart failure reduces peripheral vascular resistance and cardiac afterload, resulting in an increased cardiac index.[79] Chronic administration of testosterone also improves functional capacity and symptoms in heart failure patients.[80]

Several reports have shown that testosterone administration improves arterial stiffness and endothelial vasomotor function in men. Testosterone replacement in hypogonadal men results in acute (48 h) and chronic (3 months) decreases in pulse wave velocity.[71] It was also reported that testosterone replacement in men with coronary heart disease and low plasma testosterone decreased radial and aortic augmentation indices.[81] Acute intravenous infusion[82] and 8-week oral administration of testosterone[83] improved flow-mediated vasodilation of the brachial artery.

Testosterone therapy in hypogonadal men with type 2 diabetes mellitus suppressed the production of inflammatory cytokines by circulating monocytes.[84] A randomized, placebo-controlled, double-blind trial of 184 men with hypogonadism and metabolic syndrome showed that intramuscular administration of testosterone undecanoate decreased plasma levels of interleukin-1β, tumor necrosis factor-α and C-reactive protein in association with reductions in body mass index and waist circumference, while interleukin-6 and interleukin-10 did not change significantly.[85]

Taken together, testosterone administration, at least in hypogonadal men, may have a favorable vascular effect, including endothelium-dependent or -independent vasodilation and reduction of arterial stiffness and inflammatory markers. In contrast, the effects of testosterone replacement on the progression of carotid intima-media thickness or other atherosclerotic lesions, as well as on CVD risk,[86] are unknown.

DIRECT EFFECTS OF TESTOSTERONE ON VASCULAR WALLS

Risk factors, such as metabolic syndrome, may partly explain the association of low testosterone with CVD. As the relationship between testosterone and metabolic syndrome has been extensively reviewed,[87,88] this section focuses on the direct effects of testosterone on the vascular wall and the underlying molecular mechanism.

As mentioned above, testosterone therapy can improve vascular function and several markers of atherosclerosis in men. Therefore, vascular ECs, VSMCs and macrophages may be targets of androgen's actions. Indeed, androgen receptor (AR) has been shown to be expressed in these cells.[89–91]

Effects of testosterone on animal models of atherosclerosis and neointima formation

It has been demonstrated that the administration of testosterone in castrated male rabbits that were fed a high-cholesterol diet reduced aortic atherosclerosis, largely independent of plasma lipids.[92,93] In addition, neointima formation after coronary balloon injury in swine was increased by castration and was reversed by testosterone replacement.[94] Regarding the role of AR, conflicting findings have been reported. Nathan *et al.*[95] demonstrated the inhibitory effects of testosterone on fatty streak formation in castrated low-density lipoprotein receptor-deficient male mice, but the effects of testosterone were abrogated by treatment with an aromatase inhibitor, suggesting that estradiol converted from testosterone had a major role. Conversely, Qiu *et al.*[91] showed that nonaromatizable dihydrotestosterone suppressed atherosclerosis formation in castrated male rabbits, indicating a role for AR. Exaggerated vascular remodeling in AR-deficient mice, in response to angiotensin II infusion, also suggests an important role for AR.[96] A recent study by Bourghardt *et al.*[97] may provide a hint in addressing this issue. They administered testosterone in AR-deficient mice with apolipoprotein E-deficient backgrounds and showed that testosterone reduced atherosclerotic lesions, both in AR-deficient and castrated wild-type male mice, but testosterone was less effective in AR-deficient mice, suggesting AR-dependent and -independent mechanisms.

Effects of testosterone on ECs

Several reports have implicated the effects of testosterone on endothelial regeneration. Cai *et al.*[98] demonstrated that testosterone induced time- and dose-dependent proliferation of human aortic ECs via an AR-dependent pathway. In young hypogonadal men, low testosterone levels were associated with a small number of endothelial progenitor cells,[99] and testosterone replacement was able to increase the number of progenitor cells.[100] The synthesis and release of vasoactive substances by EC may have a role in these effects. Of the substances synthesized by EC, NO is a critical molecule that regulates vascular tone and atherosclerosis, and it is a major target of testosterone. It has been reported that testosterone-induced endothelium-dependent vasodilation is mediated in part by NO.[101] We recently demonstrated that testosterone rapidly induces NO production via AR-mediated activation of eNOS in human aortic ECs.[89] Furthermore, we showed that AR directly interacts with the p85 subunit of phosphatidylinositol 3-kinase, resulting in phosphorylation/activation of Akt/eNOS signaling. Taking together with our preliminary observation about the involvement of extracellular signal-regulated kinase 1/2 signaling and [Ca2+]i in AR-dependent eNOS activation, quite similar signaling pathways to those for estrogen can be proposed for testosterone (Figure 1), although some of these pathways should be verified in further studies. The genomic action of testosterone in ECs has not been studied extensively.

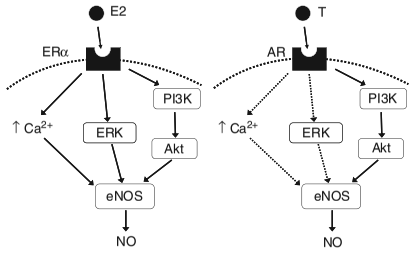

Figure 1 Signal transduction pathways of eNOS activation by estradiol and testosterone in vascular endothelial cells. AR, androgen receptor; E2, estradiol; eNOS, endothelial NO synthase; ERα, estrogen receptor α; ERK, extracellular signal-regulated kinase; NO, nitric oxide; PI3K, phosphatidylinositol 3-kinase; T, testosterone. Dotted curves indicate the plasma membrane. Dotted arrows indicate probable but undetermined pathways.

It has been reported that testosterone increases the number of ECs secreting endothelin-1,[102] although its contribution to the modulation of vascular tone and of CVD is unknown. Testosterone at physiological concentrations seems to have a beneficial influence on the hemostatic system through tissue plasminogen activator expression and inhibition of plasminogen activator inhibitor type 1 secretion by human umbilical vein ECs.[103]

Effects of testosterone on VSMCs

Most of the rapid vasodilator effects of testosterone are endothelium independent and thus are attributable to its action on VSMCs. In particular, vasodilator responses to pharmacological concentrations of testosterone seem to be AR independent. Yue *et al.*[104] reported that the relaxing response of rabbit coronary arteries to testosterone was significantly inhibited by the potassium-channel inhibitor barium chloride but not by the inhibition of NO synthesis or by removal of the endothelium. Several groups have shown that testosterone inhibits the agonist-induced rise of [Ca2+]i in VSMCs, as has been documented for estrogen. Crews and Khalil[28] reported that testosterone at supra-physiological doses (10–100 pmol l^{-1}) significantly suppresses the vasoconstriction of porcine coronary artery strips induced by prostaglandin F2α or by KCl, in parallel with the inhibition of Ca2+ entry. Hall *et al.*[105] demonstrated, using the A7r5 VSMC cell line, that testosterone and dihydrotestosterone selectively suppressed Ca2+ entry via L-type Ca2+ channels. Similar results have been reported in different experimental conditions by other groups.[106–108]

The involvement of potassium channels in testosterone-induced vasodilatation has also been studied by many researchers.[109–111] Cairrao *et al.*[112] reported that an AR antagonist, flutamide, and an adenosine triphosphate-sensitive potassium-channel inhibitor, glibenclamide, had no influence on the testosterone relaxant effect, whereas a voltage-sensitive potassium-channel inhibitor, 4-aminopyridine, decreased this effect of testosterone. Opening of voltage-sensitive potassium channels induces hyperpolarization of the plasma membrane, which in turn may lead to the closing of L-type Ca2+ channels. These pharmacological studies, most of which used chemical inhibitors, may be strengthened by studies employing molecular-targeting strategies.

Accumulation of VSMCs in damaged vascular layers is a critical process in the development of atherosclerosis and is closely related to hypertension and its complications. Many, but not all, of the previous studies indicated that testosterone might inhibit VSMC growth. Hanke *et al.*[113] reported, using an *ex vivo* organ culture system, that testosterone at 10–100 ng ml^{-1} significantly inhibited neointima formation in association with increased expression of AR in endothelium-denuded rabbit aortic rings after 21 days of incubation. Somjen *et al.*[114] demonstrated the dose-dependent inhibitory effects of dihydrotestosterone and membrane-impermeable testosterone on DNA synthesis in cultured VSMCs derived from the human umbilical artery, suggesting a role for membrane AR. The above-mentioned study by Tharp *et al.*[94] showed that the expressions of protein kinase C delta and p27 (kip1) were increased in coronary artery sections of testosterone-treated swine.

Androgen-responsive genes directly regulated by AR in VSMCs have not been determined, except for AR itself. However, we recently found that growth arrest-specific gene 6 was transactivated by testosterone in human VSMCs via binding of AR to the promoter region of the growth arrest-specific gene 6.[90] In this study, testosterone inhibited inorganic phosphate-induced VSMC apoptosis, leading to the suppression of VSMC calcification. To further elucidate the mechanism underlying the effects of testosterone on the cardiovascular system, identification of androgen-responsive genes in VSMCs, as well as in ECs, is required in future studies.

Natoli *et al.*[115] investigated, using human aortic VMSCs, and found that testosterone significantly reduced collagen and fibrillin-1 deposition, while it had no effect on elastin. They also found that testosterone increased the expression of matrix metalloproteinase-3, which has an important role in vascular remodeling.

POSSIBLE HARMFUL EFFECTS OF TESTOSTERONE ON BLOOD VESSELS

Although many studies have shown the beneficial effects of testosterone on the blood vessels, as mentioned above, other studies have suggested that long-term administration of testosterone may elicit harmful effects, especially vasoconstriction via upregulation of thromboxane A2,[116] norepinephrine synthesis,[117] angiotensin II[118] and endothelin-1.[102] It has been also reported that testosterone accelerates vascular remodeling[119] and stimulates renal prohypertensive processes, including the renin–angiotensin–aldosterone system.[120] Recent meta-analyses have revealed that CVD events were not different between testosterone and placebo groups,[86,121] indicating the complexity of testosterone therapy, as was shown for estrogen therapy in women.

TESTOSTERONE DEFICIENCY AND CVD IN WOMEN

An age-related reduction in circulating levels of androgens occurs in women as well.[122] However, it is unclear whether this decline adversely affects vascular health in women. Higher serum testosterone concentrations, within the physiological range, have been associated with lower carotid intima-media thickness,[123] suggesting potential protective effects of endogenous testosterone on cardiovascular health in pre- and postmenopausal women. Conversely, it is well known that women with polycystic ovary syndrome, who exhibit high androgen levels, are at a higher risk for CVD. Some studies have reported that high testosterone is associated with an adverse CVD risk factor profile in postmenopausal women, irrespective of polycystic ovary syndrome.[3,124] Polymorphism of the (CAG)n repeat of the AR gene was associated with CVD and risk factor profiles in postmenopausal women.[125] Thus far, evidence is lacking for an association of testosterone with CVD events in women, and it is uncertain whether testosterone could be used as a postmenopausal hormone therapy.

CONCLUSION

In this review, we illustrated the sex hormones' effects on the cardiovascular system, focusing on the action of testosterone on the blood vessels. Endogenous androgens, as well as estrogen, may display favorable effects on the vasculature, but whether HRT protects aging men and women from CVD is still unknown. Although testosterone administration seems to have diverse or contradictory effects in younger men and women, androgen therapy may provide hope for elderly hypogonadal men. This issue will remain unclear unless clinical trials of testosterone therapy are conducted. Also, progress in basic research on hormonal effects on blood vessels is essential to understanding the role of sex hormones in the development of CVD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Polypharmacy as a risk for fall occurrence in geriatric outpatients

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Objective: To investigate the predictors of falls, such as comorbidity and medication, in geriatric outpatients in a longitudinal observational study.

Methods: A total of 172 outpatients (45 men and 126 women, mean age 76.9 ± 7.0 years) were evaluated. Physical examination, clinical history and medication profile were obtained from each patient at baseline. These patients were followed for up to 2 years and falls were self-reported to their physicians. The factors associated with falls were analyzed statistically.

Results: A total of 32 patients experienced falls within 2 years. On univariate analysis, older age, osteoporosis, number of comorbid conditions and number of drugs were significantly associated with falls within 2 years. On multiple logistic regression analysis, the number of drugs was associated with falls, independent of age, sex, number of comorbid conditions and other factors that were significantly associated in univariate analysis. A receiver–operator curve evaluating the optimal cut-off value for the number of drugs showed that taking five or more drugs was a significant risk.

Conclusion: In geriatric outpatients, polypharmacy is associated with falls. Intervention studies are needed to clarify the causal relationship between polypharmacy, comorbidity and falls. **Geriatr Gerontol Int 2011; ••: ••–••.**

Keywords: bone/musculo-skeletal, elderly, falls, geriatric medicine, internal medicine, polypharmacy.

Introduction

Previous studies have assessed the risk factors for falls in community-dwelling elderly,[1–3] but not in geriatric outpatients, and history of falls, physical ability and living environment were found to be predictors of falls. Outpatients have different characteristics from community-dwelling elderly, and previous studies have not assessed whether medical comorbidity and therapeutic drugs might be risk factors for falls. Falls in patients on medication are complicated, because some drugs, such as aspirin, can cause serious bleeding when they have injurious falls, and others, such as antihypertensive[4] and hypoglycemic[5,6] agents, can cause falls.

Previously, we reported that polypharmacy was associated with the tendency for falls using four indices of fall tendency in a cross-sectional setting in geriatric outpatients,[7] though that study did not evaluate fall occurrences, and also not in a longitudinal manner. Therefore, we aimed at investigating whether polypharmacy was predictive of fall occurrences in a prospective fashion. For this purpose, we followed geriatric outpatients for up to 2 years, and assessed whether polypharmacy is a risk for fall occurrence, together with other risks.

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The validity of two novel indices of fall tendency, the 22 items fall risk index[8] and the 13 points simple screening test,[3] which were used in our previous study, have been confirmed in community-dwelling elderly, but not in geriatric outpatients. Therefore, in the present investigation, the association of these two indices with falls was also evaluated to confirm their validity in geriatric outpatients in a longitudinal study.

Methods

Patients

From 2006 to 2007, a total of 190 consecutive patients aged 65 years or older who were receiving treatment for chronic diseases, such as hypertension, dyslipidemia, diabetes and osteoporosis, who were seen every 2–4 weeks at the outpatient clinic of the Research Institute of Aging Science, Tokyo, were enrolled. All the patients were able to walk independently and their condition was stable. Patients who had acute illness or overt dementia were excluded. Anthropometric and medical information including past history of stroke, myocardial infarction, malignancy and prescribed drugs was obtained from each patient at baseline from the medical chart recorded by the physician in charge. However, 18 patients were excluded, because they were lost to follow up soon after enrolment and the medical information was not fully obtained. All prescribed drugs had not been changed in the included patients for at least 2 months before enrolment. The patients were followed up for 2 years.

Occurrence of falls

During the follow-up period, the patients and their family members responded to the annual questionnaire asking about the occurrence of falls within the past year. The questionnaire was repeated for 2 years.

Indices of fall tendency

After enrolment, the patients were examined for two indices to investigate the fall tendency. These were (i) a questionnaire of the 22 items portable fall risk index;[8] and (ii) the 13 points simple screening test to assess the fall tendency.[3]

Ethical consideration

The present study was approved by the Institutional Review Board of the Research Institute of Aging Science. We obtained written consent from all participants and/or their guardians.

Data analysis and statistical methods

Values are expressed as mean ± standard deviation. In order to analyze the relationship between falls and comorbidity or drugs, variables were compared using Student's *t*-test or χ^2-test as appropriate. Significant factors found in univariate analysis were included in multivariate logistic regression analysis to determine the association of falls with other variables. Receiver–operating curve (ROC) analysis was carried out to identify the optimal cut-off value of the number of drugs for predicting falls within 2 years. The value with the highest sum of sensitivity and specificity was used as the optimal cut-off value. Logistic regression analysis was carried out to assess the validity of the two indices of fall tendency, adjusted by age and sex. *P*-values <0.05 were considered statistically significant. Data were analyzed using JMP version 8.0.1 (SAS Institute, Cary, North Carolina, USA).

Results

Baseline medical information and two indices of fall tendency were evaluated in 172 patients (Table 1). Drugs prescribed in less than 5% of the patients are not shown. Because only patients who were in a stable condition and were able to walk independently were included, patients with Parkinson's disease, severe paresis or painful arthralgia were not included. Calcium channel blockers prescribed in the present study were all long-acting agents, and the prescribed aspirin dosage was 100 mg in all cases. Only a few patients were receiving insulin therapy, sulfonylureas, angiotensin converting enzyme inhibitors, β-blockers, α-blockers, non-steroidal anti-inflammatory drugs or anticoagulants. No patients were taking neuroleptics or antiparkinsonian drugs.

After 1 year, all patients, except for one who died of congestive heart failure, were followed up ($n = 171$, follow-up rate 99.4%). Falls occurred in 22 patients. Only a higher age was associated with falls within 1 year on univariate analysis (non-fallers: 76.4 ± 6.8 years, fallers: 81.0 ± 6.9 years, $P = 0.004$).

After another year (2 years after enrolment), one patient had died of lung cancer, and five patients were lost to follow up. A total of 165 patients were evaluated (follow-up rate 95.9%), and 10 patients had fallen during the second year; thus a total of 32 patients had fallen within 2 years. As shown in Table 2, higher age, osteoporosis, number of comorbid conditions and number of drugs were significant factors associated with falls. To determine the association of falls with these significant factors, multivariate logistic regression analysis was carried out, and as shown in Table 2, the number of drugs was the only factor that was significantly associated with falls within 2 years.

As polypharmacy was assumed to be a risk for falls within 2 years, the cut-off of the number of the drugs was analyzed. Figure 1 shows the ROC curves to define the optimal cut-off point in relation to falls within

Table 1 Characteristics and univariate analysis of association with fallers and non-fallers within 2 years and risk factors

Total		Non-fallers ($n = 133$)	Fallers ($n = 32$)	P-value (Fallers vs. Non-fallers)
Age (years)	77.0 ± 7.0	76.3 ± 6.9	80.0 ± 6.9	0.007
Body mass index (kg/cm^2)	22.7 ± 3.2	22.7 ± 3.3	22.7 ± 3.1	0.98
No. comorbid conditions	1.9 ± 1.1	1.8 ± 1.1	2.3 ± 0.9	0.009
No. drugs	3.2 ± 2.8	2.8 ± 2.7	4.9 ± 2.5	<0.0001
Female ($n = 122$)	–	72.9%	78.1%	0.66
Hypertension ($n = 106$)	–	62.4%	71.8%	0.41
Dyslipidemia ($n = 76$)	–	47.3%	40.6%	0.56
Diabetes ($n = 23$)	–	12.8%	18.8%	0.40
Osteoporosis ($n = 59$)	–	30.8%	56.3%	0.01
History of stroke ($n = 6$)	–	2.3%	9.4%	0.09
History of myocardial infarction ($n = 3$)	–	0.8%	6.3%	0.10
History of cancer ($n = 8$)	–	5.3%	3.1%	0.99
Calcium channel blocker ($n = 59$)	–	33.3%	46.9%	0.16
Angiotensin II receptor blocker ($n = 56$)	–	33.3%	37.5%	0.68
Statin ($n = 40$)	–	23.5%	28.1%	0.65
Aspirin ($n = 31$)	–	19.0%	24.1%	0.61
Bisphosphonate ($n = 9$)	–	4.6%	9.4%	0.38
H2-blocker ($n = 9$)	–	3.8%	12.1%	0.80
Proton pump inhibitor ($n = 11$)	–	5.3%	12.1%	0.23
Hypnotic ($n = 31$)	–	16.7%	28.1%	0.14

Values are expressed as mean ± SD ($n = 165$).

Table 2 Logistic regression analysis of association of falls within 2 years with age, sex, other significant factors found in univariate analysis, and polypharmacy

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/1 year)	1.08 (1.03–1.13)†	1.06 (0.99–1.13)	1.06 (0.99–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.98 (0.29–3.23)	0.75 (0.23–2.38)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)†	2.76 (0.92–7.38)	3.02 (0.96–6.15)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	0.90 (0.55–1.47)	0.99 (0.62–1.56)
No. drugs (/drug)	1.29 (1.12–1.48)‡	1.30 (1.08–1.57)*	–
Five or more drugs ($n = 0$, Y = 1)	5.04 (2.25–11.3)‡	–	4.50 (1.66–12.2)†

*$P < 0.05$, †$P < 0.005$, ‡$P < 0.0005$. CI, confidence interval.

2 years: the area under the ROC was 0.731, and the optimal cut-off value of the number of drugs was five (sensitivity 0.576, specificity 0.788). Logistic regression analysis showed that taking five or more drugs was significantly associated with an increased risk of falls (odds ratio 4.5, 95% CI 1.7–12.2) after adjustment for age, sex, osteoporosis and number of comorbid conditions (Table 2).

Also, the association between falls and two indices of fall tendency was evaluated to confirm the validity of each index in geriatric outpatients. As both indices included the questionnaire asking whether patients were "taking five or more drugs," the number of drugs was excluded from this analysis because of duplication in the statistical model. As shown in Table 3, the 22 items fall risk index showed a tendency towards an association with falls within 2 years, odds ratio 1.12 (95% CI 1.00–1.26; $P = 0.05$), whereas the 13 points screening test was significantly associated with falls after adjustment for age, sex and other factors significantly associated in the univariate analysis. Therefore, these indices are considered to be good predictors of falls in geriatric outpatients, as has been shown in community-dwelling elderly subjects.

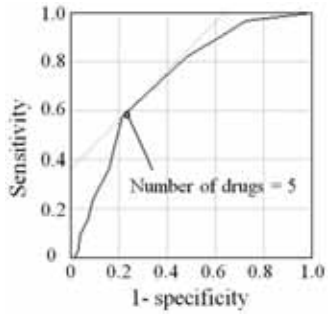

Figure 1 Receiver–operating curves to define optimal cut-off value of number of drugs at baseline in relation to falls within 2 years. Area under the curve was 0.731, optimal cut-off value of the number of drugs was five (sensitivity = 57.6%, specificity = 78.8%).

Discussion

The risk of falls has been assessed in community-dwelling elderly, and history of falls, physical ability and living environment were found to be predictors of falls. Also, in nursing home residents, cognitive function, gait disturbance and urinary incontinence are reported to be risk factors for falls,[9,10] and length of stay, disease condition, surgical procedures and some specific drugs are reported to be risk factors in hospital inpatients.[11,12]

Nevertheless, the risks in geriatric outpatients have not been sufficiently assessed, although assessment of fall risk in geriatric outpatients is important; their medical conditions or drugs might cause falls, and drugs, such as antiplatelet agents or anticoagulants, might cause critical bleeding after a fall. Also, physicians could prevent falls in their patients by giving advice during regular consultations, if risk factors are identified.

In our previous cross-sectional study assessing geriatric outpatients, polypharmacy was significantly correlated with indices of fall tendency, and the present follow-up study of geriatric outpatients showed the impact of polypharmacy on falls within 2 years. Statistical analyses showed that polypharmacy was a risk factor for falls, independent of age, sex and comorbidity.

Besides polypharmacy, several medications and comorbid conditions have been reported as risks for falls.[13–22] Among these, diabetes,[5,6] insomnia,[13] hypnotics,[13–15] antiarrhythmics[22] and antihypertensive agents[14] were not significantly associated with fall risk in the present study. Just 11 patients (45.9% of diabetic patients) were prescribed hypoglycemic agents, such as a sulfonylurea ($n = 8$) or insulin ($n = 3$), and the relatively low rate of prescription of hypoglycemic agents might have affected our result. Neither hypnotics nor antihypertensives were associated with falls. This result might be a result of the small sample size. Anti-arrhythmics were taken by just three patients (digoxin: $n = 2$, class IA anti-arrhythmic drug: $n = 1$). Other drugs, such as major tranquillizers,[14] antidepressants[17,18] and antiparkinsonian agents,[19,22] might increase fall risk; however, no patient used these drugs in the present study. In the present study, most of the patients were in a stable condition throughout the 2 years, though their drugs were changed gradually according to their medical conditions during the observation period. We only used the number of drugs at baseline for statistical analysis; however, the number of drugs increased from 3.2 ± 2.8 to 3.9 ± 3.0 during the 2 years. There were 17 patients whose number of drugs had been decreased, 70 patients not changed and 78 patients increased. The number of drugs after 2 years was also associated with falls ($P < 0.0005$). The optimal cut-off point for the number of drugs was again five (area under ROC curve 0.780, sensitivity 0.576, specificity 0.788). Furthermore, the changes in number of drugs were also associated with falls ($P < 0.05$), and the optimal cut-off point for the change in number of drugs was +1 (area under ROC curve 0.649, sensitivity 0.727, specificity 0.409).

Table 3 Logistic regression analysis of association between 2-year fall occurrences with two indices of fall tendency; 22 items fall risk index and 13 points simple screening test

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/year)	1.08 (1.03–1.15)**	1.06 (0.99–1.13)	1.06 (1.00–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.75 (0.23–2.43)	0.79 (0.24–2.56)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)**	2.56 (0.96–6.82)	2.61 (0.98–6.95)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	1.24 (0.83–1.86)	1.32 (0.88–1.97)
Fall risk index (/item)	1.23 (1.11–1.37)***	1.12 (1.00–1.26)	–
Simple screening test (/point)	1.19 (1.06–1.33)**	–	1.14 (1.01–1.29)*

*$P < 0.05$, **$P < 0.005$, ***$P < 0.0005$. CI, confidence interval.

Consequently, polypharmacy, especially taking five or more drugs, should be considered a risk for falls.

There were several limitations of the present study. First, the falls were self-reported by the patients. Although all the patients had no overt dementia, they might have forgotten the incident of falling. We attempted to count the total fall occurrences in each patient; however, we could not differentiate the repeated falls in the second year from the fall occurrence in the first year. In fact, we asked 22 patients who reported falls in the first year about fall occurrence during the second year, but they did not accurately recall whether they experienced falls in the first or second year. Second, five patients were lost to follow up at 2 years for unknown reasons. The follow-up ratio was acceptable, although some of the patients might have fallen, have been no longer able to come to the clinic and moved to nursing homes. This might have slightly influenced the result. Also, the cause of falls in polypharmacy patients is not explained. Potentially inappropriate medications, which could cause adverse drug reactions, are usually seen in patients with polypharmacy, and falls might be the consequence of adverse drug reactions, such as dizziness, instability and light-headedness. Pathophysiological assessments and drug-reducing interventions are expected to elucidate the causal relationship.

Additionally, we showed that the 22-item fall risk index and its simple screening test were useful to predict falls in geriatric outpatients. Although both indices have been validated in community-dwelling elderly people, the present finding also showed their association with fall risk among geriatric outpatients. The difference of statistical significance between fall risk index and simple screening test might be a result of small sample size or the difference in the contribution of each item to total scores between the two indices. "Taking five or more drugs" accounts for only one item out of the 22-item fall risk index; in contrast, the same questionnaire accounts two points in the 13-point simple screening test. Because polypharmacy was a strong risk factor of falls in elderly outpatients in the present study, the proportion of polypharmacy in the scores might have caused the discrepancy. Taken together, it is likely that 13-point screening test was more suitable to our subjects who were taking several medicines.

In summary, the present study showed that geriatric outpatients with polypharmacy were at a high risk of falls, especially those receiving five or more drugs. Our finding might add new information for pharmacotherapy and geriatric research in elderly patients with chronic diseases. Intervention studies examining the effect of drug reduction for the prevention of falls are required in the future.

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Disclosure statement

The authors declare no conflict of interest.

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Testosterone Deficiency Accelerates Neuronal and Vascular Aging of SAMP8 Mice: Protective Role of eNOS and SIRT1

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Abstract

Oxidative stress and atherosclerosis-related vascular disorders are risk factors for cognitive decline with aging. In a small clinical study in men, testosterone improved cognitive function; however, it is unknown how testosterone ameliorates the pathogenesis of cognitive decline with aging. Here, we investigated whether the cognitive decline in senescence-accelerated mouse prone 8 (SAMP8), which exhibits cognitive impairment and hypogonadism, could be reversed by testosterone, and the mechanism by which testosterone inhibits cognitive decline. We found that treatment with testosterone ameliorated cognitive function and inhibited senescence of hippocampal vascular endothelial cells of SAMP8. Notably, SAMP8 showed enhancement of oxidative stress in the hippocampus. We observed that an NAD^+-dependent deacetylase, SIRT1, played an important role in the protective effect of testosterone against oxidative stress-induced endothelial senescence. Testosterone increased eNOS activity and subsequently induced SIRT1 expression. SIRT1 inhibited endothelial senescence via up-regulation of eNOS. Finally, we showed, using co-culture system, that senescent endothelial cells promoted neuronal senescence through humoral factors. Our results suggest a critical role of testosterone and SIRT1 in the prevention of vascular and neuronal aging.

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Introduction

Advancing age is the most significant risk factor for the development of cognitive impairment [1,2]; however, what age-related changes underlie this effect remains uncertain. With advancing age, men experience a significant decrease in the circulating level of testosterone. Although studies have shown alterations in mood, libido, and cognition resulting from testosterone deficiency [3], the full range of consequences of age-related testosterone loss remains incompletely defined. In a small clinical study of men recently diagnosed with cognitive impairment, testosterone treatment improved performance on cognitive tests [4]. In a prospective longitudinal study using subjects from the Baltimore Longitudinal Study on Aging, men who developed Alzheimer disease (AD) were observed to exhibit low testosterone levels 5–10 years prior to the clinical diagnosis of AD [5]. With a relationship between age-related testosterone decline in men and increased risk for cognitive impairment reasonably well established, a critical issue is how testosterone contributes to the pathogenesis of cognitive decline with aging. The most likely hypothesis is through the regulation of accumulation of amyloid ß (Aß) peptides, which are widely believed to be the critical initiating step in the pathogenesis of AD. However, it is becoming increasingly clear that not all aspects of cognitive decline can be explained by Aß [6,7]. Findings from such diverse lines of investigations as neuroimaging and clinical trials suggest that non-Aß factors also contribute to memory deficit in aged men.

In *S. cerevisiae*, the *Sir2* (silent information regulator-2) family of genes governs budding exhaustion and replicative life span [8,9]. *Sir2* has been identified as an NAD^+-dependent histone deacetylase and is responsible for maintenance of chromatin silencing and genome stability. Mammalian sirtuin 1 (*Sirt1*), the closest homolog of *Sir2*, regulates the cell cycle, senescence, apoptosis and metabolism, by interacting with a number of molecules such as p53. As recently reported, overexpression of SIRT1 in the brain improved the memory deficit in a mouse model of AD via activation of the transcription of α-secretase [10].

An increasing body of evidence suggests the presence of a link between cognitive decline and vascular dysfunction, especially atherosclerosis [11]. Senescence of endothelial cells is involved in endothelial dysfunction and atherogenesis, and SIRT1 has been recognized as a key regulator of vascular endothelial homeostasis, controlling angiogenesis, endothelial senescence, and dysfunction [12–14].

In the present study, we demonstrated that cognitive impairment in senescence-accelerated mouse prone 8 (SAMP8), a model of cognitive decline with aging, is associated with endothelial senescence in the hippocampus and is ameliorated by testosterone replacement. SIRT1 plays an important role in prevention of endothelial senescence induced by oxidative stress [13]. We suggest that the protection against endothelial senescence in the hippocampus through up-regulation of testosterone and SIRT1 could contribute to a novel therapeutic strategy against cognitive decline with aging.

Results

Treatment with dihydrotestosterone ameliorated cognitive function of SAMP8

In order to assess the effects of testosterone on cognitive function, we used an in vivo model of aging, SAMP8, and a control counterpart strain, SAMR1. SAMP8 was originally derived from AKR/J strain, litters of which show the characteristic of cognitive decline with aging. These mice exhibit age-related deficits in learning and memory at an early age, and are considered a suitable animal model to study aging and memory deficit. Body weight, appearance, and plasma testosterone level of SAMR1 and SAMP8 at 12 weeks of age were determined. Body weight and appearance did not differ between SAMR1 and SAMP8, but plasma testosterone level in SAMP8 was lower than that in SAMR1 (Figure 1A). By determining the time required to find the platform (escape latency) as a function of days of training in the Morris water maze, we observed a marked decline in performance in SAMP8 compared with SAMR1 (Figure 1B). Because testosterone acts in part through aromatase-dependent conversion to estradiol, non-aromatizable dihydrotestosterone (DHT) was used to examine a direct role of androgens through androgen receptor (AR). SAMP8 treated with DHT showed significantly reduced escape latency time compared with untreated SAMP8. There was no difference in swim speed between the groups; however, % time in the quadrant was increased in DHT-treated SAMP8 (Figure 1B). These results indicate that DHT treatment ameliorated cognitive dysfunction in SAMP8. The water-maze is appropriate for hippocampal-dependent paradigms. However, DHT administration may affect behavior and how animals respond to different stimuli. Therefore, we performed an open field test to examine locomotion, exploratory behavior, and anxiety. No significant effect of DHT on locomotor performance was observed in SAMR1 and SAMP8, whereas SAMR1 moved significantly more compared with SAMP8 (Figure 1C). The ratio of the distance travelled in the central area to that in the total area in the open- field, an indirect measure of exploratory behavior and anxiety [15], was also observed. In SAMP8, DHT increased this ratio (Figure 1C), suggesting that DHT promoted exploratory behavior and diminished anxiety.

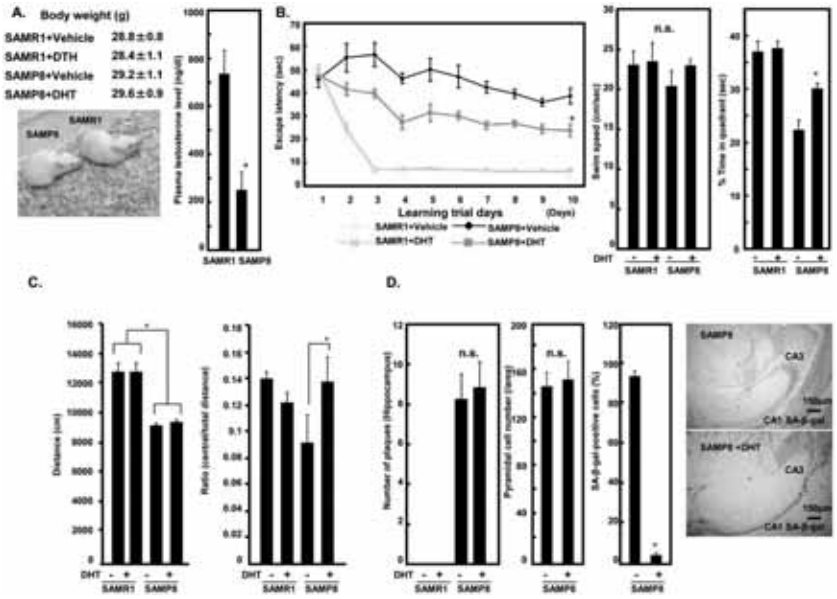

Figure 1. Testosterone deficiency causes senescence of hippocampus and cognitive impairment in SAMP8 mice. A. Body weight, appearance, and plasma testosterone level of male SAMR1 and SAMP8 mice at 12 weeks of age. **B.** Escape latency of SAMR1 (N = 10) and SAMP8 mice (N = 10). Male mice were treated daily for 2 weeks with DHT (500 μg s.c) before trials. Swim speed during quadrant test on day 10. **C.** Total distance and the ratio of central/total distance were measured in open field tests. **D.** Number of amyloid ß plaques, pyramidal cells, and SA-ßgal-positive cells in CA1 and CA3 areas of hippocampus in SAMR1 and SAMP8. (*$p<0.05$, n.s: not significant).
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Next, we assessed the number of amyloid ß plaques, pyramidal cells, and SA-ßgal-positive cells in CA1 and CA3 areas of the hippocampus in these mice (Figure 1D). The number of plaques was increased in SAMP8 compared with SAMR1, but was unaltered by treatment with DHT. The number of SA-ßgal-stained cells was significantly increased in SAMP8 compared with SAMR1, but treatment with DHT prevented this in SAMP8 despite no difference in pyramidal cell number (Figure 1D).

DHT treatment increased protein and mRNA expression of SIRT1 in SAMP8

Furthermore, to estimate the role of testosterone deficiency in SAMP8, we examined the effect of testosterone supplementation on cognitive function in much older SAMR1 and SAMP8. Similarly to young mice, we observed a marked decline in performance in SAMP8 compared with SAMR1 at 18 months of age. SAMP8 implanted with testosterone pellets showed significantly reduced escape latency time compared with placebo-treated SAMP8 (Figure 2A). Plasma testosterone level in SAMP8 at 18 months of age was lower than that in SAMR1, but implanted mice showed recovery to the level in young mice (Figure 2A). These results indicated that similar to DHT, testosterone also showed the improvement of cognitive function in SAMP8. Next, we examined the cause of low plasma testosterone in SAMP8. SAMP8 showed no testicular atrophy (Figure S1A), but more senescent phenotypes in Leydig cells, which produce testosterone in testes, than SAMR1 (Figure 2B). Moreover, we tried to allotransplant testes from SAMR1 to SAMP8 (Figure S1B). Although performance gradually responded to treatment up to 8–10 weeks, castrated SAMR1 showed a marked decline in performance whereas recipient SAMP8 showed cognitive improvement (Figure 2C).

As recently reported, overexpression or activation of SIRT1 inhibits cellular senescence and protects cellular function in various cell lines [13,16]. Therefore, we examined SIRT1 expression in the hippocampus of SAMP8 with or without DHT treatment, at 12 weeks of age. DHT treatment increased the protein and mRNA expression of SIRT1 in SAMP8 (Figure 2D). To investigate further the involvement of AR, we examined the expression of AR in SAMR1 and SAMP8 brains. The expression of AR was more abundant in the hippocampus than in other brain regions of SAMR1 and SAMP8 (Figure 2E).

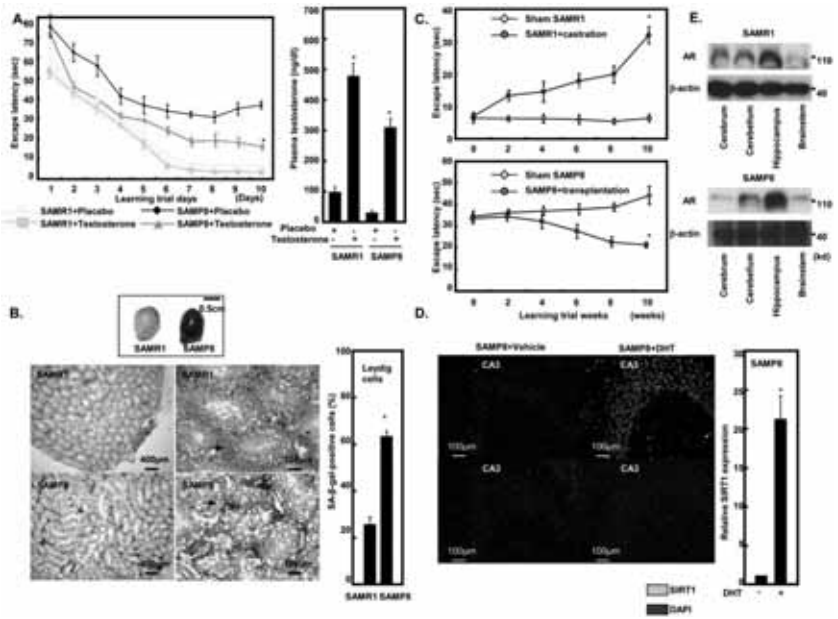

Figure 2. Supplementation of testosterone improves cognitive function in SAMP8 mice. A. Escape latency and plasma testosterone level of male SAMR1 (N = 10) and SAMP8 mice (N = 10) at 18 months of age. These mice were implanted subcutaneously with a placebo or a 21-day-release 2.5 mg testosterone pellet in the dorsal neck. **B.** Number of SA-βgal-stained Leydig cells in testes in SAMR1 and SAMP8. Arrows indicate Leydig cells. Representative SA-βgal-stained testes from SAMR1 and SAMP8. **C.** Escape latency of castrated SAMR1 (upper, N = 5) and recipient SAMP8 (lower, N = 5). Observation (0–10 weeks) was started from 3 weeks after operation. **D.** SIRT1 expression in hippocampus of SAMP8 with or without DHT treatment. Immunofluorescent staining for SIRT1 (green) and DAPI (blue). **E.** Expression of AR in SAMR1 and SAMP8 brains. (*p<0.05).
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Oxidative stress was increased in hippocampal cells of SAMP8

Oxidative stress may be closely related to senescence and age-related diseases. Also, an increase in oxidative stress has been suggested to be one of the earliest pathological changes in the brain in conditions with cognitive impairment such as AD [17]. Then, we examined the level of oxidative stress, using the SAMR1 and SAMP8 hippocampus at 12 weeks of age. SAMP8 hippocampus showed an increase in the level of oxidative stress compared with SAMR1 as judged by detection of carbonylated proteins. DHT treatment decreased carbonylated proteins in the SAMP8 hippocampus (Figure 3A). In parallel, the concentration of the neurotransmitter acetylcholine in hippocampal lysates was decreased in SAMP8 compared with that in SAMR1, and DHT treatment prevented this (Figure 3B).

Testosterone and DHT acts on vascular endothelial cells and stimulates the PI3K/Akt pathway, leading to eNOS activation through direct interaction of AR [18,19]. The eNOS/SIRT1 axis is recognized as one of the fundamental determinants of endothelial senescence, and SIRT1 acts as a driver of cellular stress resistance [20]. To examine the influence of DHT treatment on endothelial cells, we determined the degree of senescence and the expression of SIRT1 in endothelial cells around the CA3 area of the hippocampus. DHT-treated SAMP8 showed a reduction of SA-βgal-stained endothelial cells and increased SIRT1 expression compared to untreated SAMP8 (Figure 3C and D). To confirm that these cells were endothelial cells, not neuronal cells, cerebral microvessels were isolated from SAMR1 and SAMP8. In parallel with immunohistological staining, SAMP8 showed a reduction of SIRT1 expression compared to SAMR1, and DTH treatment increased SIRT1 expression compared to that in untreated SAMP8 (Figure 3E). These results suggest that vascular endothelial senescence in the hippocampus may be related to the memory deficit in SAMP8. Since testosterone and DHT activates eNOS, a NOS inhibitor, N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME), and N^5-(1-Imino-3-butenyl)-L-ornithine (L-VNIO), a

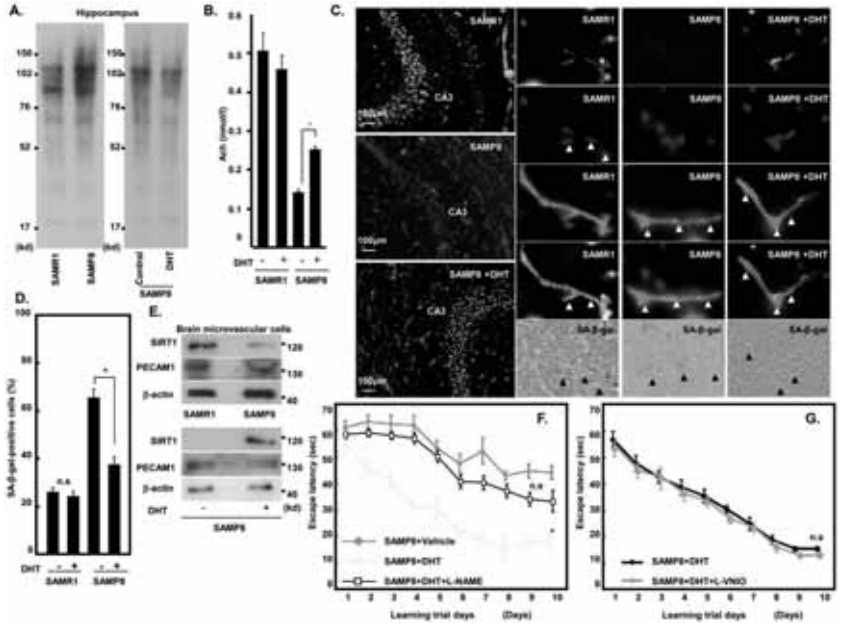

Figure 3. Senescent endothelial cells of hippocampus are decreased by treatment with DHT. A. Oxidative stress level was measured by detection of carbonyl groups introduced into proteins. **B.** Acetyl-choline concentration was measured by a colorimetric method. **C.** SA-βgal-stained endothelial cells and SIRT1 expression in CA3 area of hippocampus in SAMR1 and SAMP8 with or without DHT treatment. Immunofluorescent staining for SIRT1 (green), PECAM-1 (red), and DAPI (blue). **D.** Number of SA-βgal-stained endothelial cells in CA3 area of hippocampus in SAMR1 and SAMP8 with or without DHT treatment. **E.** Expression of SIRT1, PECAM-1, and β-actin was analyzed using cerebral micro vascular cells. **F.** Escape latency of SAMR1 (N = 10) and SAMP8 mice (N = 10). Male mice were treated daily for 2 weeks with DHT (500 µg s.c) and L-NAME (20 mg/kg gavage) before trials. **G.** Escape latency of SAMR1 (N = 5) and SAMP8 mice (N = 5). Male mice were treated daily for 2 weeks with DHT (500 µg s.c) and L-VNIO (5 mg/kg IP) before trials. (*p<0.05, n.s: not significant).
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selective neuronal NOS (nNOS) inhibitor, were applied to examine the involvement of NOS in this process. L-NAME abrogated the effects of DHT on cognitive function (Figure 3F). In contrast, L-VNIO did not change the effect of DHT (Figure 3G). These results suggest that eNOS/SIRT1 in endothelial cells may play an important role in the protective effect of testosterone against senescence of the hippocampus.

SIRT1 plays an important role in the protective effect of testosterone against endothelial senescence

Following the animal experiments, we examined whether testosterone inhibited endothelial senescence *in vitro* using cultured cells. We induced premature endothelial senescence by addition of H_2O_2 100 μmol/L for 1 hour. DHT or testosterone treatment inhibited SA-βgal activity and the morphological appearance of senescence (Figure 4A). We observed that oxidative stress decreased eNOS and SIRT1 and increased PAI-1 expression, and DHT or testosterone treatment prevented these changes and increased the phosphorylation of eNOS at Ser1177 (Figure 4B). Overexpression of SIRT1 significantly inhibited oxidative stress-induced senescence, and DHT accelerated the effect of SIRT1 through phosphorylation of eNOS at Ser1177 (Figure 4C). To determine the role of endogenous SIRT1, DHT-treated endothelial cells were transfected with SIRT1 siRNA or treated with sirtinol, a chemical inhibitor of SIRT1. SIRT1 siRNA or sirtinol abrogated the effect of DHT on SA-βgal activity (Figure 4D). We previously reported that testosterone activated eNOS [18], and eNOS activation promoted SIRT1 expression [21]. Accordingly, we examined the role of eNOS in the protective effect of testosterone. We observed that DHT or testosterone treatment increased NOS activity that was reduced by oxidative stress (Figure 4E). Treatment with eNOS siRNA or L-NAME decreased the inhibitory effect of DHT on a senescent phenotype in parallel with SIRT1 expression (Figure 4F and G). These results indicate that eNOS/SIRT1 play an important role in the protective effect of testosterone and DHT against a senescent phenotype.

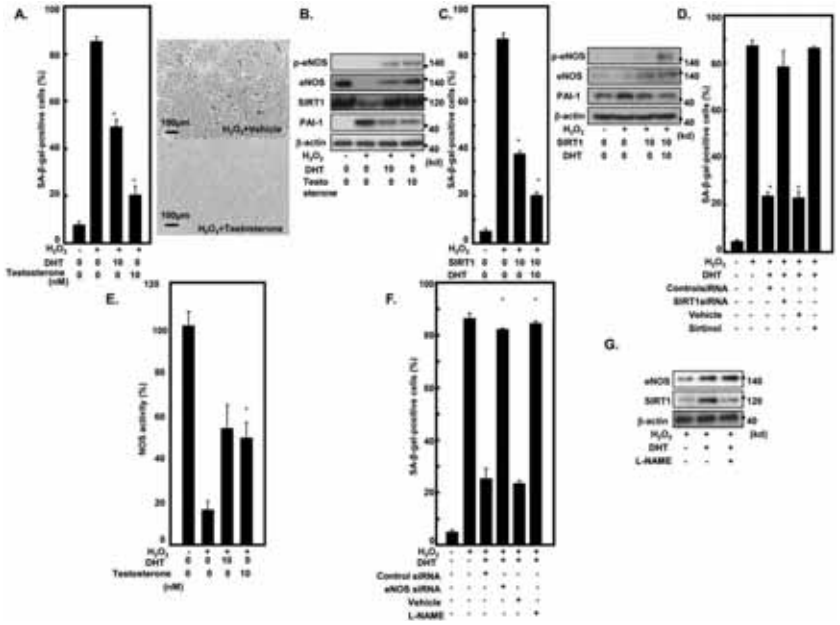

Figure 4. Testosterone inhibits oxidative stress-induced endothelial senescence through eNOS/SIRT1. A. Testosterone inhibited SA-βgal activity and senescent morphological appearance induced by hydrogen peroxide (100 μmol/L). **B.** Expression of eNOS, SIRT1, and PAI-1 in hydrogen peroxide (100 μmol/L)-treated HUVEC under treatment with DHT or testosterone. **C.** Overexpression of SIRT1 and DHT reduced SA-βgal activity. eNOS expression was increased by overexpression of SIRT1, and DHT increased phosphorylation of eNOS (Ser1177). **D.** SIRT1 inhibition by siRNA or sirtinol (100 μmol/L) abrogated the effect of testosterone on SA-βgal activity. **E.** Treatment with testosterone or DHT increased eNOS activity. **F.** eNOS inhibition by siRNA or L-NAME (10 mM) abrogated the effect of testosterone on SA-βgal activity. **G.** Treatment with L-NAME decreased SIRT1 expression in DHT-treated HUVEC. (*$p<0.05$, N = 3).
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Senescent endothelial cells induced by oxidative stress promoted neuronal senescence

Finally, we hypothesized that endothelial senescence promotes senescence of adjacent neuronal cells. To test this hypothesis, we used a co-culture system of endothelial cells (HUVEC) with neuronal cells (mouse hippocampal neuronal cells; MHC) (Figure 5A). Both cells were co-cultured, but were separated by a microporous polycarbonate membrane, for 10 days after endothelial cells were treated with hydrogen peroxide, and the senescent phenotype of MHC was analyzed. We found that the number of SA-βgal-positive cells and the senescent appearance of MHC were increased, and the concentration of acetylcholine in cells was decreased by co-culture with senescent endothelial cells (Figure 5B). In parallel with this, MHC showed increased PAI-1 and p53, and decreased SIRT1 expression (Figure 5C). We also found that senescent endothelial cells showed increased expression of inflammatory cytokines such as IL-6, IL-8, MCP-1, and TNF-α (Figure 5D). Both MHC and HUVEC, or HUVEC alone were treated with testosterone at 3 days before HUVEC were treated with hydrogen peroxide, and both cells were co-cultured for 10 days, and the senescent phenotype of MHC was analyzed. We found that the number of SA-βgal-positive MHC was decreased by treatment of HUVEC with testosterone irrespective of the treatment of MHC with testosterone (Figure 5E). In addition, we found that a SIRT1 activator, resveratrol treatment rescued the senescent phenotype of MHC (Figure 5F). These results suggest that senescent endothelial cells exhibit a senescence-associated secretory phenotype [22], induce neuronal senescence, and testosterone rescues it through up-regulation of SIRT1 (Figure 5G).

Discussion

Testosterone level and cognitive function show a decline with age in men. A series of evidence suggests that this association is not just age related [23]. Results from cell culture and animal studies provide evidence that testosterone could have protective effects on brain function, especially in the hippocampus [24]. Here, we demonstrated that administration of testosterone restored cognitive function in male SAMP8 in association with improvement of the senescent phenotype in the hippocampus and cerebral vessels.

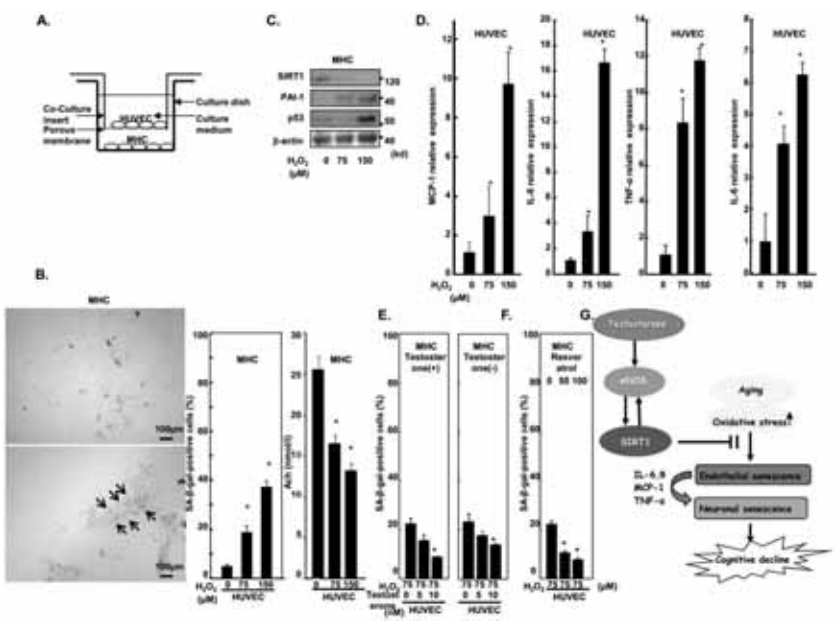

Figure 5. Oxidative stressed-induced endothelial cell senescence promotes adjacent neuronal cell senescence. A. Co-culture cell culture dish. **B.** Number of SA-βgal-stained MHC and senescent appearance of MHC were increased, and acetyl-choline concentration was decreased by co-culture with senescent endothelial cells. Senescent MHC are indicated by arrows. **C.** Expression of SIRT1, PAI-1, p53, and β-actin in MHC co-cultured with senescent endothelial cells. **D.** Expression of IL-6, IL-8, MCP-1, and TNF-α in endothelial cells were analyzed by RT-PCR. **E.** The number of SA-βgal-stained MHC was decreased by treatment with testosterone in both MHC and HUVEC (MHC, testosterone (+)), or HUVEC (MHC, testosterone (−)) alone. **F.** Resveratrol decreased the number of SA-βgal-stained MHC co-cultured with senescent endothelial cells. (*$p<0.05$, N = 3). **G.** Hypothetical signal transduction pathways of testosterone in endothelial cells.
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We also showed that testosterone ameliorated endothelial senescence through eNOS/SIRT1-dependent mechanisms *in vitro*. The present study demonstrated that testosterone and SIRT1 interacts with each other and inhibited the senescence of hippocampal vascular and neuronal cells, suggesting that testosterone replacement therapy is a treatment option for cognitive decline with aging.

Testosterone may act in part through aromatase-dependent conversion to estradiol. To estimate a direct effect of androgens through AR, testosterone and DHT were used in this study. Both compounds showed significant protective effects on cognitive function.

In the present study, we used SAMP8 mice. SAMP is comprised of 14 strains derived from selective inbreeding of the AKR/J strain. SAMP8 exhibits age-related learning and memory deficits, as well as amyloid-like deposits in the brain [25]. Increased expression of hyperphosphorylated tau has also been detected in SAMP8 [26]. Given such features, SAMP8 has been proposed as a plausible age-associated AD animal model, and a suitable rodent model for studying the molecular mechanism underlying cognitive impairment [27]. A previous study has shown an age-related decrease in serum testosterone in SAMP8, and suggesting that impaired cognitive function in SAMP8 is due to reduced testosterone [28]. We observed that AR expression was abundant in the hippocampus of SAMR1 and SAMP8. Several studies have demonstrated that testosterone has a neuroprotective effect through AR in the hippocampus [29,30], and testosterone induced NO productions via AR-dependent activation of eNOS in endothelial cells [18,19].

Accumulating evidence suggests that NAD^+-dependent deacetylase SIRT1 play an essential role for cellular senescence and cognitive function. SIRT1 modulates endothelial cellular senescence [13], and overexpression of SIRT1 exhibits neuroprotective effects in hippocampus, and cognitive function of *Sirt1*-KO mice is markedly impaired [10,31,32].

The precise etiologic mechanism of the cognitive decline with aging is unclear, but it has been identified that cardiovascular risk factors are associated with a higher incidence of cognitive impairment [33]. In addition, age-associated vascular inflammation is an early manifestation of chronic stress responses, i.e. overloading of ROS on endothelial cells [34]. Indeed, SAMP8 showed enhancement of oxidative stress and a senescent phenotype in the hippocampus. Notably, senescent endothelial cells were increased in the hippocampus of SAMP8 accompanied by a reduction of SIRT1, and L-NAME abrogated the effect of DHT on cognitive function. Therefore, we hypothesized that testosterone influenced cerebral endothelial senescence via eNOS/SIRT1, and that pro-inflammatory cytokines, which were derived from senescent endothelial cells, promoted senescence in adjacent neuronal cells. Indeed, we observed that testosterone induced eNOS activity, and subsequently increased SIRT1 expression in endothelial cells. Inhibition of eNOS/SIRT1 abrogated the effect of testosterone on endothelial senescence. In a co-culture system, we found that senescent endothelial cells promoted senescence of adjacent neuronal cells, and treatment of endothelial cells with testosterone inhibited senescence of adjacent neuronal cells. It can reasonably be speculated, therefore, that SIRT1 may exert salutary actions against cognitive decline with aging by preventing a senescence-associated secretory phenotype of endothelial cells. Because L-NAME is a non-selective inhibitor of NOS, it is possible that the effect of L-NAME might be in part a result of inhibition of nNOS in concert with eNOS. However, a specific nNOS inhibitor, L-VNIO did not change the effect of DHT in SAMP8. In co-culture experiments, we found that treatment with resveratrol or testosterone did not change the expression or activation of nNOS in MHC (Figure S1C and D). Further studies are needed to address the differential role of eNOS and nNOS, and the exact role of SIRT1 *in vivo*.

In conclusion, supplementation of testosterone prevented cognitive impairment of SAMP8, in which testosterone secretion was decreased in association with the senescence of testis Leydig cells, through an eNOS/SIRT1-dependent mechanism. Unprecedented reversal of the senescent hippocampal changes and vascular protection may justify exploration of a neuronal rejuvenation strategy by utilizing testosterone for the prevention of cognitive decline with aging, particularly through up-regulation of eNOS/SIRT1.

Methods

Materials

Dihydrotestosterone (DHT), testosterone, and N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME) were purchased from Sigma (St. Louis, MO). Hydrogen peroxide (H_2O_2) and resveratrol were purchased from Wako Pure Chemical Industries (Osaka, Japan). Testosterone and placebo pellets were purchased from Innovative Research of America (Sarasota, FL). N^5-(1-Imino-3-butenyl)-L-ornithine (L-VNIO) was purchased from Enzo Life Sciences (Plymouth Meeting, PA).

Cell culture

Human umbilical vein endothelial cells (HUVEC) were purchased from CAMBREX (Walkersville, MD). Population doubling levels (PDL) were calculated as described previously [35], and all experiments were performed at PDL of 10–11. In our preliminary experiments, HUVEC were cultured in EBM without phenol red (Clonetics, Walkersville,MD) with 10% dextran-charcoal-stripped serum to remove steroids from the culture medium. This condition, however, induced marked growth arrest and an increase in senescent cells. Consequently, we performed all experiments in EBM-2 (Clonetics) with 10% complete serum-supplemented medium.

Animal experiments

The animal experiments were approved by our institutional review board (animal experiments ethics board, Graduate School of Medicine and Faculty of medicine, The university of Tokyo (approval ID: M-P-09-056)). Senescence-accelerated mice prone (SAMP) 8 and control senescence-accelerated mice resistant (SAMR) 1 male mice were all housed and maintained in a room at 22±2°C with automatic light cycles (12 h light/dark) and relative humidity of 40–60%. Mice were purchased from Japan SLC, Inc. (Shizuoka, Japan). Food and tap water were provided ad libitum throughout the study. In the water maze test of this study, a group of male SAMR1 (N = 10) and SAMP8 (N = 10) was first tested. Male mice of 12 weeks of age were treated daily for 2 weeks with DHT (500 μg in 0.05 ml/mouse) by subcutaneous injection (s.c.) in the neck before the water maze test. Male mice of 18 months of age underwent subcutaneously implantation of a placebo (N = 5) or a 21-day-release 2.5 mg testosterone (N = 5) pellet into the dorsal neck region. L-NAME was given by gavage once a day (20 mg/kg) [36]. L-VNIO was given by intraperitoneal injection (0.5 mg/kg) [37]. Small fragments of testis tissue fragments from SAMR1 were grafted under the back skin of castrated male SAMP8 as previously described [38]. Briefly, after removal of the capsule and obvious connective tissue, donor testes were cut into small fragments. Testis fragments were kept in Dulbecco's modified Eagle's medium (Gibco Lab Inc., Grand Island, NY, USA) on ice until grafting. SAMR1 were anesthetized and castrated, and testicular tissue fragments were grafted under the back skin of SAMP8. Mice were anesthetized with enflurane, killed by cervical dislocation, and trunk blood collected within 1 min. The blood was centrifuged and plasma testosterone was measured by radioimmunoassay method. The brain was removed for histological examination, after systemic perfusion with phosphate-buffered saline (PBS). For immunohistochemical studies, mouse brains were processed and labeled with anti-amyloid-β antibody (Immuno-Biological Laboratories Co., Ltd., Gunma, Japan) to visualize extracellular amyloid plaques, anti-NeuN antibody (Millipore, Billerica, MA) to assess pyramidal cell number, or DAPI (Dojindo Molecular Technologies, Inc., Tokyo, Japan) for nuclear staining. The primary antibody was purified rat anti-mouse CD31 (platelet endothelial cell adhesion molecule; PECAM-1) monoclonal antibody from Pharmingen (San Jose, CA, USA). Secondary antibodies (Alexa Fluor 488 donkey anti-rat IgG and Alexa Fluor 594 donkey anti-rat IgG) and antifade reagent were from Molecular Probes (Invitrogen). Fluorescent images were analyzed using a fluorescence microscope (BZ-9000, KEYENCE, Osaka, Japan).

Plasmids and siRNA transfection

Proliferating cells were washed three times with growth medium and exposed to the indicated concentrations of testosterone or DHT diluted in medium. pIRES-SIRT1 plasmid was provided by Dr. M. Takata [39], and Dr. R.A. Weinberg [40]. Each plasmid was overexpressed by transfection using Lipofectamine LTX and PLUS reagents (Invitrogen) for HUVEC according to the manufacturer's instructions. Proliferating cells were transfected with each siRNA using siIMPORTER (Upstate Cell Signaling Solutions). siRNAs for SIRT1 (GAT GAA GTT GAC CTC CTC A [41] and TGA AGT GCC TCA GAT ATT A), and eNOS were purchased from Santa Cruz Biotechnology, Inc.

Immunoblotting and immunoprecipitation

Cells were lysed on ice for 1 hour in buffer (50 mmol/L Tris-HCl, pH 7.6, 150 mmol/L NaCl, 1% NP-40, 0.1% SDS, 1 mmol/L dithiothreitol, 1 mmol/L sodium vanadate, 1 mmol/L phenylmethylsulfonyl fluoride, 10 μg/mL aprotinin, 10 μg/mL leupeptin and 10 mmol/L sodium fluoride). Equal amounts of protein were separated by SDS/PAGE gel electrophoresis and transferred to nitrocellulose membranes. After blocking, the filters were incubated with the following antibodies; anti-SIRT1, anti-nNOS, anti-AR (Cell Signaling, Danvers, MA), anti-eNOS (BD Transduction Laboratories, San Jose, CA), anti-PAI-1 (Molecular Innovations, Southfield, MI), anti-PECAM-1 (Santa-Cruz Biotechnology, CA), and anti-ß-actin (Sigma). After washing and incubation with horseradish peroxidase-conjugated anti-rabbit or anti-mouse IgG (Amersham, Piscataway, NJ) for 1 hour, antigen-antibody complexes were visualized by using an enhanced chemiluminescence system (Amersham).

Senescence-associated ß-galactosidase (SA-ßgal) staining

HUVEC were pretreated with diluted EGM-2 medium for 3 day. HUVEC were then washed three times with EGM-2 and treated for 1 hour with 100 μmol/l H_2O_2 diluted in EGM-2. After treatment, HUVEC were trypsinized, re-seeded at a density of 1×10^5 in 60-mm dishes, and cultured with EGM-2 containing DHT or testosterone for 10 days. The proportion of SA-ßgal-positive cells was determined as described by Dimri et al [42].

NOS activity assay

NOS activity was determined using an NOS assay kit (Calbiochem) according to the manufacturer's instructions.

Measurement of acetylcholine

The concentration of acetylcholine was measured with a choline/acetylcholine quantification kit (BioVision, CA, USA) according to the manufacturer's instructions.

Real-time quantitative reverse transcription PCR

Total RNA was isolated with ISOGEN (Nippon Gene Inc., Toyama, Japan). After treatment with Rnase-free Dnase for 30 min, total RNA (50 ng/μl) was reverse transcribed with random hexamers and oligo d(T) primers. The expression levels of SIRT1, IL-6, IL-8, MCP-1, and TNF-α relative to ß-actin were determined by means of staining with SYBR green dye and a LineGene fluorescent quantitative detection system (Bioflux Co., Tokyo, Japan). The following primers were used: SIRT1 F 5′-CCTGACTTCAGGTCAAGGGATGGTA-3′, R 5′-CTGATTAAAAATATCTCCTCGTACAG-3′; ß-actin F 5′-TGGGCATGGGTCAGAAGGAT-3′, R 5′-AAGCATTTGCGGTGGACCAT-3′; IL-6 F 5′-GGGAAGGTGAAGGTCGG-3′, R 5′-TGGACTCCACGACGTACTCAG-3′, IL-8 F 5′-CTGGCCGTGGCTCTCTTG-3′, R 5′-CCTTGGCAAAACTGCACCTTT-3′; TNF-α F 5′-GTAGCCCACGTCGTAGCAAAC-3′, R 5′-CTGGCACCACTAGTTGGTTGTC-3′; MCP-1 F 5′-CATTGTGGCCAAGGAGATCTG-3′, R 5′-CTTCGGAGTTTGGGTTTGCTT-3′.

Co-culture system

For these experiments, co-culture dishes were used as outlined in Figure 5A. They were obtained from BD Biosciences (Erembodegem, Belgium) with a 6-well format. HUVEC were treated with H_2O_2 (100 μM) for 1 h and cultured on the permeable microporous (0.4 μm) membrane in the insert, and mouse hippocampus neuronal cells on the base of the culture dish, kept physically separated but allowing the passage of micromolecules through the porous membrane for 10 days. Mouse hippocampus neuronal cells were purchased from DS Pharma Biomedical Inc. (Osaka, Japan).

Quantitative analysis of amyloid β

Measurement of amyloid β was performed using an amyloid β (1–40) (FL) assay kit (Immuno-Biological Laboratories Co., Ltd., Gunma, Japan) according to the manufacturer's instructions.

Morris water maze test

The procedure of the Morris water maze test was described previously [43]. SAMR1 and SAMP8 mice were trained to find a visible platform with three trials on the first day, and then tested to find the hidden platform for 10 consecutive days. In each trial, the mice were allowed to swim until they found the hidden platform, or until 2 min had passed, and the mouse was then guided to the platform. On the test days, the platform was hidden 1 cm beneath the water. The escape latency was recorded by a video camera. The swim speed of each mouse was calculated by means of a video tracking system. Probe tests were performed on the 10^{th} day. During percent time quadrant test, the platform was removed from the pool. Mice were started in a position opposite the location of the platform position and allowed to swim for 60 seconds.

Open field test

The open field test fear response to novel stimuli was used to assess locomotion, exploratory behavior, and anxiety. Open field test protocols were modified from that of Lukacs et al [44]. The open field test consisted of a wooden box (60×60×60 cm) and was indirectly illuminated by two fluorescent lights. A 10 cm area near the surrounding wall was delimitated and considered the periphery. The rest of the open field was considered the central area. The distance travelled, the ratio of the distance travelled in the central area/total distance travelled, and the time in the center of the open- field were analyzed as a measure of anxiety-like behavior. During the test, mice were allowed to move freely around the open field and to explore the environment for 15 min.

Isolation of cerebral microvessels

Cerebral microvessels were isolated from the remaining brain tissue as previously described by Zhang et al [45] with minor modifications. Brain tissue, devoid of large vessels, was homogenized in ice cold PBS with Dounce homogenizer and centrifuged twice at 2000 g at 4°C. The supernatant, containing the parenchymal tissue, was discarded. The pellet was resuspended in PBS and centrifuged as described above. The resulting pellet was resuspended and layered over 15% Dextran (in PBS) (Sigma, St.Louis, MO) and centrifuged at 4500 g for 30 minutes at 4°C. The top layer was aspirated and discarded and the remaining pellet resuspended in 15% Dextran and centrifuged. The final pellet was resuspended in 1% bovine serum albumin (BSA), the suspension was then passed though a 40-µm nylon mesh (BD Falcon). Microvessels retained on the mesh were washed with BSA/PBS and collected by centrifugation at 900 g for 10 minutes at 4°C.

Data analysis

Values are shown as mean ± S.E.M in the text and figures. Differences between the groups were analyzed using one-way analysis of variance, followed by Bonferroni test. Probability values less than 0.05 were considered significant.

Supporting Information

Figure S1 Testes of SAMP8 and SAMR1 mice and role of nNOS in neuronal senescence. A. Testis weight of SAMR1 and SAMP8 with or without testosterone. **B.** Photographs of SAMR1 donor and SAMP8 recipient mice. White arrows indicate operation scar. **C.** Expression of nNOS in MHC treated with resveratrol or testosterone under the oxidative stress. **D.** Activity of nNOS in MHC treated with resveratrol or testosterone under the oxidative stress. ($^{*}p<0.05$, N = 3, n.s: not significant).
(TIF)

Acknowledgments

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Author Contributions

Conceived and designed the experiments: HO MA YO. Performed the experiments: HO TA. Analyzed the data: HO SO KI ME MA. Contributed reagents/materials/analysis tools: TK MS. Wrote the paper: HO MA.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Association of polypharmacy with fall risk among geriatric outpatients

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Aim: To investigate the association of fall risk with comorbidities and medications in geriatric outpatients in a cross-sectional design.

Methods: A total of 262 outpatients (84 men and 178 women, mean age 76.2 ± 6.8 years) were evaluated. Physical examination, clinical histories and medication profile were obtained from each patient. History of falls in the past year, 22-item fall risk index, 13-point simple screening test for fall, and time interval of one-leg standing test were examined as markers of fall risk.

Results: On univariate analysis, older age, female sex, hypertension, osteoporosis, history of stroke, number of comorbidities, use of antihypertensives, aspirin, bisphosphonates, hypnotics and number of prescribed drugs were significantly associated with either of four indices. On multiple regression analysis, the number of drugs was associated with all of the four indices, independent of other factors associated in the univariate analysis. The association of number of drugs with fall risk indices was stepwise.

Conclusion: In geriatric outpatients, polypharmacy rather than number of comorbidities was associated with fall risk. Prospective and intervention studies are needed to clarify the causal relationship between polypharmacy, comorbidities and fall risk. **Geriatr Gerontol Int 2011; 11: 438–444.**

Keywords: elderly, fall, polypharmacy, risk factors.

Introduction

Falls occur in more than 10% per year of community-dwelling elderly people,[1–3] and approximately 10% of falls lead to bone fracture. Also, falls are reported to be the third leading cause of a bedridden state among the elderly.[4] Previous studies assessed the risk factors of falls in community-dwelling elderly,[5–7] and history of falls, physical ability and living environment were found to be predictors of fall risk. However, these studies have not sufficiently assessed medical comorbidities and therapeutic drugs as risk factors of falls, although many elderly subjects have chronic illness such as hypertension, diabetes, cardiovascular diseases, osteoporosis and insomnia. Falls in patients on medications are more complicated, because some drugs such as aspirin could cause serious bleeding when they have injurious falls, and others such as antihypertensives[8] and hypoglycemic agents[9,10] could cause falls. Therefore, it is important to evaluate the association between fall risk and medical comorbidities or therapeutic drugs. Multiple drug use or polypharmacy is frequently seen in elderly patients because most of them have multiple chronic diseases to be treated. Moreover, inappropriate drug use is frequently seen in patients with polypharmacy.[11]

In Japan, a 22-item fall risk index questionnaire covering physical, cognitive, emotional and social aspects of functioning and environmental factors was established.[7] Also, by evaluating the validity of this questionnaire in community-dwelling older people, a simple screening test consisting of five items and total of 13 points was constructed.[2] Using these questionnaires and one-leg standing test[12] as indices of fall risk, we investigated the association of fall risk with comorbidities and medications in geriatric outpatients.

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Methods

Patients

A total of 262 consecutive outpatients aged 65 years or older were enrolled who were referred for the treatment of chronic diseases such as hypertension, dyslipidemia, diabetes and osteoporosis every 2–4 weeks at a geriatric clinic located in Tokyo, Japan. All the patients were able to walk independently and were in stable conditions. Patients who had acute illness or overt dementia were excluded. Anthropometric and medical information were obtained including past history of stroke, myocardial infarction and malignancy. All the medical information including diagnoses and the prescribed drugs were obtained from the medical chart recorded by their physicians in charge. The patients whose prescriptions were changed within 1 month before enrollment were excluded. Accordingly, the included subjects had been taking the same drugs for at least 1 month before enrollment.

Ethical consideration

This study was approved by the Institutional Review Board of the Research Institute of Aging Science. We obtained written consent from all participants and/or their guardians.

Four indices of fall tendency

On the day of the enrollment, all patients were examined for four indices to investigate the fall risk: (i) history of fall in the past year (no or yes); (ii) a 22-item portable fall risk index questionnaire developed by the working group of the Ministry of Health, Labor and Welfare (see Appendix I);[7] (iii) 13-point simple screening test to assess the risk of fall which was also developed by the same working group (see Appendix II);[2] and (iv) duration time of open-eye one-leg standing test.

Table 1 Characteristics of study subjects

Age			76.2 ± 6.8 years old
Male	32.1%	(*n* = 84)	75.3 ± 6.6 years old
Female	67.9%	(*n* = 178)	76.6 ± 6.8 years old
Comorbidities			
Hypertension	64.1%	(*n* = 168)	
Dyslipidemia	47.7%	(*n* = 125)	
Diabetes	18.7%	(*n* = 49)	
Osteoporosis	24.0%	(*n* = 63)	
History of stroke	6.5%	(*n* = 17)	
History of myocardial infarction	3.4%	(*n* = 9)	
History of cancer	5.3%	(*n* = 14)	
Number of comorbidities	1.90 ± 1.09		
Drug use			
Antihypertensive use	57.6%	(*n* = 151)	
Calcium channel blockers	39.3%	(*n* = 103)	
Angiotensin-II receptors blockers	34.7%	(*n* = 91)	
Beta-blocker	6.9%	(*n* = 18)	
Angiotensin converting enzyme inhibitors	5.7%	(*n* = 15)	
Diuretics	5.0%	(*n* = 13)	
Statins	24.4%	(*n* = 64)	
Sulfonylureas	6.5%	(*n* = 17)	
Aspirin	20.6%	(*n* = 54)	
Vitamin D	4.6%	(*n* = 12)	
Bisphosphonates	6.5%	(*n* = 17)	
H_2-blockers	9.9%	(*n* = 26)	
Proton pump inhibitors	6.5%	(*n* = 17)	
Hypnotics	18.3%	(*n* = 48)	
Number of drugs	3.4 ± 2.8		

Values are expressed as mean ± standard deviation.

Experience of falls in the past year is an established and powerful tool for assessing fall risk,[2] and was reported by the patient and/or his or her family members. Duration time of one-leg standing test, which can be carried out in a narrow limited space of the outpatient office, was measured using the leg with the eyes open, until the raised leg was put down on the floor. We examined both right and left legs once for each, and the longer of the two measurements was used for statistical analysis.[12]

Data analysis and statistical methods

Values are expressed as means ± standard deviation. In order to analyze the relationship between each fall risk index and comorbidities or drugs, variables were compared using Student's *t*-test or the χ^2-test as appropriate. The correlations between the two continuous variables were analyzed using Pearson's *r* coefficient. In multivariate analysis, logistic regression analysis was performed for history of falls and multiple regression analysis for the remaining three indices, to determine the association of fall risk with the variables. Differences between the groups of number of drugs and three indices of fall tendency were analyzed using one-factor ANOVA followed by Tukey–Kramer test. Data were analyzed using JMP version 8.0.1.

Results

The characteristics of the study subjects are shown in Table 1. Calcium channel blockers, angiotensin-II receptor blockers (ARB), statins and aspirins were prescribed in more than 20% of all the patients. Calcium channel blockers prescribed in this study were all long-acting agents, and aspirin dosage prescribed were all 100 mg. Less than 10 patients received insulin therapy, took non-steroidal anti-inflammatory drugs or anticoagulants. No patients were taking neuroleptics, nor antiparkinsonian drugs. Patients prescribed five drugs or more were 36.3%.

On univariate analyses, the number of drugs was the only factor which was significantly associated with history of falls in the past year (no/yes 3.2 ± 2.6/4.0 ± 3.1 drugs, $P < 0.05$). Older age, female, hypertension, osteoporosis, history of stroke, the number of comorbidities, use of ARB, aspirin, bisphosphonates, hypnotics and number of prescribed drugs were significantly associated with either one of three indices of fall risk (Table 2). Number of drugs was significantly correlated with three scores excluding the question on polypharmacy. Number of comorbidities was significantly associated with age ($r = 0.32$, $P < 0.0001$) and with the number of drugs ($r = 0.62$, $P < 0.0001$).

Next, on multivariate analyses, the questionnaire asking "whether taking five or more drugs" were excluded from the fall risk index and the simple screening test. Therefore, the fall risk index was analyzed by a total of 21 items and the simple screening test by a total of 11 points in this analysis. To evaluate the association of four fall risk indices with comorbidities and drugs, all the variables that were significantly associated in either one of four univariate analyses were entered into the model. As shown in Table 3, the number of drugs was the only factor which was significantly associated with all four indices, independent of age, sex and other variables. Because each disease variable or drug variable might have affected the number of comorbidities or the number of drugs in this analysis, we just compared the number of comorbidities and the number of drugs to exclude the double count in next analysis. As shown in Table 4, the number of drugs was significantly associated with all of the four fall risk indices independent of age, sex and the number of comorbidities, while the number of comorbidies was inversely associated with history of falls and simple screening test. As shown in Figure 1, the association of the number of drugs with

Table 2 Univariate analysis of association between risk factor variables and three fall indices: fall-predicting score, simple screening test, one-leg standing test

		Fall risk index (points)	Simple screening test (points)	One-leg standing test (seconds)
Age		0.23***	0.23***	–0.46***
Female	No/Yes	7.0 ± 3.1/8.4 ± 4.0**	3.8 ± 3.3/4.7 ± 3.6*	19.7 ± 11.7/16.2 ± 11.7*
Hypertension	No/Yes	7.2 ± 3.6/8.4 ± 3.8*	3.7 ± 3.3/4.8 ± 3.5*	18.9 ± 11.1/16.2 ± 12.1
Osteoporosis	No/Yes	7.6 ± 3.7/8.9 ± 4.0*	4.3 ± 3.6/4.8 ± 3.1	17.9 ± 11.7/15.6 ± 11.9
History of stroke	No/Yes	7.8 ± 3.7/9.7 ± 4.1*	4.3 ± 3.4/5.6 ± 4.1	17.9 ± 11.8/8.5 ± 8.7**
Number of comorbidies		0.27***	0.17*	–0.24***
Antihypertensives				
	No/Yes	7.3 ± 3.6/8.5 ± 3.8*	3.7 ± 3.3/4.9 ± 3.5*	18.8 ± 11.4/15.9 ± 12.0
Angiotensin-II receptor blockers				
	No/Yes	7.6 ± 3.7/8.7 ± 3.8*	3.9 ± 3.4/5.2 ± 3.5**	17.6 ± 11.5/16.3 ± 12.2
Calcium channel blockers				
	No/Yes	7.6 ± 3.7/8.5 ± 3.7	4.1 ± 3.5/4.8 ± 3.5	18.8 ± 11.6/14.3 ± 11.6**
Aspirin	No/Yes	7.7 ± 3.8/8.9 ± 3.8*	4.1 ± 3.5/5.5 ± 3.7*	18.0 ± 11.8/13.5 ± 11.5*
Bisphosphonates	No/Yes	7.8 ± 3.8/9.9 ± 2.5*	4.3 ± 3.5/6.5 ± 2.7*	17.3 ± 11.8/14.9 ± 11.7
Hypnotics	No/Yes	7.6 ± 3.6/9.7 ± 4.1***	4.2 ± 3.6/5.2 ± 3.1	17.6 ± 11.9/15.2 ± 11.3
Number of drugs		0.30***†	0.27***†	–0.35***

*$P < 0.05$; **$P < 0.005$; ***$P < 0.0005$, compared to "No" by simple Student's *t*-test. For age, number of comorbidities and number of drugs, Pearson's correlation coefficient between each indices of fall tendency are shown. †For analysis of number of drugs, a questionnaire asking "whether taking five or more drugs" were excluded for analysis. Therefore, fall risk index was analyzed by a total of 21 items, and a simple screening test by a total of 11 points. For other risk factor variables shown in the table, mean ± standard deviations are expressed. Other risk factor variables not shown in this table showed no statistically significant relationship with either one of three indices.
[Table 2 amended after online publication date September 27, 2011]

Table 3 Multivariate analysis of association between risk factor variables and four fall indices: history of falls in a year, fall risk index, simple screening test, one leg standing test

		History of fall in a year (No = 0/Yes = 1) Odds ratio (95% CI)	Fall risk index (21 items)† β	Simple screening test (11 points)† β	One-leg standing test (s) β
Age		1.00 (0.96–1.05)	0.073	0.127	–0.370***
Female	(No = 0/Yes = 1)	2.36 (1.12–5.00)*	0.199**	0.197**	–0.149*
Hypertension	(No = 0/Yes = 1)	1.87 (0.61–5.76)	0.166	0.218*	–0.110
Osteoporosis	(No = 0/Yes = 1)	0.67 (0.28–1.60)	0.093	0.027	0.023
History of stroke	(No = 0/Yes = 1)	1.43 (0.38–5.45)	0.080	0.032	–0.083
Number of comorbities		0.60 (0.38–0.95)*	–0.062	–0.237*	–0.024
Antihypertensives					
	(No = 0/Yes = 1)	0.52 (0.18–1.54)	–0.141	–0.158	0.142
Aspirin	(No = 0/Yes = 1)	1.59 (0.72–3.50)	0.053	0.046	0.002
Bisphosphonates	(No = 0/Yes = 1)	2.27 (0.73–7.07)	0.055	0.105	0.033
Hypnotics	(No = 0/Yes = 1)	0.84 (0.33–2.15)	0.094	–0.018	0.084
Number of drugs		1.24 (1.07–1.45)*	0.247**	0.335***	–0.250**

*$P < 0.05$; **$P < 0.005$; ***$P < 0.0005$. Logistic regression analysis was performed for history of fall in a year, and multiple regression analysis for the remaining three. The risk factor variables used in these multivariate analyses were those associated in either of the four univariate analysis significantly. †The questionnaire asking "whether taking five or more drugs" were excluded from the scores in this analysis. Therefore, fall risk index were analyzed by a total of 21 items and simple screening test by a total of 11 points. CI, confidence interval; β, standardized regression coefficient.
[Table 3 amended after online publication date September 27, 2011]

Table 4 Multivariate analysis of association between number of comorbidities and drugs with four fall indices: history of falls in a year, fall risk index, simple screening test, one-leg standing test

	History of fall in a year (No = 0/Yes = 1) Odds ratio (95% CI)	Fall-risk index (21 items)† β	Simple screening test (11 points)† β	One-leg standing test (s) β
Age	1.00 (0.96–1.05)	0.101	0.115	–0.376***
Female (No = 0/Yes = 1)	1.73 (0.90–3.34)	0.207**	0.191**	–0.110
Number of comorbidities	0.63 (0.45–0.89)*	0.073	–0.137	–0.034
Number of drugs	1.23 (1.08–1.41)*	0.223*	0.316***	–0.233**

*$P < 0.05$; **$P < 0.005$; ***$P < 0.0005$. Logistic regression analysis was performed for history of fall in a year, and multiple regression analysis for the remaining three. †The questionnaire asking "whether taking five or more drugs" were excluded from the scores in this analysis. Therefore, fall risk index was analyzed by a total of 21 items and simple screening test by a total of 11 points. CI, confidence interval; β, standardized regression coefficient.

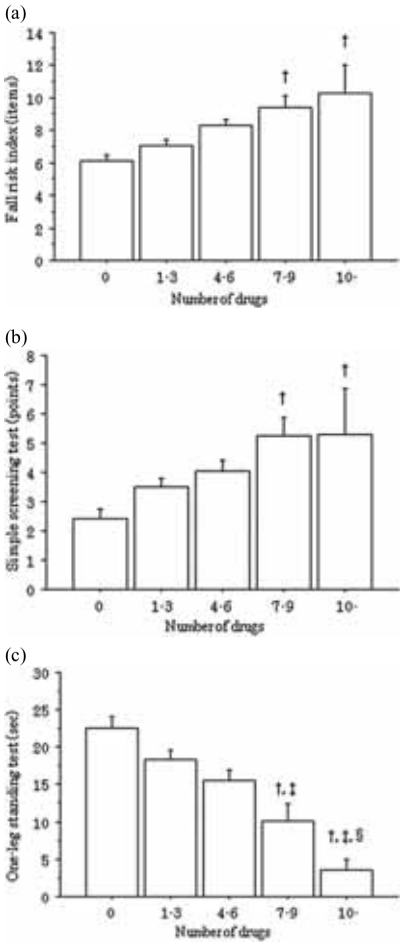

Figure 1 Averages of fall risk according to the number of drugs. (a) Fall risk index excluding the questionnaire concerning polypharmacy. (b) Simple screening test excluding the questionnaire concerning polypharmacy. (c) Duration time of one-leg standing test. The differences between the number of the drugs were compared through ANOVA, $P < 0.0001$ for (a), $P < 0.005$ for (b), $P < 0.0001$ for (c). For post-hoc analysis, $^{\dagger}P < 0.05$ vs 0 drug; $^{\ddagger}P < 0.05$ vs 1–3 drugs; $^{\S}P < 0.05$ vs 4–6 drugs. Values are expressed as mean ± standard error.

fall predicting score, simple screening test and duration time of one-leg standing test was stepwise.

Discussion

Epidemiological studies have assessed the risk of falls in community-dwelling people, but not in geriatric outpatients, who are likely to fall and need special consideration for the treatment of their illness. This cross-sectional study investigated the association between comorbidities, medications and fall risks in Japanese elderly outpatients and found that all four indices were significantly associated with the number of drugs. Because polypharmacy is frequently seen in patients with multiple comorbidities, this study compared the impact of the number of drugs with that of the number of comorbidities on fall risk, and found the significance of polypharmacy as fall risk in elderly outpatients.

In the present study, the number of comorbidities was inversely associated with the history of fall in the past year and with an 11-point simple screening test in the multivariate analysis. The reason is unclear; however, there are some speculations about this. None of the patients with four or more comorbidities ($n = 19$, 79.4 ± 5.2 years old) had history of fall in the past year. This accounts for the lower points of the simple screening test in these patients, because the history of fall consists of 5 points out of a total of 11 points in the simple screening test. So the question is why they had lower frequency of falling experiences, although they are at higher risk of falls according to fall risk index and one-leg standing test (9.6 ± 3.8 items and 8.6 ± 9.4 s, respectively). These patients may take care not to fall in their daily lives because of their consciousness of fall risk or frailty, or maybe due to elevated vigilance of caregivers and their constant physical assistances. They might have simply forgotten their fall experiences due to subclinical cognitive impairment, although demented patients were not included in this study. It is also possible that the patients who had more comorbidities and had fallen did not meet our inclusion criteria because of their recent injurious falls or their severe conditions.

Several medications and comorbidities have been reported as risks of fall.[6,7,13–19] Among these, diabetes,[9,10] imsonia,[13] hypnotics[13–15] and antihypertensive use[8] were not significantly associated with fall risk in our study. Only 20 patients (40.8% of diabetic patients) were prescribed hypoglycemic agents such as sulfonylurea ($n = 17$) or insulin ($n = 3$) in this study. Because hypoglycemia is considered to be the main cause of accidental falls in diabetic patients, relatively less prescription of hypoglycemic agents might have affected our result. The patients who were prescribed hypnotics tended to be at higher risk of falls in univariate analysis, which did show statistical significance. Also, antihypertensives such as diuretics are reported to increase the fall risk.[8] No

association between these drugs and fall risk in our study might be due to the small sample size. Other drugs such as major tranquillizers,[14] antidepressants[17,18] and antiparkinsonians[19] might increase fall risk; however, very few patients used these drugs in this study.

There are some other limitations. First, the causal relationship of the associations observed in this study is unknown because of the cross-sectional design. Polypharmacy has been regarded as a risk in several aspects in elderly patients. Previous studies have shown that adverse drug events were seen more frequently in the polypharmacy patients during their stay in the geriatric inpatient ward,[20] and polypharmacy was one of the important predictors for postdischarge mortality in elderly patients after emergent hospitalization.[21] Because patients with multiple diseases and in severer conditions are likely to take more medications, we used the number of comorbidities in analysis as fall risk variables. However, it is still unclear whether polypharmacy is a risk of falls independent of severity of each comorbidity. Interventional studies to reduce the number of drugs are needed to clarify the causal relationship between polypharmacy and fall risk. Second, this study did not evaluate the fall itself. The validity of four indices used in this study is well established as fall risk markers. However, prospective studies which evaluate the incidence of fall should be carried out in the future. Third, although the included subjects were receiving the same prescriptions for more than 1 month, the exact duration of each drug use or polypharmacy was not assessed in this study. Consequently, the long-term adverse effects over months or years seen in elderly patients should be more precisely investigated.

In summary, this study demonstrated that geriatric outpatients with polypharmacy were at higher risk of falls, consistent with the previous studies conducted in community-dwelling elderly. Our finding may add new information on pharmacotherapy in elderly patients with chronic diseases. Prospective studies and intervention studies examining the effect of drug reduction are needed in the future.

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Appendix I. 22 items of fall-predicting score (questionnaire)

Q1.	Have you fallen during the last 12 months?	Yes, 1; No, 0.
Q2.	Have you tripped during the last 12 months?	Yes, 1; No, 0.
Q3.	Can you climb stairs without help?	Yes, 0; No, 1.
Q4.	Do you feel your walking speed has declined recently?	Yes, 1; No, 0.
Q5.	Can you cross a road within the green signal interval?	Yes, 0; No, 1.
Q6.	Can you walk 1 km without stopping?	Yes, 0; No, 1.
Q7.	Can you stand on one foot for about five seconds?	Yes, 0; No, 1.
Q8.	Do you use a stick when you walk?	Yes, 1; No, 0.
Q9.	Can you squeeze a towel tightly?	Yes, 0; No, 1.
Q10.	Do you feel dizzy at times?	Yes, 1; No, 0.
Q11.	Is your back bent?	Yes, 1; No, 0.
Q12.	Do you have knee pain?	Yes, 1; No, 0.
Q13.	Do you have a problem with your vision?	Yes, 1; No, 0.
Q14.	Do you have a hearing problem?	Yes, 1; No, 0.
Q15.	Do you think you are forgetful?	Yes, 1; No, 0.
Q16.	Do you feel anxious about falling when you walk?	Yes, 1; No, 0.
Q17.	Do you take five or more prescribed medicines?	Yes, 1; No, 0.
Q18.	Do you feel unsafe because your home is dark?	Yes, 1; No, 0.
Q19.	Are there any obstacles in your house?	Yes, 1; No, 0.
Q20.	Is there any difference in level within your home?	Yes, 1; No, 0.
Q21.	Do you have to use stairs in daily living?	Yes, 1; No, 0.
Q22.	Do you have to walk on a steep slope around your house?	Yes, 1; No, 0.

Appendix II. Simple screening test for risk of falls

Q1.	Have you fallen during the last 12 months?	Yes, 5 points; No, 0.
Q2.	Do you feel your walking speed has declined recently?	Yes, 2 points; No, 0.
Q3.	Do you use a cane when you walk?	Yes, 2 points; No, 0.
Q4.	Is your back bent?	Yes, 2 points; No, 0.
Q5.	Do you take five or more prescribed medicines?	Yes, 2 points; No, 0.

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OBSTRUCTIVE SLEEP APNEA EXACERBATES ENDOTHELIAL DYSFUNCTION IN PEOPLE WITH METABOLIC SYNDROME

To the Editor: The process of aging can be found in a variety of organs, frequently overlapping in the metabolic, cardiopulmonary, and nervous systems. A recent study showed that visceral fat accumulation is associated with metabolic risk factor clustering in older adults.[1] Obstructive sleep apnea (OSA) and metabolic syndrome (MetS) are well known as risk factors for cardiovascular disease and comorbid disorders in obese and older adults,[2] but whether OSA affects vascular endothelial dysfunction, a surrogate marker of cardiovascular disease,[3] in people with MetS has not been determined. Flow-mediated dilation (FMD) of the brachial artery, an indicator of endothelial vasomotor function, was therefore examined in people with MetS with or without OSA.

Forty-nine consecutive overweight subjects (body mass index $\geq 25.0\,kg/m^2$, aged 35–69) who were referred for medical examinations were enrolled and categorized into three groups; with MetS but not OSA (MetS group, n = 21), with MetS and OSA (MetS+OSA group, n = 14), and with no metabolic risk factors but overweight (control group, n = 14). MetS was defined using the International Diabetes Federation criteria and OSA using polysomnography. Participants who had some risk factors but did not meet the criteria for MetS and those who declined to undergo polysomnography were excluded. Blood sampling and measurement of FMD were performed early in the morning after an overnight fast. FMD was measured using ultrasound as percentage change in brachial artery diameter as previously described.[4]

The MetS and MetS+OSA groups had significantly lower plasma high-density lipoprotein cholesterol (HDL-C) (41.9 ± 9.4 and 40.7 ± 5.9 vs 57.9 ± 12.5 mg/dL, $P < .001$) and higher triglycerides (192.2 ± 57.7 and 157.3 ± 52.4 vs 104.1 ± 34.4 mg/dL, $P = .008$) and glycosylated hemoglobin ($5.71 \pm 0.87\%$ and $5.81 \pm 0.90\%$ vs $4.80 \pm 0.38\%$, $P = .001$) than the control group. Although the apnea-hypopnea index was 34.0 ± 13.6 events per hour in MetS+OSA group, in contrast to 3.1 ± 1.6 events in the MetS group ($P < .001$), there were no significant differences between the MetS and MetS+OSA groups in terms of cardiovascular risk factors, including age, body mass index, waist circumference, blood pressure, low-density lipoprotein cholesterol (LDL-C), and homeostasis model assessment of insulin resistance (data not shown).

The control group had a significantly lower increase in percentage of FMD (%FMD) than the other two groups. Moreover, %FMD in the MetS and OSA group was significantly lower than that in the MetS group (Figure 1), whereas nitroglycerine-induced endothelium-independent dilation was comparable between the groups ($15.0 \pm 4.2\%$ control, $13.5 \pm 3.2\%$ MetS, $11.5 \pm 3.5\%$ MetS+OSA). On multiple regression analysis, OSA (yes = 1, no = 0) was significantly related to %FMD, independent of age, waist circumference, systolic blood pressure, LDL-C, HDL-C, triglycerides, fasting plasma glucose, and smoking ($\beta = -0.324$, $P = .04$). The results of other multiple regression models were similar (data not shown).

It has been shown that continuous positive airway pressure treatment improves endothelial vasomotor function with no influence on metabolic risk factors,[5,6] indicating that vascular endothelial dysfunction in people with OSA is attributable to OSA-induced hypoxia. These findings imply that OSA is an additional risk factor in people with MetS. Consistent with the present results, it has been reported that OSA is independently associated with carotid intima-media thickness and pulse wave velocity, other

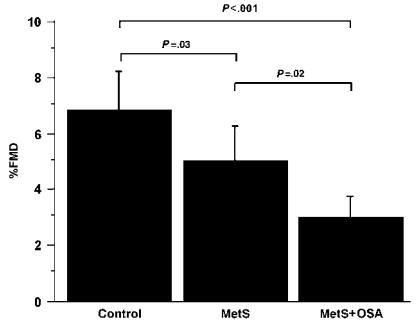

Figure 1. Increase in percentage of flow-mediated diameter (%FMD) of the brachial artery in control overweight subjects (control, n = 14), patients with metabolic syndrome (MetS, n = 21), and patients with MetS and obstructive sleep apnea (MetS+OSA, n = 14). Data are shown as means ± standard deviations.

markers of atherosclerosis, in people with MetS.[7] In conclusion, the results of the current study suggest that OSA exacerbates endothelial dysfunction in people with MetS, possibly leading to greater risk of cardiovascular disease.

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COMMENTS/RESPONSES

RELEVANT OUTCOMES IN INTERVENTION TRIALS FOR SARCOPENIA

To the Editor: We read with interest the paper by Brass and Sietsema on drug development to treat sarcopenia.[1] The authors raise important points to consider when designing clinical trials addressing sarcopenia-related outcomes.

As they state, a universally accepted definition for sarcopenia needs to be established. The difficulty encountered in doing so is a direct result of the complexity of the problem. The European Working Group for Sarcopenia in Older Persons (EWGSOP) has recently developed and published a practical clinical definition and consensus diagnostic criteria for age-related sarcopenia[2] that several international scientific societies, namely the European Geriatric Medicine Society (EUGMS), the European Society for Clinical Nutrition and Metabolism (ESPEN), the International Association of Gerontology and Geriatrics—European Region, and the International Association of Nutrition and Aging, have endorsed. In line with Brass and Sietsema's suggestion, the EWGSOP advocates a definition that allows chronic disease, besides aging per se, to contribute to sarcopenia.

For the diagnosis of sarcopenia, EWGSOP recommends using the presence of low muscle mass and reduced muscle function (strength or performance) and variously applies these characteristics to further define such conceptual stages as presarcopenia, sarcopenia, and severe sarcopenia. EWGSOP also reviewed a wide range of tools that can be used to measure the specific variables of muscle mass, muscle strength (e.g., hand grip), and physical performance (e.g., gait speed). The report summarizes currently available data defining sarcopenia cutoff points according to age and sex; suggests an algorithm for sarcopenia case finding in older individuals based on measurements of gait speed, grip strength, and muscle mass; and presents a list of suggested primary and secondary outcome domains for research.

In their review, Brass and Sietsema emphasize the standards that trials should meet to establish efficacy. They point out that efficacy should be measured according to meaningful clinically relevant end points and that surrogate markers of benefit will not be sufficient to validate Food and Drug Administration (FDA) approval. This is a complex issue for sarcopenia, because it fulfills criteria for a geriatric syndrome and is thus characterized by a complex interplay

Sirtuin 1 Retards Hyperphosphatemia-Induced Calcification of Vascular Smooth Muscle Cells

Aya Takemura, Katsuya Iijima, Hidetaka Ota, Bo-Kyung Son, Yuki Ito, Sumito Ogawa, Masato Eto, Masahiro Akishita, Yasuyoshi Ouchi

Objective—Arterial calcification is associated with cardiovascular disease as a complication of advanced atherosclerosis. Aged vascular cells manifest some morphological features of a senescent phenotype. Recent studies have demonstrated that mammalian sirtuin 1 (SIRT1), a histone deacetylase, is an exciting target for cardiovascular disease management. Here, we investigated the role of SIRT1 in a calcification model of vascular smooth muscle cells (SMCs).

Methods and Results—In adenine-induced renal failure rats with hyperphosphatemia, massive calcification was induced in the aortic media. Senescence-associated β-galactosidase (SAβ-gal) activity, a marker of cellular senescence, in medial SMCs was significantly increased, and its induction was positively associated with the degree of calcification. In cultured SMCs, inorganic phosphate (Pi) stimulation dose-dependently increased SAβ-gal-positive cells, and Pi-induced senescence was associated with downregulation of SIRT1 expression, leading to p21 activation. The activation via SIRT1 downregulation was blunted by inhibition of Pi cotransporter. Activation of SIRT1 by resveratrol significantly reduced the senescence-associated calcification. Conversely, SIRT1 knockdown by small interfering RNA accelerated the Pi-induced SMC senescence and subsequent calcification. In addition, SIRT1 knockdown induced phenotypic change from a differentiated state to osteoblast-like cells. The senescence-related SMC calcification was completely prevented by p21 knockdown. In addition to Pi-induced premature senescence, SMCs with replicative senescence were also more sensitive to Pi-induced calcification compared with young SMCs, and this finding was attributable to augmented p21 expression.

Conclusion—SIRT1 plays an essential role in preventing hyperphosphatemia-induced arterial calcification via inhibition of osteoblastic transdifferentiation. In addition, Pi-induced SMC calcification may be associated with both premature and replicative cellular senescence. (***Arterioscler Thromb Vasc Biol.*** **2011;31:2054-2062.**)

Key Words: cellular senescence ■ hyperphosphatemia ■ longevity gene SIRT1 ■ vascular calcification ■ vascular smooth muscle cell

Atherosclerotic vascular damage associated with aging manifests several features, namely atherosis, sclerosis, and calcific change, finally leading to cardiovascular events. These pathological changes result in arterial wall thickening (localized morphological changes) and arterial stiffening (functional changes).[1] Arterial calcification makes the management of hemodynamics more difficult in the elderly, because ectopic calcium deposition in the aorta and arteries contributes to vessel wall stiffening and loss of elastic recoil.[2] These pathological conditions result in unstable hemodynamic consequences, finally leading to a decline in end-organ perfusion and subsequent ischemic events. Recently, several reports have demonstrated that aortic calcification detectable on chest X-ray examination is a strong predictor of future cardiovascular events beyond traditional risk factors.[3]

Arterial calcification is anatomically separated into two types, intimal and medial calcification.[4] Intimal calcification, which is seen as patchy scattered deposits only occurring within atherosclerotic plaques, is shown to be associated with plaque vulnerability.[5] On the other hand, medial calcification, which is frequently seen in the elderly and in diabetes and chronic renal failure, is observed as continuous linear deposits along the internal elastic lamina.[6] Advanced atherosclerosis with both types of calcified lesions is the consequence of overlapping pathological mechanisms.

Ectopic calcification in the vasculature has been shown to result from passive precipitation of calcium with aging and osteoporosis, the so-called calcium shift theory, as a previous hypothesis.[7] However, accumulating recent evidence has shown it to be attributable to an active "cell-mediated process" resembling osteogenesis in bone rather than passive mineral precipitation in vascular smooth muscle cells (SMCs).[8,9]

Silent information regulator-2 (Sir2), an NAD^+-dependent HDAC, is highly conserved in organisms ranging from Archaea

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to humans.[10] In yeast, Sir2 has been shown to play critical roles in DNA repair, stress resistance, and longevity. Mammalian sirtuin 1 (SIRT1), the closest homolog of Sir2, regulates the cell cycle, apoptosis, and metabolism by interacting with a number of molecules, including p53, promyelocytic leukemia protein, Foxo, Ku70, and peroxisome proliferator-activated receptor-γ.[11] A previous study has shown that SIRT1 antagonizes p53-mediated premature senescence in mouse embryo fibroblasts.[12] In addition, we have recently demonstrated that SIRT1 inhibits oxidative stress-induced premature senescence in vascular endothelial cells.[13] However, the detailed mechanism of how SIRT1 affects vascular SMC senescence and arterial calcification remains unclear.

In this study, we hypothesized that SIRT1 plays an important role in preventing arterial calcification due to renal failure, in association with modulation of cellular senescence. Here, we demonstrated the protective potential of SIRT1 against hyperphosphatemia-induced premature and replicative senescence and subsequent calcification in SMCs.

Methods

Aortic Calcification in Renal Failure Rats

Renal failure was induced in rats by a 0.75% adenine-containing diet as previously described.[14] All procedures and animal care were in accordance with the Guide for the Care and Use of Laboratory Animals of the University of Tokyo. Detailed methods are described in the supplemental materials, available online at http://atvb.ahajournals.org.

Induction of SMC Calcification

Primary human aortic SMCs (HASMCs) were treated with a pathological concentration of inorganic phosphate (Pi) up to 3.2 mmol/L in culture medium as previously described.[29] To quantitatively measure Pi-induced calcification, two distinct experiments were performed as previously described[14]: (1) intracellular calcium deposition as determined by *o*-cresolphthalein complexone method, and (2) visualization of mineralization as determined by von Kossa staining, Detailed methods are described in the supplemental materials.

Senescence-Associated β-Galactosidase Staining

To assess senescent changes in the phenotype of cultured HASMCs or aortic medial cells of rats, staining for senescence-associated β-galactosidase (SAβ-gal), a well-established biomarker of cellular senescence, was performed. Detailed methods are described in the supplemental materials.

Knockdown of SIRT1 or p21 by Small Interfering RNA

HASMCs were transfected with 200 pmol/L small interfering RNA (siRNA) for SIRT1, $p21^{WAF1/CIP1}$, or both. Detailed methods are described in the supplemental materials.

Real-Time Polymerase Chain Reaction Analysis: Osteoblastic Markers

To examine whether Pi stimulation induces change to an osteoblastic phenotype, the expression of Runx-2/Cbfa-1 and alkaline phosphatase, which are well known to be representative osteoblastic markers, was checked using real time-polymerase chain reaction analysis. In addition, the effect of knockdown of SIRT1, p21, or both by siRNA on the osteoblastic phenotypic change in HASMCs was examined. Primer sequences are shown in Supplemental Figure I.

Results

Association of Senescent Vascular Cells With Aortic Medial Calcification in Renal Failure Rats

The adenine-fed rats had severe renal failure, with a huge increase in serum creatinine (3.0±0.9 mg/dL in renal failure rats versus 0.3±0.0 mg/dL in control rats), similar to a previous report.[14] The renal failure rats showed an approximately 2.0-fold increase in serum phosphorus (18.9±4.7 mg/dL) compared with control rats (9.8±0.9 mg/dL). Histological assessment using von Kossa staining showed that the aorta in renal failure rats had extensive linear calcification, which was localized in the aortic media, resembling the typical Mönckeberg's pattern (Figure 1A). Numerous SAβ-gal positive cells were found in the aortic media of renal failure rats, whereas the aortic wall in control rats did not contain senescent cells (Figure 1B). The senescent cells were mainly localized to the calcified area and its surrounding area, which was defined as the area not stained black by von Kossa staining. Quantitative assessment showed that the number of senescent cells with high SAβ-gal activity was positively correlated with the calcified area in the aortic media (Figure 1C).

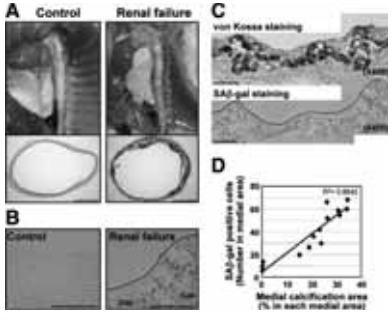

Figure 1. Presence of senescent vascular cells colocalized with calcification in aortic media of renal failure rats. A, Rats with severe renal failure had massive calcification throughout the aorta (right) compared with control rats (left) (n=5). Yellow arrows indicate calcified area. Morphological assessment by von Kossa staining showed extensive calcification in the aortic media of renal failure rats. Scale bar=500 μm. B, Senescent vascular cells (senescence-associated β-galactosidase [SAβ-gal]-positive: blue) were significantly detected throughout the calcified area (Calc) in renal failure rats, whereas these senescent cells were not present in control rats. Scale bar=100 μm. C, Localized association between calcification and senescent cells is shown in renal failure rats. SAβ-gal-positive cells were frequently found in areas with marked calcification. D, The association of the number of SAβ-gal-positive cells with the calcified area in each photograph was evaluated. The senescent cell number was linearly correlated with the area of calcification in the aortic media of renal failure rats (calcified area in media: percentage).

Pi Induces Cellular Senescence in Cultured SMCs

On the basis of our results obtained from animal experiments, we hypothesized that senescent SMCs in the aortic media are strongly associated with the development of arterial calcification. Therefore, the effect of excessive Pi stimulation (2.6 mmol/L) on cellular senescence in cultured SMCs was examined. SAβ-gal-positive senescent HASMCs were significantly induced by not only angiotensin II (Ang II) but also Pi

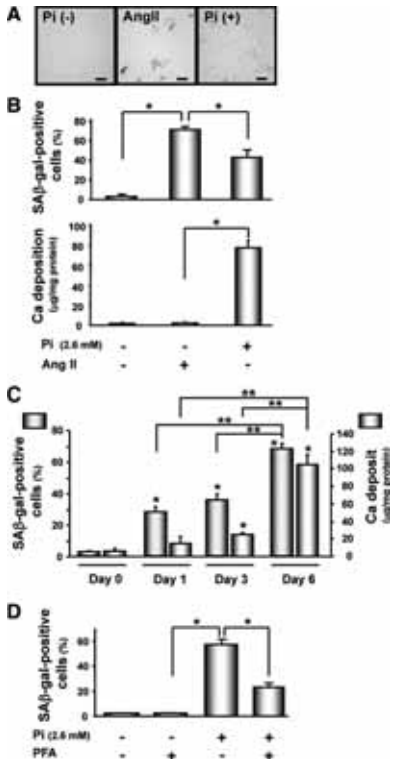

Figure 2. Inorganic phosphate (Pi) stimulation induces cellular senescence in vascular smooth muscle cells (SMCs) via its cotransporter. A, The effect of Pi on senescent transition in human aortic SMCs (HASMCs) was examined. Representative photographs showed that senescence-associated β-galactosidase (SAβ-gal) activity (blue) in cells was significantly induced by not only angiotensin II (Ang II: 10 pmol/L, as a positive control) but also Pi stimulation (2.6 mmol/L). B, The number of senescent cells was significantly increased by not only Ang II but also Pi. Calcium deposition was significantly increased by Pi; however, calcification in HASMCs was not induced by Ang II alone in the absence of Pi. C, Senescent cells were significantly increased by Pi stimulation even on day 1; however, a statistically significant increase in calcium deposition was found from day 3 and later. D, Inhibition of the phosphate cotransporter Na-dependent phosphate cotransporter by the inhibitor phosphonoformic acid (PFA) (100 μmol/L) reduced SAβ-gal activity, which was increased by Pi (2.6 mmol/L) in HASMCs. Each experiment was performed al least 3 times.

stimulation (Figure 2A). Notably, Pi stimulation increased calcium deposition; however, Ang II alone did not (Figure 2B). It suggests that high-dose Pi condition, but not stress by Ang II alone, is indispensable to induce SMC calcification. These findings also suggest that intracellular Pi influx at least is essential to induce this SMC calcification model.

In addition, to determine how many days after the initiation of Pi stimulation the cells showed a senescent phenotype and subsequent calcification, the time-dependent effects of Pi stimulation on both SAβ-gal activity and calcium deposition were examined. As shown in Figure 2C, SAβ-gal-positive cells were significantly increased by Pi stimulation even on day 1, although calcium deposition was not markedly increased at the same time point. A statistically significant increase in calcium deposition was found from day 3 and later. Cotreatment with phosphonoformic acid, an inhibitor of Na-dependent phosphate cotransporter (NPC), showed significant inhibition of Pi-induced senescence (Figure 2D). Our previous report showed that treatment with PFA completely inhibited Pi-induced SMC calcification,[15] suggesting the importance of increased intracellular influx of phosphate in Pi-induced SMC senescence.

Downregulation of SIRT1 by Pi

Treatment of HASMCs with Pi caused downregulation of SIRT1 expression in a time-dependent manner (Figure 3A). The decline was dependent on Pi concentration (data not shown). An increase in acetylation of both substrates of SIRT1, histone-3 and p53 (a nonhistone substrate), was found according to the decline in SIRT1 deacetylase activity. In addition, expression of p21, a downstream molecule of p53, was significantly induced by Pi as well. Quantitative assessment showed that an increase in these expression levels of acetylated (Ac)-p53 and p21 on day 3 and day 6 was statistically significant compared with the pretreatment levels, suggesting that downregulation of SIRT1 activity may mediate the subsequent increase in Ac-p53 and p21 expression.

To address whether SIRT1 downregulation-related SMC senescence and calcification are reversible or not, the effects of continuation or termination of high-dose Pi were examined. As shown in Figure 3B, the continuation of Pi up to day 10 was associated with SIRT1 downregulation and subsequent upregulation of Ac-p53 and p21, leading to induction of senescence-related calcification. However, the slight increase in senescent cells was not statistically significant, although calcification was significantly induced. Of note, the Pi-induced downregulation of SIRT1 was almost completely reversed by withdrawal (termination) of Pi stimulation (exchange of Pi from 2.6 mmol/L to 1.4 mmol/L as a normal level on day 6) as shown in Figure 3B. According to the restoration of SIRT1, levels of both Ac-p53 and p21 were also decreased without more progression. In addition, termination of Pi showed no progression of senescence-related calcification; however, preexisting senescent cells and calcification on day 6 continued without regression.

Next, NPC inhibition by PFA completely blunted Pi-induced SIRT1 downregulation and subsequent activation of its downstream p53/p21 pathway (Figure 3C).

Regulation of SIRT1 Modulates Pi-Induced SMC Senescence and Calcification

The effects of modulation of SIRT1 activity on Pi-induced cellular senescence were investigated. First, sirtinol, a chemical inhibitor of SIRT1, induced an increase in SAβ-gal-positive cells even under a normal Pi (1.4 mmol/L), and the increased number of senescent cells induced by Pi was significantly augmented by sirtinol (Figure 4A). Sirtinol dose-dependently augmented Pi-induced calcification, although no augmentation was found under a normal Pi (Figure 4B and 4C). Conversely, treatment with resveratrol, an activator of SIRT1, significantly reduced both Pi-induced senescent transition and calcification in a dose-dependent manner (Figure 4D to 4F).

Second, complete knockdown of SIRT1 by siRNA caused a significant increase in acetylation of both substrates (histone-3 and p53) and p21 expression (Figure 5A). Similarly to sirtinol, SIRT1 inhibition by siRNA also augmented not only senescent transition (Figure 5A, bottom) but also calcium deposition (Figure 5C, top).

Although stimulation with Ang II alone could increase the number of SAβ-gal-positive cells, it did not increase calcium deposition. To understand the mechanism of these discrepant phenomena, the effect of Ang II alone on osteoblastic phenotypic change was examined. Ang II alone did not increase the expression of Runx2 in the absence of Pi stimulation, unlike Pi stimulation (Figure 5B).

To understand the detailed mechanism by which SIRT1 modulates senescence-related calcification, the effect of SIRT1 on phenotypic change in HASMCs was examined. Pi inhibited the expression of caldesmon, a differentiated SMC lineage marker, and complete knockdown of SIRT1 augmented the Pi-induced partial downregulation of caldesmon (Figure 5C, middle). In contrast, real-time polymerase chain reaction analysis showed that Pi induced the expression of two representative osteoblastic markers, Runx-2/Cbfa-1 and alkaline phosphatase (Figure 5C, bottom) with statistical significance. In addition, complete knockdown of SIRT1 using siRNA significantly accelerated the Pi-induced os-

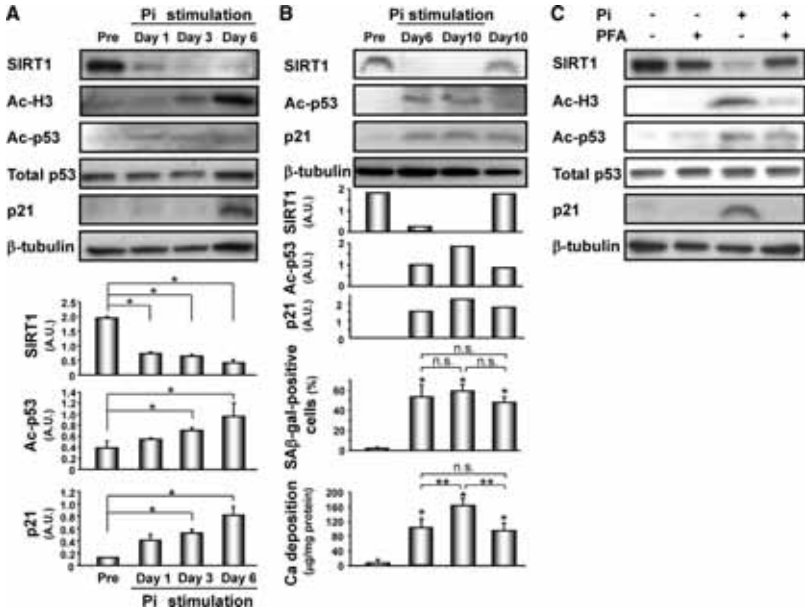

Figure 3. Inorganic phosphate (Pi) stimulation leads to sirtuin 1 (SIRT1) downregulation and subsequent p21 activation. A, The effect of Pi on SIRT1 expression and its downstream pathway was examined. Treatment of human aortic SMCs (HASMCs) with Pi (2.6 mmol/L) showed downregulation of SIRT1 expression, leading to an increase in acetylation of its substrates (acetylated [Ac]-H3 and Ac-p53) and p21 expression. Bottom: Quantitative analysis showed that Pi gradually induced not only SIRT1 downregulation but also upregulation of Ac-p53 and p21. B, To address whether SIRT1 downregulation-related senescence and subsequent calcification are reversible, the effects of continuation or termination of high-dose Pi were examined. As shown in 4th lane from left, termination (on day 6) of Pi showed no progression of senescence-related calcification in association with restoration of SIRT1, whereas continuation (up to day 10, 3rd lane from left) of Pi stimulation showed further progression of calcification. C, Treatment with phosphonoformic acid (PFA), a Na-dependent phosphate cotransporter inhibitor, completely reversed Pi-induced SIRT1 downregulation. A decline in Ac-H3 and Ac-p53 reflected the restoration of SIRT1 deacetylase activity. Pi-induced p21 activation was significantly inhibited by inhibition of Pi transport.

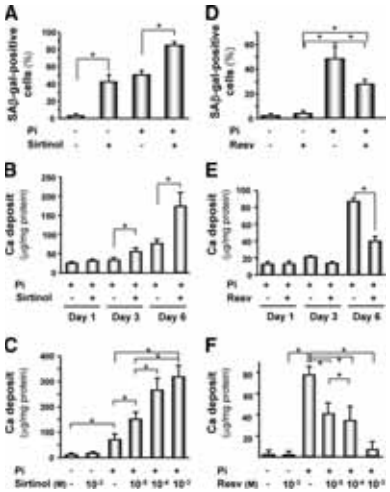

Figure 4. Modulation of sirtuin 1 (SIRT1) affects inorganic phosphate (Pi)–induced senescent phenotypic change and calcification in smooth muscle cells (SMCs). The effects of sirtinol (a chemical inhibitor of SIRT1 activity; A to C) and resveratrol (an activator of SIRT1; D to F) on Pi-induced senescent phenotypic change and calcification were examined (n=6). A, SIRT1 inhibition by sirtinol (10 μmol/L) showed an increase in the number of senescence-associated β-galactosidase (SAβ-gal)-positive cells even without Pi stimulation. The increase in Pi-induced senescence was significantly augmented by sirtinol. Sirtinol augmented Pi-induced calcium deposition in human aortic SMCs (HASMCs) in a time-dependent (B) and dose-dependent manner on day 6 (C). Conversely, treatment with resveratrol (Resv; 10 μmol/L) showed a reduction of the Pi-induced senescent phenotype (D) and calcification (E). The inhibitory effect of resveratrol on calcification was dose dependent (F).

teoblastic phenotypic change, suggesting that modulation of SIRT1 is associated with osteoblastic phenotypic change in SMCs.

Inhibition of Senescence-Related Calcification in SMCs by p21 Knockdown

To address the association of p21 with senescence-related calcification, knockdown of p21 using siRNA was performed. Treatment of p21 siRNA (up to 200 pmol/L) completely inhibited p21 (Figure 5D). p21 knockdown completely inhibited Pi-induced senescence and subsequent calcification (Figure 5E).

Regulation of NPC-Mediated Runx2 Expression by SIRT1/p21 Pathway

As the next step, the role of SIRT1 in NPC-mediated Runx2/Cbfa1 expression was examined. First, complete knockdown of SIRT1 did not show any change in both osteoblastic markers, Runx2 and alkaline phosphatase, in a normal Pi (Supplemental Figure I). As shown in Figure 5F, Pi-induced Runx2 was significantly blunted by PFA, an NPC inhibitor. SIRT1 activation by resveratrol inhibited Pi-induced Runx2 activation. The Runx2 induction was augmented by knockdown of SIRT1 by siRNA, and the activation was completely inhibited by PFA. Surprisingly, Runx2 activation was strongly inhibited by knockdown of p21 alone. In addition, the inhibition of Runx2 induction by double knockdown of SIRT1 and p21 was less than that by single knockdown of SIRT1.

To address a difference in senescent induction by Pi or Ang II, immunohistological assessment of SIRT1 in HASMCs was examined (Supplemental Figure II). Although SIRT1 was predominantly localized in nucleus without Pi, the translocation of SIRT1 to cytoplasm was observed after Pi stimulation for 24 hours, and its expression disappeared in both areas on day 6. In contrast, Ang II stimulation did not show the dynamic translocation.

High Sensitivity of SMCs With Replicative Senescence to Pi-Induced Calcification

Not only Pi-induced "premature senescence" in HASMCs but also the effects of Pi on "replicative senescence" were evaluated. Senescent cells (passage 18) were more sensitive to Pi-induced calcification compared with young cells (passage 7) (Figure 6A). SIRT1 expression was downregulated in senescent cells compared with young cells, and the downregulation was significantly augmented by Pi stimulation (Figure 6B, top). In parallel with this finding, senescent cells showed an increase in Ac-p53 and p21 expression. Statistical analyses using densitometric measurement showed that (1) downregulation of SIRT1 and upregulation of Ac-53 and p21 were augmented by replicative senescence, and (2) Pi inhibited the SIRT1-p21 pathway even in cells with replicative senescence (passage 18) (Figure 6B, bottom).

Discussion

Vascular aging, leading to cardiovascular disease, manifests complex and diverse vascular changes (eg, impairment of distensibility due to loss of arterial elasticity).[1,16] Arterial wall stiffness resulting from ectopic calcification is a complication of advanced atherosclerosis and makes the management of hemodynamics more difficult in the elderly. Few reports have addressed whether cellular senescence is associated with SMC calcification. This study showed the importance of SIRT1, a longevity gene, in arterial calcification in association with cellular senescence.

First, our data obtained from animal experiments clearly showed the association of senescent SMCs with aortic medial calcification in the renal failure rats with hyperphosphatemia. Senescent cells showed significant colocalization with calcium deposition. Intriguingly, numerous senescent cells could be detected before microscopic calcification occurred at 4 weeks after the start of renal failure induction (data not shown), suggesting that the transition to a senescent phenotype in medial SMCs may be associated with the initiation and progression of calcification. Therefore, hyperphosphatemia, a potent uremic factor, may be a stimulator to induce senescent phenotypic transition of medial SMCs.

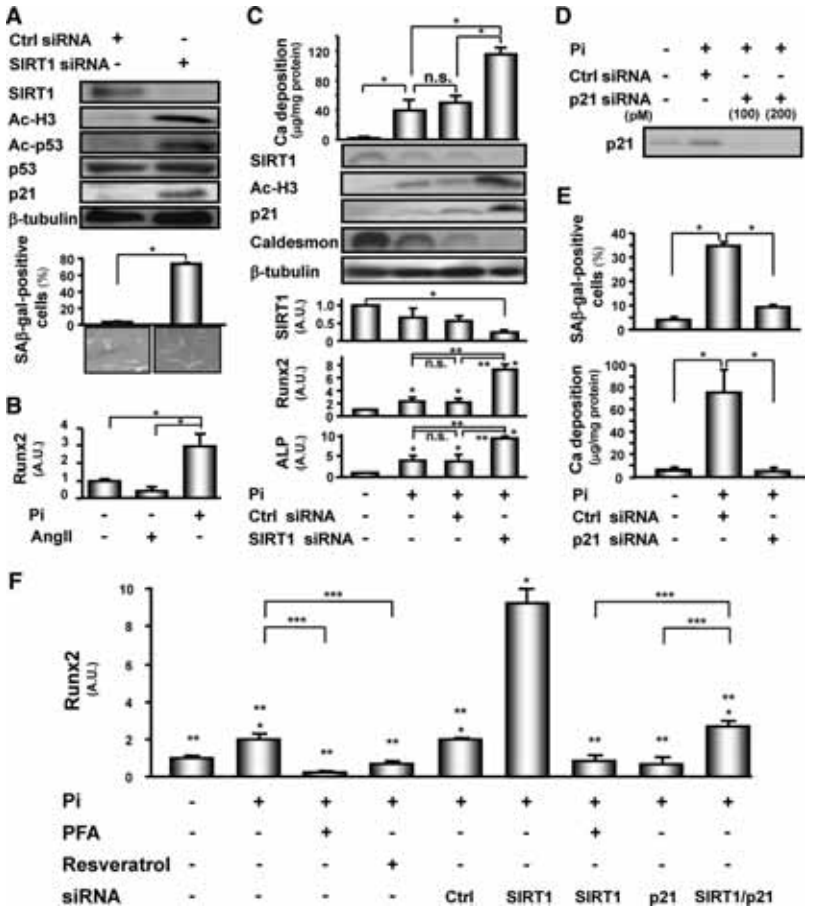

Figure 5. Augmentation of senescence-related smooth muscle cell (SMC) calcification by sirtuin 1 (SIRT1) knockdown in association with osteoblastic phenotypic change and prevention of inorganic phosphate (Pi)–induced changes by p21 knockdown. A, To achieve SIRT1 knockdown in human aortic SMCs (HASMCs), small interfering RNA (siRNA) was simultaneously administered at the start of Pi stimulation (2.6 mmol/L). Complete inhibition of SIRT1 showed a significant increase in acetylation of both substrates (acetylated [Ac]-H3 and Ac-p53), p21 expression and senescence-associated β-galactosidase (SAβ-gal)-positive cells. B, Angiotensin II (Ang II) alone (10 pmol/L) did not increase the expression of Runx2 in the absence of Pi stimulation, unlike Pi stimulation. C, top: SIRT1 knockdown by siRNA significantly accelerated Pi-induced calcification (n=6), whereas control (Ctrl) siRNA did not. C, middle and bottom: Western blots showed that Pi partially inhibited the expression of a differentiated SMC marker, caldesmon, and complete knockdown of SIRT1 by siRNA augmented its downregulation. Real-time polymerase chain reaction analysis showed that Pi induced the expression of Runx-2 and alkaline phosphatase (ALP). Complete knockdown of SIRT1 significantly accelerated the Pi-induced osteoblastic markers. A.U. indicates arbitrary units. *$P<0.05$. D and E, Knockdown of p21 by siRNA (200 pmol/L) significantly reduced the senescent phenotypic change and subsequent calcification (n=6). F, The role of SIRT1/p21 axis in Na-dependent phosphate cotransporter-mediated Runx2 expression was evaluated. Augmentation of Pi-induced Runx2 expression by SIRT1 knockdown was significantly inhibited by double knockdown of SIRT1 and p21. *$P<0.05$ vs control without Pi stimulation (left column), **$P<0.05$ vs Pi-stimulated cells with SIRT1 siRNA (sixth column from left).

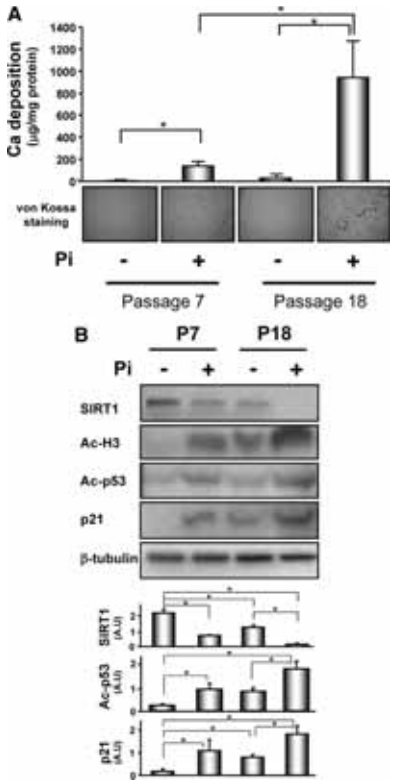

Figure 6. High sensitivity of smooth muscle cells (SMCs) with replicative senescence to inorganic phosphate (Pi)–induced calcification. The effects of replicative senescence in human aortic SMCs (HASMCs) on Pi-induced calcification (A) and sirtuin 1 (SIRT1)-related molecules (B) were also evaluated. A, Senescent cells (passage 18 [P18]) were more sensitive to Pi-induced calcification compared with young cells (passage 7 [P7]) (n=6). Representative photographs of von Kossa staining (bottom) show strong induction of calcium deposition by Pi (2.6 mmol/L). B, Senescent HASMCs (P18) showed a decline in SIRT1 expression and an increase in p21 expression compared with young cells (P7). Pi stimulation of senescent cells significantly inhibited SIRT1 expression and accelerated the increase in p21 and acetylated (Ac)-p53. Densitometric analysis confirmed these more sensitive responses in senescent cells. A.U. indicates arbitrary units. *$P<0.05$.

Second, we also confirmed the association of Pi-induced SMC senescence with calcification in in vitro experiments. Senescent SMCs were significantly increased by Pi even on day 1, although calcium deposition was not markedly increased at the same time point. A statistically significant increase in calcium deposition was found from day 3 and later. Considering these data, we hypothesize that (1) calcium deposition may be more readily induced in senescent cells compared with nonsenescent cells, and (2) Pi-induced senescent change is observed earlier than calcium deposition. In other words, senescent transition associated with Runx2 induction may lead to progressive calcification.

Senescent SMCs were associated with the SIRT1-related p53/p21 pathway, based on the findings that SIRT1 knockdown augmented not only cellular senescence but also calcification. In addition, p21 knockdown completely inhibited senescence-related calcification induced by Pi. This raises the question of how cellular senescence in SMCs is associated with calcification. Our experiments to understand the detailed mechanisms by which SIRT1 modulates senescence-related calcification showed that Pi-induced SIRT1 downregulation led to the phenotypic change from a differentiated state to osteoblast-like cells in SMCs. It has been reported that Pi induces osteoblastic change, in which NPC plays a role in inducing Runx2/Cbfa-1 expression, in SMCs.[17] As the next step, to determine how SIRT1 regulates NPC-mediated Runx2 expression, we examined the effects of knockdown of SIRT1, p21, or both by siRNA on Pi-induced Runx2 expression. Our data shown in Figure 5F suggested that (1) NPC plays an essential role in Pi-induced Runx2 expression, (2) SIRT1 has an inhibitory effect on NPC-mediated Runx2 expression, (3) knockdown of p21 alone ameliorates Runx2 induction, and (4) p21-related osteoblastic change is at least in part dependent on SIRT1.

There is now the new question of how SIRT1 regulates Runx2 regulation. A report by Jeon[18] has shown that acetylation of Runx2 itself is important in osteoblast differentiation, and it is downregulated by HDAC activities. Based on this evidence, SIRT1, 1 of the HDACs, may be able to deacetylate Runx2, leading to inhibition of Runx2-related osteoblastic transition in SMCs. Therefore, the inhibition of SIRT1 by hyperphosphatemia may lead to Runx2 activation via its hyperacetylation. Further investigation of the detailed mechanism of the SIRT1/p21/osteoblastic gene axis is needed. These data clearly suggest that SIRT1 activation may inhibit the hyperphosphatemia-induced osteoblastic phenotypic change of SMCs, and the degree of change may be dependent on SIRT1 expression level. It is possible that the inhibition of SIRT1 expression by Pi alone is "partial," because complete downregulation of SIRT1 by siRNA worsened the dynamic phenotypic change compared with Pi only. We have already shown that tumor necrosis factor-α, a potent atherogenic cytokine, augmented Pi-induced SMC calcification, as previously described.[19] In addition, tumor necrosis factor-α significantly decreased Pi-induced SIRT1 downregulation further (data not shown). According to these results, we currently hypothesize that hyperphosphatemia induces SIRT1 downregulation and subsequent osteoblastic phenotypic change in SMCs, leading to calcification, and these changes are worsened by some harmful atherogenic factors, which decrease SIRT1 expression/activity further. These results provide a new insight, showing that SIRT1 plays an essential role in the prevention of arterial calcification and that the beneficial effect may be associated with an inhibition in Pi-induced SMC senescent transition.

In addition, Ang II did not increase calcium deposition, although the stimulation increased the number of senescent cells. Of note, Ang II alone did not increase Runx2 expression in the absence of Pi (Figure 5B). This result suggests that SMC senescence shows two different features: one is SAβ-gal-positive cells with an increase in Runx2 and the other is SAβ-gal-positive cells without. First, it has recently been reported that SMCs with replicative senescence, rather than the cells without senescence, show hypersensitivity in response to induction of calcification with the more induction of osteoblastic markers,[20] suggesting that the induction of osteoblastic transdifferentiation is strongly associated with the senescent change in SMCs. In addition, the translocation of SIRT1 to cytoplasm was observed after Pi stimulation for 24 hours, although SIRT1 predominantly localized in nucleus without Pi. In contrast, Ang II did not show the dynamic translocation. Thinking about the mechanism for regulating the activity of HDACs, including SIRT1, recent several reports show the importance of their coordinated shuttling between nucleus and cytoplasm. A report demonstrates that HDAC7, an HDAC, represses the transcriptional activity of Runx2 and that osteogenic stimuli induce export of HDAC7 from nucleus, leading to a decline in the repressive potentials of HDAC7 for Runx2.[21] On the basis of our findings and a previous report, the reason that stimulation with Ang II alone did not induce Runx2 expression and subsequently SMC calcification may in part depend on the difference of SIRT1 translocation after stimulation. Therefore, we strongly hypothesize that in the senescent SMCs with upregulation of p21, Pi stimulation, but not Ang II stimulation, may activate Runx2 via at least two phenomena, the hyperacetylation of Runx2 by SIRT1 downregulation and the dynamic SIRT1 translocation, leading to marked osteoblastic transdifferentiation and subsequent calcification. In addition, we have another hypothesis. In general, it has been shown that high-dose Pi navigates release of matrix vesicles from SMCs in parallel with osteoblastic transdifferentiation. The vesicles play an essential role in the initiation of hydroxyapatite aggregation, so-called nucleation. Accumulating recent reports show that the nanocrystal formation as an initial step under hyperphosphatemia accelerates the harmful cascade of osteoblastic transdifferentiation in SMCs via endocytosis.[22,23] Maybe Ang II alone does not induce the nanocrystal formation and the cascade of osteoblastic change. Therefore, we explain that the difference of senescent phenotypic changes in SMCs between both stimulations, Pi and Ang II alone, may depend on (1) SIRT1 translocation and (2) nanocrystal formation to accelerate calcification. Further investigation to address the detailed mechanisms by which SIRT1 regulates osteoblastic transdifferentiation in SMCs under the cellular senescence is needed.

Are SIRT1 downregulation-related SMC senescence and subsequent calcification reversible or not? To answer this question, the effects of continuation or termination of high-dose Pi were examined. As shown in Figure 3B, termination (on day 6) of Pi showed no progression of senescence-related calcification in association with the restoration of SIRT1, whereas continuation (up to day 10) of Pi stimulation showed further progression of calcification. It is suggested that a therapeutic strategy to manage hyperphosphatemia to the normal range of serum phosphate concentration may lead to at least termination of progressive calcification via reversal of SIRT1 activity.

Cellular senescence has been shown to have two features: not only stress-induced premature senescence but also replicative senescence, indicating a limited number of divisions in culture.[24] In fact, both endothelial cells and SMCs derived from human atherosclerotic plaques show a senescent phenotype earlier than do cells from normal vessels.[25] Notably, we found that senescent HASMCs were significantly more sensitive to Pi-induced calcification compared with young cells. These results suggest that calcium deposition may be more readily induced in arterial medial SMCs with replicative senescence. This insight may explain the mechanisms by which arterial calcification occurs in the elderly more frequently than in the young population. Therefore, these observations support our hypothesis that arterial calcification is accelerated by both senescent types (premature and replicative senescence) in SMCs. To explore new therapeutic strategies against arterial calcification, it is essential to investigate how to maintain a higher SIRT1 level in the vasculature, leading to prevention of medial SMC senescence and which drug is capable of achieving it.

How does SIRT1 exert protective effects against SMC calcification? This study clearly showed that inhibition of SIRT1 was associated with increases in both Ac-p53 and p21 expression. These findings were significantly induced by not only replicative senescence but also Pi-induced premature senescence. SIRT1-mediated deacetylation of p53 inhibits p53-dependent transactivation of target genes, including p21. A report showed that a decline in cellular deacetylase activity increases the half-life of endogenous p53,[26] suggesting that p53 acetylation is also associated with p53 stabilization. Therefore, the increased Ac-p53 by Pi-induced SIRT1 downregulation may induce SMC senescence because of a decline in degradation of p53, leading to calcification. In addition, p53 itself can inhibit SIRT1 transcription because the SIRT1 promoter has two response elements to p53.[27] Further investigation to address how the SIRT1-p53 negative regulatory pathway is associated with SMC calcification is needed.

On the other hand, regarding p21 activation, it is reported that inhibition of p21 expression in the vasculature significantly attenuates cellular senescence, leading to prevention of atherosclerosis.[28] This evidence suggests a pivotal role of p21 in the development of atherosclerosis. p21 activation has been shown to be regulated by a pathway that is p53 dependent, p53 independent, or both. Okamoto et al have demonstrated that inhibition of HDAC by trichostatin A showed activation of p21 promoter activity by the Sp1 site even in vascular SMCs, and the induction of p21 was independent of the p53 pathway.[29] The p21 transcriptional activation in response to HDAC inhibitors was mediated by histone hyperacetylation in its promoter region. Based on these findings, Pi-induced p21 activation via SIRT1 downregulation may be in part involved in a p53-independent pathway, leading to a senescent phenotype of SMCs. Further investigation exploring which molecule activates the p21 promoter under hyperphosphatemia is needed.

Conclusion

We showed that SIRT1 exerts a protective role in hyperphosphatemia-based arterial calcification via inhibition of osteoblastic transdifferentiation, in association with cross-talk between calcification and cellular senescence. This ability of SIRT1 may orchestrate an analogous protective/longevity paradigm even in vascular SMCs, leading to maintenance of healthy elasticity of the arterial wall. Strategies to maintain a higher level of SIRT1 activity may provide novel therapeutic opportunities for the prevention of arterial calcification.

Acknowledgments

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Disclosures

None.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Plasma sex hormone levels and mortality in disabled older men and women

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Aim: To investigate the relationship between circulating sex hormone levels and subsequent mortality in disabled elderly.

Methods: This prospective observational study was comprised of 214 elderly subjects aged 70–96 years (117 men and 97 women; mean ± standard deviation age, 83 ± 7 years), receiving services at long-term care facilities in Nagano, Japan. All-cause mortality by baseline plasma sex hormone levels was measured.

Results: After excluding deaths during the first 6 months, 27 deaths in men and 28 deaths in women occurred during a mean follow up of 32 months and 45 months (up to 52 months), respectively. Mortality rates differed significantly between high and low testosterone tertiles in men, but did not differ significantly between middle and low tertiles. Compared with subjects in the middle and high tertiles, men with testosterone levels in the low tertile (<300 ng/dL) were more likely to die, independent of age, nutritional status, functional status and chronic disease (hazard ratio [HR] = 3.27, 95% confidence interval [CI] = 1.24–12.91). In contrast, the low dehydroepiandrosterone sulfate (DHEA-S) tertile was associated with higher mortality risk in women (multivariate adjusted HR = 4.42, 95% CI = 1.51–12.90). Exclusion of deaths during the first year and cancer deaths had minimal effects on these results. DHEA-S level in men and testosterone and estradiol levels in women were not related to mortality.

Conclusion: Low testosterone in men and low DHEA-S in women receiving care at facilities are associated with increased mortality risk, independent of other risk factors and pre-existing health conditions. **Geriatr Gerontol Int 2011; 11: 196–203**.

Keywords: dehydroepiandrosterone, disabled elderly, mortality risk, testosterone.

Introduction

Japan has the longest life expectancy at birth in the world for both men and women, although women live 8 years longer than men on average.[1,2] One explanation for this phenomenon is that estradiol production during the premenopausal years partially protects women from cardiovascular disease (CVD). In contrast, there has been a suspicion that testosterone itself is harmful; however, recent studies support the hypothesis that testosterone may be beneficial to survival in aging men.[3–8]

It is well established that endogenous androgens decline with advancing age in men.[9] Because testosterone has important physiological effects on muscle, bone, brain, erythropoietin and the vascular system, decreased testosterone levels could contribute to age-associated symptoms and diseases in older men, such as decreased muscle mass and strength,[10] impaired physical performance,[11,12] osteoporosis[13] and fractures,[12,14] depressed mood,[15] cognitive impairment,[16,17] anemia[18,19] and frailty.[20] In our previous study in which older persons receiving day-care services or admitted to a facility were investigated, higher plasma testosterone levels were associated with better activities of daily living (ADL), cognitive function and vitality in men.[21] On the other hand, several epidemiological studies have demonstrated that a decline in testosterone level was associated with mortality risk in community-dwelling middle-aged or older men.[3–8] In cause-specific analyses, some studies have shown that a low testosterone level was associated with an increased risk of death due to CVD.[4,5] However, the above-mentioned studies were performed in community samples of Caucasian men, and this issue remains to be clarified in frail or disabled older men.

The majority of dehydroepiandrosterone (DHEA), an endogenous steroid precursor to testosterone and estrogen, exists as the sulfated form (DHEA-S) in the circulation, and DHEA and DHEA-S are the most abundant adrenal sex steroid hormones, with concentrations reported to be more than 100-fold higher than those of testosterone and estradiol,[22] suggesting an important physiological role of DHEA(-S). Their circulating levels also peak in young adults and decline with age in both men and women. Although the role of androgens in older women's health is not fully understood, postmenopausal women with intact ovaries continue to produce androgens, DHEA and testosterone, while their production of estradiol is minimal.[23] In our previous study,[21] in older women, higher DHEA and DHEA-S levels were related to better ADL, while estradiol and testosterone levels showed no relations. Other reports have shown a correlation between DHEA level and cognitive function,[24] depression,[25] osteoporosis[26] and frailty in older women.[27] Several studies that examined the association between DHEA-S and mortality in women have shown mixed results,[28–32] and mostly found no relation; however, both low and high levels of DHEA-S at baseline[28] and some trajectory patterns such as a steep decline or extreme variability[32] have been reported to correlate with increased mortality.

These lines of evidence suggest that endogenous androgens, including testosterone and DHEA(-S), may play a role in physical and mental function as well as longevity in older individuals. We hypothesized that low plasma androgen levels could be a mortality risk factor even in elderly with disability who are receiving facility services.

Methods

Study population

In this longitudinal observational study, 218 consecutive persons aged 70 years or older (121 men aged 70–96 years and 97 women aged 70–95 years; mean ± standard deviation [SD] age, 83 ± 6 and 83 ± 5 years, respectively) who attended health service facilities for the elderly (facilities that provide nursing care and rehabilitation services to elderly people with disability, *Mahoroba-no-Sato*) located in Nagano Prefecture, Japan were enrolled. The participants were in a chronic stable condition and receiving services under Long-term Care Insurance, which is provided by the Japanese Government, either under admission or as day care. The principal exclusion criteria were malnutrition (serum albumin <3.5 mg/dL or body mass index [BMI] <16 kg/m^2), extremely low ADL status (Barthel Index[33] <50), malignancy, acute inflammation (fever, white blood cell count >10 000/μL, or other signs of infection within 4 weeks before enrollment), severe anemia (blood hemoglobin <10.0 g/dL) and overt endocrine disease because these conditions may affect both plasma sex hormone levels and mortality. Deaths that occurred during the first 6 months of follow up (four men and no women) were also excluded to minimize the influence of comorbidity on both sex hormone levels and mortality; therefore, the remaining 214 persons were analyzed in this study. The institutional review board of *Mahoroba-no-Sato* approved the study protocol, and all participants and/or their family members gave written informed consent.

Hormone measurements

Blood samples were obtained from the participants in the morning after an overnight fast, and plasma hormone levels in addition to blood cell counts and blood chemical parameters were determined by a commercial laboratory (Health Sciences Research Institute, Yokohama, Japan). Testosterone and estradiol were assayed using chemiluminescence immunoassays with minimum detection limits of 7 ng/dL (0.2 nmol/L) and 4 pg/mL (14.7 pmol/L), respectively. DHEA-S was assayed using a sensitive radioimmunoassay with a minimum detection limit of 2.0 μg/dL (0.05 μmol/L). The intra-assay coefficients of variation for these measurements were less than 5%.

Functional and anthropometric measurements

Trained nurses and physical therapists visited the participants at the health facilities and performed comprehensive geriatric assessments. Basic ADL was assessed by Barthel Index,[33] cognitive function by Hasegawa Dementia Scale – Revised (HDS-R, 30-point scale),[34] mood by the Geriatric Depression Scale (GDS, 15 items),[35] and ADL-related vitality by Vitality Index (10-point scale).[36] BMI was calculated

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as weight in kilograms divided by the square of height in meters.

Comorbidity

Diseases were ascertained by experienced physicians according to pre-established criteria that combine information from self-reported physician diagnoses, medical records, current medication, clinical examinations and blood tests. Diseases included in the current analysis were hypertension, heart disease (including any of angina pectoris, myocardial infarction, congestive heart failure and arrhythmia), stroke, diabetes mellitus, osteoarthropathy (arthritis, rheumatism, osteoporosis and history of fractures), lung disease (including bronchial asthma and chronic obstructive pulmonary disease) and other chronic diseases (chronic kidney disease, gastrointestinal disease, Parkinson's disease and psychological disorders). We also obtained data on anti-androgenic treatment and intake of glucocorticoids, opiates and hormone supplements that could affect plasma hormone levels, but no subject was taking any of these.

Follow up

The subjects were followed up in 2002–2009, for a period of up to 52 months (mean ± SD, 32 ± 13 [34] months in men and 45 ± 11 [49] months in women). Time and causes of death of deceased persons were ascertained using medical records and death certificates. All deaths were registered with International Classification of Diseases, 10th version (ICD-10) codes,[37] based on the information from death certificates. We categorized deaths into the following four specific causes: (i) diseases of the circulatory system (I00–I99) including heart disease and cerebrovascular disease; (ii) diseases of the respiratory system (J00-J99); (iii) neoplasms (C00-D48); and (iv) other causes. Subjects who were alive were confirmed by checking appointment records of the facilities. Survival of 16 subjects whose records were not available was ascertained by the phone interview of each subject. Causes of death were determined for all the subjects without any missing cases.

Statistical analysis

Differences between testosterone tertiles in men and between DHEA-S tertiles in women were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. Survival was analyzed using Kaplan–Meier plots and log–rank tests. Hazard ratios (HR) for mortality were analyzed using Cox proportional hazards regression. Significance tests were two-sided, with an α-level of 0.05. Data were analyzed using SPSS statistical software.

Results

Characteristics of study subjects

Over the follow-up period, 27 men and 28 women died, yielding a mortality rate of 86.5/1000 person-years at risk in men; and 69.9/1000 person-years at risk in women. Of those, 13 deaths were due to diseases of the circulatory system (eight to ischemic and other heart disease and five to cerebrovascular disease), 10 to diseases of the respiratory system and four to cancer in men; while 14 deaths were due to diseases of the circulatory system (nine to ischemic and other forms of heart disease and four to cerebrovascular disease), eight to diseases of the respiratory system, five to cancer and two to other causes in women. Men who died were significantly older, had lower serum albumin and cholesterol, lower ADL and cognitive status, higher prevalence of heart disease, and lower testosterone level than survivors; whereas in women, subjects who died were older, had lower hemoglobin, higher prevalence of heart disease and lower plasma DHEA-S level than survivors (data not shown).

Table 1 shows the baseline characteristics of the male subjects by tertile of plasma testosterone. A significant difference was observed in serum albumin and hemoglobin levels, ADL and cognitive status among tertiles of testosterone in men. Table 2 shows the baseline characteristics of the female subjects by tertile of plasma DHEA-S. A significant difference was found in age and ADL status among DHEA-S tertiles in women, while other variables did not differ between the tertile groups.

Mortality and plasma sex hormone levels in men

As shown in Figure 1(a), Kaplan–Meier survival analysis by tertile of plasma testosterone level revealed that testosterone level was associated with mortality in men. After adjusting for age, Cox proportional hazards models showed that there was an inverse relation between testosterone level and mortality. Mortality rate differed significantly between the high and low testosterone tertiles, but not significantly between the middle and low tertiles: tertile 3 (high), reference; tertile 2 (middle), HR = 2.51 (95% confidence interval [CI] = 0.66–9.50); and tertile 1 (low), HR = 6.63 (95% CI = 1.92–23.21). Accordingly, we investigated the increased mortality in tertile 1 versus tertiles 2–3 (Table 3). Compared with subjects within tertiles 2–3,

Table 1 Association between potential confounding variables and testosterone tertiles in men

Characteristic	Testosterone tertiles			*P*-value
	T1 <10.4 nmol/L (<300 ng/dL), *n* = 39	T2 10.4–16.3 nmol/L (300–470 ng/dL), *n* = 40	T3 >16.3 nmol/L (>470 ng/dL), *n* = 38	
Age, years	83 ± 7	83 ± 6	81 ± 6	0.11
Nutritional parameters				
Body mass index, kg/m^2	21.3 ± 3.4	22.8 ± 3.8	21.7 ± 3.0	0.21
Hemoglobin, g/dL	12.7 ± 1.9	13.8 ± 1.3	14.0 ± 1.7	<0.01
Albumin, g/dL	4.0 ± 0.3	4.1 ± 0.2	4.2 ± 0.3	<0.01
Total cholesterol, mg/dL	173 ± 38	195 ± 36	176 ± 28	0.05
Prevalent diseases, *n* (%)				
Hypertension	17 (44)	16 (40)	12 (32)	0.53
Heart disease	10 (26)	5 (13)	7 (18)	0.32
Stroke	12 (31)	15 (38)	8 (21)	0.34
Diabetes mellitus	8 (21)	5 (13)	8 (21)	0.31
Osteoarthropathy	8 (21)	9 (23)	7 (18)	0.94
Lung disease	2 (5)	3 (8)	3 (8)	0.52
Other chronic diseases	17 (44)	19 (48)	18 (47)	0.95
Functional parameters				
Barthel Index	79 ± 12	82 ± 11	87 ± 13	0.04
HDS-R	18 ± 7	19 ± 6	22 ± 5	0.02
Vitality Index	9.2 ± 1.1	9.3 ± 0.9	9.5 ± 0.9	0.46
GDS	5.0 ± 3.1	5.6 ± 3.7	5.6 ± 2.9	0.66
Sex hormone levels				
Testosterone, nmol/L	7.6 ± 2.5	13.3 ± 1.6	20.9 ± 3.9	<0.01
(ng/dL)	(219 ± 73)	(382 ± 43)	(602 ± 112)	
DHEA-S, μmol/L	1.7 ± 1.1	1.8 ± 1.6	1.7 ± 1.2	0.94
(μg/dL)	(64 ± 42)	(69 ± 57)	(63 ± 45)	

Values are shown as mean (standard deviation). Differences between the groups were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. DHEA-S, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale – Revised.

a testosterone level within tertile 1 was associated with approximately fourfold higher mortality risk. Adjustment for age, nutritional parameters (BMI, albumin, hemoglobin, total cholesterol) and functional parameters (Barthel Index, HDS-R, Vitality Index, GDS), and prevalent diseases showed no major influence on the result. In order to examine how follow-up time and cancer impacted on the results, assuming that the subjects may have had subclinical cancer or a fatal illness at baseline, we performed further analyses excluding deaths that occurred in the first 12 months ($n = 9$) and deaths from cancer ($n = 4$). However, the significant associations remained after these exclusions (Table 3). On the other hand, DHEA-S level was not associated with mortality when DHEA-S was entered as tertiles (data not shown).

Although the statistical power was not strong enough, we studied the risk for cause-specific mortality by tertiles of testosterone level in men. Neither deaths from diseases of the circulatory system nor those from non-circulatory causes showed a significant association with testosterone tertiles (tertile 1 vs tertile 2–3, HR = 3.18, 95% CI = 1.87–11.6, $P = 0.17$; HR = 3.46, 95% CI = 0.29–7.29, $P = 0.64$, respectively).

Mortality and plasma sex hormone levels in women

As shown in Figure 1(b), a low DHEA-S level was associated with higher mortality by Kaplan–Meier survival analysis. Age-adjusted Cox proportional hazards models revealed that the association was not significant when each tertile of DHEA-S was entered as a continuous variable; however, a significant association was observed when tertile 1 was compared with tertiles 2–3 (Table 3). The association remained significant after excluding deaths that occurred in the first 12 months ($n = 2$) and deaths from cancer ($n = 5$). Moreover, further adjustment had no major influence on the result. In women, testosterone and estradiol levels were not associated with mortality when they were entered as tertiles (data not shown).

In cause-specific mortality analysis, compared with tertiles 2–3, the low tertile of DHEA-S level was associated with higher risk of death from diseases of the

Table 2 Association between potential confounding variables and DHEA-S tertiles in women

Characteristic	DHEA-S tertiles T1 <1.17 μmol/L (<43 μg/dL), *n* = 33	T2 1.17–1.49 μmol/L (43–55 μg/dL), *n* = 32	T3 >1.49 μnmol/L (>55 μg/dL), *n* = 32	*P*-value
Age, years	83 ± 6	82 ± 6	80 ± 6	0.08
Nutritional parameters				
Body mass index, kg/m^2	22.3 ± 2.7	22.5 ± 3.2	23.7 ± 2.7	0.31
Hemoglobin, g/dL	12.6 ± 1.4	12.6 ± 1.2	13.1 ± 1.1	0.16
Albumin, g/dL	4.1 ± 0.3	4.2 ± 0.3	4.3 ± 0.2	0.18
Total cholesterol, mg/dL	205 ± 30	204 ± 35	205 ± 35	0.99
Prevalent diseases, *n* (%)				
Hypertension	10 (30)	14 (44)	15 (47)	0.47
Heart disease	4 (12)	7 (22)	8 (25)	0.46
Stroke	5 (15)	4 (13)	6 (19)	0.79
Diabetes mellitus	5 (15)	4 (13)	5 (16)	0.90
Osteoarthropathy	8 (24)	11 (34)	13 (40)	0.47
Lung disease	3 (9)	2 (6)	2 (6)	0.56
Other chronic diseases	17 (52)	19 (59)	18 (56)	0.90
Functional parameters				
Barthel Index	90 ± 7	93 ± 8	95 ± 8	0.04
HDS-R	23 ± 6	22 ± 7	25 ± 5	0.39
Vitality Index	9.2 ± 1.4	9.1 ± 2.2	8.8 ± 2.9	0.35
GDS	6.8 ± 2.6	5.9 ± 3.4	6.9 ± 3.3	0.16
Sex hormone levels				
DHEA-S, μmol/L	0.8 ± 0.2	1.3 ± 0.1	2.0 ± 0.3	<0.01
(μg/dL)	30 ± 7	49 ± 4	73 ± 12	
Testosterone, nmol/L	1.2 ± 0.6	1.2 ± 0.6	1.3 ± 0.5	0.81
(ng/dL)	35 ± 17	36 ± 17	37 ± 13	
Estradiol, pmol/L	56 ± 32	57 ± 37	67 ± 46	0.41
(pg/mL)	15.3 ± 8.6	15.5 ± 10.2	18.3 ± 12.5	

Values are shown as mean (standard deviation). Differences between the groups were analyzed using ANOVA for continuous variables and χ^2-test for categorical variables. DHEA-S, dehydroepiandrosterone sulfate; GDS, Geriatric Depression Scale; HDS-R, Hasegawa Dementia Scale – Revised.

circulatory system (HR = 13.1, 95% CI = 2.39–72.3, $P < 0.01$), while there was no association with deaths from non-circulatory causes (HR = 0.93, 95% CI = 0.86–1.02, $P = 0.14$).

Discussion

In this small prospective study of Japanese elderly who were receiving care in facilities, a low testosterone level was associated with mortality in men independent of multiple risk factors and pre-existing health conditions. In addition, a low DHEA-S level in older women was related to increased mortality. In contrast, DHEA-S level in men and testosterone and estradiol levels in women were not related to mortality.

Recent prospective cohort studies in Western countries have yielded inconsistent findings about the use of a low total testosterone level as a predictor of all-cause and cardiovascular mortality in middle-aged to older men.[4,5,38,39] In the two studies that found no significant prediction of mortality,[38,39] the populations were younger (mean or median ages were in the early 50s), testosterone levels were higher and mortality rates were lower (11.6 and 15.4/1000 person-years, respectively) compared to those in studies that found positive results. In the present study, although the sample size was small, the subjects were frail and older than those in any previously reported studies, with a relatively small age range and higher mortality rate. Therefore, the relation between testosterone level and mortality might have been easier to detect in our study than in other studies with healthy middle-aged and older men.

There could be several mechanisms by which endogenous testosterone affects mortality in men. Although the number of subjects was too small to perform cause-specific analysis in the present study, other studies have reported that a low testosterone level predicted increased risk of death due to CVD.[4,5] Further, in addition to the relation to muscle strength, physical performance and ADL,[10–12,21] some but not all reports have

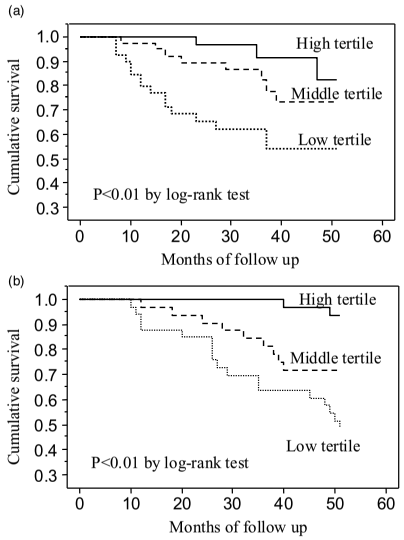

Figure 1 (a) Survival curves by tertile group of plasma testosterone level in men. (b) Survival curves by tertile group of plasma dehydroepiandrosterone sulfate level in women.

demonstrated an association between low testosterone level in older men and risk of a fall or fracture and frailty.[12–14,20] It is noteworthy that in the 10 men who died of respiratory infection, four had a history of a fall and fracture, which resulted in worse disability. Accordingly, a low testosterone level may contribute to frailty, which influences men's susceptibility to illness and falls and the capability to recover from disease or fractures, and thereby affects mortality.

Other than aging, systemic illness can result in decreased testosterone levels; therefore, low testosterone levels in older men could be attributable to acute and chronic diseases,[40] and the possible reverse causality should be considered. To evaluate this possibility, we excluded the first 12 months of observation and still found that in 12–52 months of observation, men in the low testosterone tertile had a greater risk of mortality from all causes than those in higher tertiles. We carefully excluded subjects with critical diseases and conditions at baseline, although our subjects were old with multiple chronic diseases, and it is difficult to exclude the possibility that men with subclinical critical conditions might have been included. Moreover, at baseline, there was a significant difference in functional status (ADL and cognition) and nutritional parameters (serum albumin and hemoglobin levels) between testosterone tertiles, as reported previously;[21] thus, our results need to be confirmed in a cohort with no difference in these factors between testosterone groups to exclude the influence of these biases on mortality. Also, it needs to be explored whether low testosterone in older men plays a pathogenic role, such as affecting the immune system, developing physical frailty and depression, or simply serves as a marker for biological vulnerability and poor prognosis. Long-term studies also need to test whether testosterone treatment should yield clinically significant improvements in mortality in appropriately selected older men, with consistent symptoms and signs and unequivocally low serum testosterone levels.

Low DHEA-S has been associated with increased all-cause and cardiovascular mortality in older men;[26,27,41] however, no association was found in the present study. Because DHEA(-S) is an inactive prohormone and we and others have found an association between testosterone and mortality,[3–8] it is suggested that testosterone could be a stronger predictor of mortality in older men.

On the other hand, a low DHEA-S level in older women was associated with a poor prognosis after adjusting for multiple factors related to mortality. Other previous reports showed an inconsistent relationship between DHEA-S level and mortality in older women,[29–31] possibly due to differences in the cohorts including age, DHEA-S level, heterogeneity of health status and mortality rate, and the method of statistical analysis used to demonstrate the relationship, regression models with linear/non-linear assumption.

Previous studies support a potential physiological role of DHEA-S, which could contribute to reduced mortality, an anti-inflammatory action and immune regulatory activity.[42] However, there are still many unanswered questions regarding DHEA's role in aging, and there is insufficient evidence to support DHEA replacement for increasing longevity in older women. It also needs to be explored whether the DHEA-S level contributes to mortality or is merely a biomarker of the underlying health condition of older women.

Our study has some limitations. First, the sample size was too small to reach a clear conclusion with strong statistical power, thus limiting the precision of the estimates, which is reflected in the broad range of HR for mortality. Second, the results are based on single measurements of sex hormones, which do not allow assessment of changes in levels over time; therefore, they may overestimate or underestimate the association between hormone levels and mortality. Third, we did not measure estradiol levels in men, although it would have been helpful to see whether the effects of testosterone on mortality are mediated by testosterone itself or by aromatization to estradiol in older men. Finally, active forms of testosterone such as bioavailable and

Table 3 Hazard ratios for low tertile 1 vs tertiles 2–3 of plasma sex hormone levels for all-cause mortality in men and women

	Unadjusted	Model 1	Model 2
Men ($n = 117$)			
HR of low testosterone for mortality	3.83 (1.74–8.40)**	3.71 (1.54–8.04)**	3.27 (1.24–12.91)*
Excluding first-year deaths ($n = 108$)	3.81 (1.53–6.93)**	3.49 (1.14–7.39)**	3.08 (1.11–13.62)*
Excluding deaths from cancer ($n = 113$)	4.18 (1.77–9.86)**	4.03 (1.70–9.58)**	5.02 (1.51–15.41)*
Women (N = 97)			
HR of low DHEA-S for mortality	3.77 (1.77–8.07)**	3.86 (1.79–8.32)**	4.42 (1.51–12.90)*
Excluding first-year deaths ($n = 95$)	3.38 (1.55–7.37)**	3.43 (1.56–9.54)**	3.58 (1.12–11.46)*
Excluding deaths from cancer ($n = 92$)	3.82 (1.69–8.60)**	3.55 (1.54–8.19)**	3.92 (1.28–11.98)*

*$P < 0.05$; **$P < 0.01$ vs reference group (tertile 2–3). Values are expressed as HR (95% CI). Model 1, adjusted for age; Model 2, adjusted for age, nutritional parameters, functional parameters and prevalent disease. DHEA-S, dehydroepiandrosterone sulfate; HR, hazards ratio.

calculated free testosterone were not measured, because a direct assay of bioavailable testosterone or an assay of sex hormone binding globulin, which is necessary for free testosterone calculation, is not available in Japan. However, because most of the above-mentioned previous reports have shown an association of total testosterone with mortality, the fundamental findings might not have differed if active forms of testosterone had been analyzed.

In conclusion, a low testosterone level in men and a low DHEA-S level in women are associated with increased mortality risk, independent of multiple risk factors and several pre-existing health conditions in disabled elderly. To our knowledge, the present study is the first that showed testosterone as a predictor of mortality in Asian men. Also, this is the first study that investigated frail or disabled older persons receiving care at facilities. Our results imply the clinical importance of measuring plasma androgen levels even in disabled elderly to estimate their prognosis.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Relationship between interleukin-6 and cerebral deep white matter and periventricular hyperintensity in elderly women

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Aim: We evaluated the relationships between serum levels of high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 with the severity of leukoaraiosis.

Methods: One hundred and thirty-seven elderly women who attended the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were enrolled in this study. Leukoaraiosis was assessed by periventricular hyperintensity (PVH) score and deep white matter hyperintensity (DWMH) score.

Results: Serum log IL-6 level correlated with PVH and DWMH scores, but hsCRP did not. By multinomial logistic analysis, IL-6 was significantly related to DWMH score, independent of age and systolic blood pressure.

Conclusion: IL-6 is presumably an important marker of leukoaraiosis, as is the case with silent cerebral infarction. **Geriatr Gerontol Int 2011; 11: 328–332.**

Keywords: interleukin-6, leukoaraiosis, white matter hyperintensity.

Introduction

Leukoaraiosis, an isointense lesion on T_1-weighted images and hyperintense lesion on T_2-weighted images of magnetic resonance imaging (MRI), is considered to be a type of ischemic change in the brain on the basis of decreased blood flow in the area of leukoaraiosis.[1] In addition, leukoaraiosis is likely to have a relationship with vascular risk factors such as hypertension and diabetes.[2] On the other hand, the severity of leukoaraiosis also has a relationship with symptoms of the geriatric syndromes such as dementia, gait disturbance and functional disability.[3–5] Hence, leukoaraiosis is regarded as a significant brain lesion linking vascular risk factors and the occurrence of geriatric syndromes. Previous research on leukoaraiosis showed that women tended to have more white matter lesions than men,[6] and progression of deep white matter hyperintensity (DWMH) lesion was grater in women than men.[7] Furthermore, Gouw *et al.* showed that leukoaraiosis tended to develop greater in women than men and lacunes were vice versa.[8] Recently, many studies have focused on the relationships between brain ischemia and inflammation. Above all, Hoshi *et al.* demonstrated that serum high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 levels correlated with silent brain infarction.[9] They suggested an involvement of inflammation in cerebral infarction. However, few studies have examined the relationships between inflammatory markers and other cerebral ischemic changes such as leukoaraiosis.Therefore, we investigated whether serum levels of hsCRP and IL-6 have a relationship with leukoaraiosis in elderly women.

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Methods

Patients

One hundred and thirty-seven women who attended the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were included in this study. This study was approved by the Ethics Committee of Kyorin University School of Medicine. Accordingly, written informed consent was obtained from all patients.

MRI

Magnetic resonance imaging (MRI) was performed on 1.5-T scanners (Toshiba Medical Systems, Tochigi, Japan). T_1-weighted images (repetition time [TR] = 496 msec, echo time [TE] = 12 msec), T_2-weighted images (TR = 4280 msec, TE = 105 msec) and fluid attenuated inversion recovery-weighted images (TR = 8000 msec, TE = 105 msec, 5 mm slice thickness) were obtained in the axial planes.

Periventricular hyperintensity and DWMH Score

Leukoaraiosis was classified as periventricular hyperintensity (PVH) adjacent to the lateral ventricle, and DWMH located in the deep white matter apart from the lateral ventricles. PVH was evaluated in six regions in three slices. Each region was rated as five grades (0–4) according to the systematic quantification method developed by Junque *et al.*[3] The sum of all grades in the six regions was defined as the PVH score (range 0–40).[4] DWMH was evaluated in the frontal, temporal, parietal and occipital lobes and in the basal ganglia in both hemispheres. Each lesion was rated as three grades according to the diameter, as described by de Groot *et al.*[5] The sum of all grades in five regions in both hemispheres was defined as the DWMH score.[4]

Laboratory tests

Blood samples were obtained in the morning after an overnight fast. Serum levels of hsCRP and IL-6 were measured using nephelometry and enzyme-linked immunosorbent assay, respectively. The intra-assay coefficients of variation for the measurements of hsCRP and IL-6 were 1.3% and 2.9%, respectively.

Statistical analysis

Because the distribution of hsCRP and IL-6 levels appeared to be left-skewed, they were normalized by logarithmic transformation. We used Spearman's ρ to investigate correlations between parameters and PVH score or DWMH score. Also, to test independently the effect of the inflammatory markers associated with the severity of leukoaraiosis, multinomial logistic regression analysis was performed with the grade of PVH (tertiles of PVH score) or DWMH (tertiles of DWMH score) as the dependent variable; and hsCRP or IL-6, together with age and systolic blood pressure (SBP) as independent variables. $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS ver. 17.0.

Results

The characteristics of the study subjects are shown in Table 1. They were non-obese normolipidemic elderly persons, however, SBP was elevated. The distribution of PVH score and DWMH score of these subjects were 1–24 and 0–209, respectively. In Spearman's correlation coefficient, IL-6 correlated with PVH score ($\rho = 0.340$, $P \leq 0.05$) and DWMH score ($\rho = 0.299$, $P \leq 0.05$) (Fig. 1), whereas hsCRP showed no relation to PVH score or DWMH score (Table 2). PVH score and DWMH score also correlated with age and SBP. When log IL-6 and log hsCRP were grouped by tertile (see legend to Fig. 2), it was found that the average PVH score and DWMH score were higher in the highest tertile of IL-6 level than in the lowest tertile according to the Kruskal–Wallis test (Fig. 2a,b). On the other hand, this increment was not found in hsCRP (Fig. 2c,d).

Because leukoaraiosis can be observed on MRI even in normal elderly persons,[10] and hypertension is known to be a risk factor for leukoaraiosis,[11] we performed multinomial logistic regression analysis using PVH or DWMH severity (tertiles of PVH and DWMH score) as the dependent variable, and age, SBP and inflammatory

Table 1 Clinical characteristics of study subjects (women, $n = 137$)

Age (years)	76 ± 7
BMI (kg/m^2)	20.8 ± 3.3
SBP (mmHg)	142 ± 26
DBP (mmHg)	80 ± 14
PVH score (points)	8.2 ± 4.0
DWMH score (points)	61.4 ± 51.0
Total cholesterol (mmol/L)	5.38 ± 0.91
HDL cholesterol (mmol/L)	1.50 ± 0.36
LDL cholesterol (mmol/L)	3.23 ± 0.65
Triglyceride (mmol/L)	1.08 ± 0.46
Log IL-6 (ng/L)	0.35 ± 0.46
Log hsCRP (μg/L)	2.58 ± 0.58

All parameters are expressed as mean ± standard deviation. IL-6 and CRP are shown as log transformed. BMI, body mass index; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensity; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; PVH, periventricular hyperintensity; SBP, systolic blood pressure.

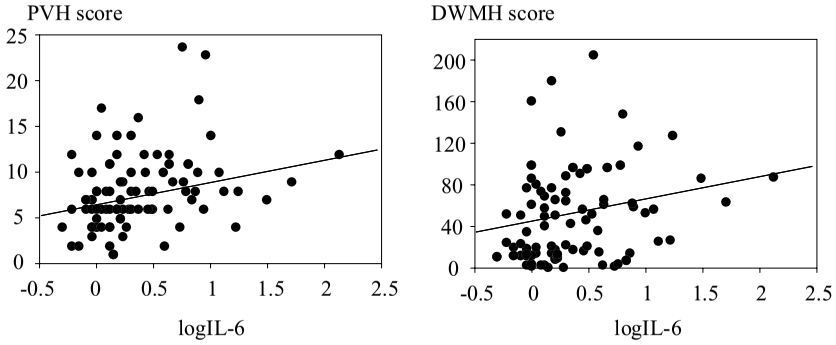

Figure 1 Relations between periventricular hyperintensity (PVH) score and log interleukin (IL)-6 (left panel; ρ = 0.340, $P \leq 0.05$, $n = 137$), and deep white matter hyperintensity (DWMH) score and log IL-6 (right panel; ρ = 0.299, $P \leq 0.05$, $n = 137$).

Table 2 Spearman's correlation coefficient between leukoaraiosis and parameters

	PVH score		DWMH score	
	ρ	*P*	ρ	*P*
Age	0.411	<0.001	0.271	0.002
BMI	−0.156	0.085	−0.124	0.179
SBP	0.215	0.014	0.232	0.009
Total cholesterol	−0.128	0.192	−0.149	0.134
HDL cholesterol	−0.053	0.595	−0.205	0.041
LDL cholesterol	−0.093	0.349	−0.025	0.802
Triglyceride	−0.014	0.885	0.080	0.421
Smoke	0.337	0.005	0.443	0.000
Log IL-6	0.340	0.002	0.299	0.006
Log hsCRP	−0.018	0.867	0.019	0.855

BMI, body mass index; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensity; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; PVH, periventricular hyperintensity; SBP, systolic blood pressure.

markers as independent variables. As shown in Table 3, it was confirmed that the level of IL-6 was significantly associated with the progression of PVH grade (from lowest to middle and middle to highest) and DWMH score (from middle to highest). However, this trend was not found in hsCRP.

Discussion

In this study, we showed relationships between IL-6 and PVH score and IL-6 and DWMH score. It is assumed that IL-6 has an association with cerebral ischemic changes such as leukoaraiosis as well as silent brain infarction.[9] Additionally, PVH and DWMH were correlated with IL-6, but not with hsCRP. With respect to this point, Schmidt *et al.* suggested that CRP is a marker of active carotid atherosclerosis, but not of a small vessel disease-related brain lesion.[12] On the other hand, it is envisaged that elevated hsCRP levels generally reflect large vessel atherosclerosis. Because leukoaraiosis is regarded as one of the brain changes caused by small vessel disease, our results support the idea of Schmidt *et al.*

Interleukin-6 is one of the principal acute-phase reactants, playing a significant role in the activation of the coagulation–fibrinolysis system. On the other hand, leukoaraiosis has been associated with a hypercoagulable condition. Endothelium-derived adhesion molecules have been reported to be elevated in patients with great leukoaraiosis or lacunar infarcts. Leukocyte-mediated injury of the small vessels and ensuing upregulation of endothelial adhesion molecules are implicated in the pathogenesis of leukoaraiosis.[13]

The Rotterdam Scan Study showed that higher hsCRP levels were associated with presence and progression of leukoaraiosis after adjustment for cardiovascular risk factors and carotid atherosclerosis.[14] The subjects in the Rotterdam Scan Study were a population-based cohort ($n = 1033$), while the subjects in the present study were outpatients in the memory clinic ($n = 137$). In this respect, the difference in characteristics and numbers of the subjects may have given rise to the different results in terms of hsCRP in the present study and the Rotterdam Scan Study.

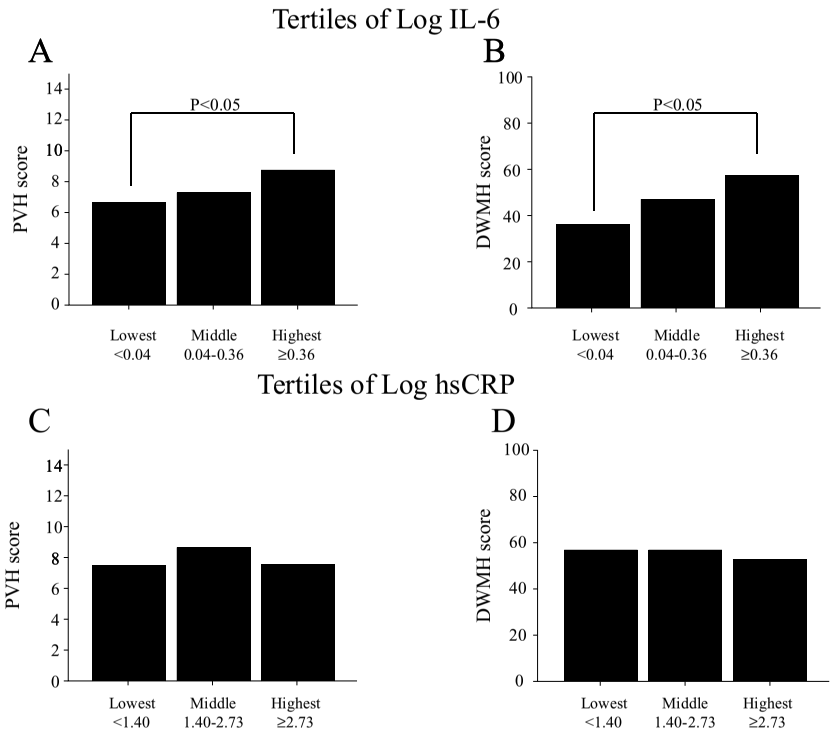

Figure 2 Average of periventricular hyperintensity (PVH) score and deep white matter hyperintensity (DWMH) score by tertile of interleukin (IL)-6 (a,b) and tertile of high-sensitivity C-reactive protein (hsCRP) (c,d). Log IL-6 tertile; lowest, <0.04 pg/mL, $n = 55$, 73.4 ± 7 1 years old (y/o); middle, 0.04–0.36 pg/mL, $n = 38$, 76.9 ± 6.8 y/o; highest, ≥0.36 pg/mL, $n = 44$, 79.5 ± 5.3 y/o. Log hsCRP; lowest, <1.40 ng/mL, $n = 44$, 73.9 ± 7.0 y/o; middle, 1.40–2.73 ng/mL, $n = 46$, 77.6 ± 7.1 y/o; highest, ≥2 73 ng/mL, $n = 41$, 77.8 ± 6.3 y/o.

In the Framingham Heart Study, no association was found between hsCRP and leukoaraiosis on MRI.[15] In the Cardiovascular Health Study, hsCRP level was modestly associated with semi-quantified leukoaraiosis volume, but the effect attenuated after excluding prevalent cerebrovascular and coronary disease cases.[13] In addition, Wright *et al.* was not able to find an association between hsCRP and leukoaraiosis volume.[16] Together, the relationships between leukoaraiosis and hsCRP varied depending upon different reports. This may come from the difference in study subjects and analytical methods. Further investigation is necessary to hold more definite opinion about which inflammatory biomarker represents the presence and development of leukoaraiosis.

Several lines of evidence suggest a relationship between IL-6 and symptoms of the geriatric syndromes, unique features of common health problems associated with poor morbidity in elderly people, such as dementia,[17] functional disability[18] and frailty.[19] On the other hand, the severity of leukoaraiosis also has a relationship with symptoms of geriatric syndromes such as dementia, falls, gait disturbance and functional disability.[3–5] Therefore, IL-6 may be an important biomarker linking the severity of leukoaraiosis to the geriatric syndromes. Because the present study is

Table 3 Associations between inflammation markers and the severity of leukoaraiosis according to tertiles (PVH score or DWMH score) adjusting for age and systolic blood pressure (logistic regression analysis)

	Log hsCRP, μg/L Odds ratio (95% CI)	Log IL-6, ng/L Odds ratio (95% CI)
PVH grade (tertiles)		
Lowest to middle	1.84 (0.78–4.31)	5.80 (1.43–23.60)
Middle to highest	0.39 (0.12–1.32)	4.39 (1.02–18.85)
DWMH grade (tertiles)		
Lowest to middle	0.81 (0.333–1.99)	3.18 (0.78–12.95)
Middle to highest	1.25 (0.48–3.29)	7.85 (1.69–36.38)

Grade of leukoaraiosis according to tertiles of PVH score or DWMH score. CI, confidence interval; DWMH, deep white matter hyperintensity; IL-6, interleukin-6; hsCRP, high-sensitivity C-reactive protein; PVH, periventricular hyperintensity.

cross-sectional, a longitudinal study would corroborate the associations of IL-6 with leukoaraiosis, and IL-6 with the geriatric syndromes.

In conclusion, we demonstrated that IL-6 level is significantly associated with the severity of PVH and DWMH lesions. The results of the present study, together with the previous studies, suggest that IL-6 is an important marker of the progression of cerebral ischemic disease, linking to the presence of geriatric syndromes.

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ORIGINAL ARTICLE

Lower physical activity is a strong predictor of cardiovascular events in elderly patients with type 2 diabetes mellitus beyond traditional risk factors: The Japanese elderly diabetes intervention trial

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Aim: It is well known that a decline in physical activity is associated with lifestyle-related diseases including cardiovascular (CV) events. However, little is known about the association between physical activity and CV events in elderly patients, because recent accumulating reports have mainly dealt with middle-aged populations. In this study, we investigated the correlation between physical activity and CV events in Japanese elderly patients with type 2 diabetes mellitus (T2DM).

Methods: A total of 938 Japanese elderly patients with T2DM (447 men and 491 women, mean age 71.9 years) enrolled (2000–2002) in the Japanese Elderly Diabetes Intervention Trial (J-EDIT) were used in this study. Physical activity consisting of three components, work, sports and leisure-time, of their lifestyle was evaluated using the Baecke questionnaire at baseline. Total activity score (TAS) as a sum of each activity score was divided into four quartiles (Q1 to Q4).

Results: During a follow-up period of 65.2 months, 165 events and 71 deaths in total occurred. Higher TAS grade was associated with reduced risk of all events (hazard ratios: 0.82, 0.77 and 0.54 in Q2, Q3 and Q4, respectively) with statistical significance. Even after multivariate adjustment for covariates, higher TAS grade was a strong predictor of all events, and the prediction by TAS of cerebrovascular events was more effective than that of cardiac events. In contrast, all-cause mortality gradually decreased according to TAS grade; however, no statistical significance was found. Among the four grades of TAS, no significant change in several parameters, such as profiles of lipid and glucose metabolism, blood pressure, physical measurements, cognitive function and depression scale, was found throughout the follow-up period, suggesting that the higher level of physical activity itself was associated with the risk reduction of primary events.

Conclusion: Lower physical activity is a strong and independent predictor of all CV events in the elderly with T2DM beyond traditional risk factors. In addition to strict management of each atherosclerotic risk factor, engagement with patients to augment and maintain the level of physical activity in their lifestyle is also essential in clinical practice. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 77–87.**

Keywords: elderly, engagement in physical activity, Japanese Elderly Diabetes Intervention Trial study, physical activity, risk reduction, type 2 diabetes mellitus.

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Background

A decline in physical activity has been shown to lead to increased risk of several cardiovascular (CV) diseases, such as cerebrovascular disease (CVD) and coronary heart disease (CHD).[1–6] In developed countries, 80% of all deaths from CV disease occur in people aged 65 years and older.[7] Unfortunately, 60% or more of USA adults are not physically active in their lifestyle.[8] Accordingly, in 1995 the Centers for Disease Control (CDC) and the American College of Sports Medicine (ACSM) recommended a moderate amount of physical activity on most days, and preferably all days, of the week.[9] However, the precise mechanisms through which physical activity lowers the risk of CV disease are not well understood.

Little is known about the crucial correlation between physical activity and CV events in elderly patients, because recent accumulating reports have mainly dealt with middle-aged populations. In fact, the evidence as a whole has been derived from studies targeting the middle-aged and the elderly combined, including three previous studies in Japan.[10–12] In addition, few studies have evaluated the association between physical activity and long-term outcomes in Japanese. The Framingham Heart Study showed an inverse association between physical activity and mortality risk as a result of CV disease, even in 285 elderly individuals.[13] However, no statistical significance was reached, possibly as a result of the limited number of events. To our knowledge, how effective and beneficial encouragement of physical activity is in the elderly is still controversial. In general, although activity has been believed to be beneficial even in the elderly,[14–16] some studies have emphasized that physical activity might be harmful to the elderly.[13,17] Therefore, it is essential to investigate the precise association of physical activity with CV events and mortality in Japanese elderly patients.

In the present study, the correlation between grade of physical activity and events (all CV events and all-cause mortality) was investigated in Japanese elderly patients with type 2 diabetes mellitus (T2DM). In addition, analysis was also carried out to address which component was more effective as a good predictor.

Methods

Study population

The subjects were participants who were enrolled in the Japanese Elderly Diabetic Intervention Trial (J-EDIT), a randomized, double-blind, recently completed trial of intensive or standard treatment of diabetes for the prevention of CV disease in elderly patients with T2DM. J-EDIT involved 1173 diabetic subjects who were aged 65 years or older (mean age 71.8 ± 4.6 years) and whose serum glycated hemoglobin A1c (HbA1c) level was >7.4% from 39 institutions and hospitals (the University of Tokyo Hospital, Kobe University Hospital, Nagoya University Hospital and Tokyo Metropolitan Geriatric Hospital etc.) in Japan. Written informed consent was obtained from all patients.

From among these patients enrolled in the J-EDIT, we selected 938 patients in whom complete data regarding physical activity (Baecke physical activity questionnaire) were obtained at baseline. We excluded participants who had difficulty communicating, dementia or serious deterioration of activities of daily living (ADL).

Physical activity assessed by Baecke questionnaire

To evaluate physical activity at enrolment in this trial, Baecke physical activity questionnaire was carried out as previously reported.[18,19] The reliability of this score has been confirmed by many previous reports. Therefore, it is suggested that it might be a valuable monitoring tool for assessing the association of multiple domains of physical activity with the metabolic syndrome (MetS) in elderly patients with T2DM, with acceptable reliability and validity. The activity score is classified into three

domains: work activity, sports activity and non-sporting leisure activity. These three components consisted of items on the frequency, duration, average amount of time spent weekly on walking, hobbies and so on, and the average amount of time spent on odd jobs and sports monthly. The types of odd jobs, sports and hobbies (e.g. dancing, gardening or fishing) were also assessed.

In analyses, each component was also divided into several groups as follows: three groups in "work activity" score (WAS; None: =0, Low: ≥1 and <3.25, High: >3.25), two groups in "sports activity" score (SAS; Low: <4.0, High: ≥4.0), and four groups (quartiles) in "non-sporting leisure-time activity" score (LTAS; L-Q1: <2.0, L-Q2: ≥2.0 and <2.25, L-Q3: ≥2.25 and <2.75, L-Q4: ≥2.75). Scores from each component were summed to yield total physical activity score (TAS; maximum 15 points). TAS was divided into four quartiles (Q1 to Q4) as follows: Q1: <5.7, Q2: ≥5.7 and <7.7, Q3: ≥7.7 and <10.5, Q4: ≥10.5.

Physical measurement, cognitive function, ADL and mood status

At enrolment, body mass index (BMI) was calculated by physical measurement of body height and weight. Both waist circumference and hip circumference were also measured, and waist-to-hip ratio (W/H ratio) was calculated. Cognitive function was determined by Mini-Mental State Examination (MMSE). Each basic or instrumental ADL was determined by Barthel index or Tokyo Metropolitan Institute of Gerontology (TMIG) index,[21] respectively. Mood status was checked using the Geriatric Depression Scale (GDS-15).

Blood pressure and laboratory measurements

Blood pressure (BP) was measured in the clinic. Laboratory data obtained from blood sample collection at enrolment included lipid profile (total cholesterol [TC]), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C; calculated by Friedewald equation: TC-HDL-C-TG/5), profile of glucose metabolism (fasting blood glucose; FBS, HbA1c, fasting insulin concentration [FIRI]), and renal function (serum creatinine). All parameters were obtained every year. Changes in each parameter were calculated as the difference between baseline and end of follow up.

Clinical outcomes

Patients in the present study were continuously monitored for the occurrence of all events and deaths. In this trial, the CV events according to our definition were specified clearly as cardiac events including coronary heart disease (CHD; angina pectoris and myocardial infarction), cerebrovascular disease (CVD) including transient ischemic attack (TIA), stroke and cerebral hemorrhage, peripheral artery disease (PAD), and heart failure (HF). Individual diagnoses were classified according to the 9th International Classification of Disease (ICD-9) codes. We also classified each event into diabetes-related events (CHD, CVD, coronary revascularization, heart failure, sudden death, renal death, diabetic foot) and diabetes-independent events.

Statistical analysis

Differences in baseline characteristics across the four quartiles of physical activity (Q1 to Q4) were evaluated using analysis of variance for normally distributed variables. *P*-values for sex and previous CHD/CVD were calculated based on the Cochran–Armitage trend test, and others were based on the linear contrast test. Event-free survival during the follow-up period was analyzed using Kaplan–Meier curves and log–rank test. Hazard ratios (HR) for all CV events and all-cause deaths were analyzed using a Cox proportional hazards model. HR, 95% confidence intervals (CI) and *P*-values were presented using the lowest quartile (Q1) as the reference category.

Results

Baseline characteristics

The baseline characteristics of all the eligible subjects ($n = 938$) are shown according to TAS category, which was divided into four quartiles (Q1 to Q4), in Table 1.

First, patients with higher TAS grade tended to be slightly younger. Scores of each of the three components (work, sports and non-sporting leisure time) were positively associated with TAS. No significant association between BP and TAS was observed. In the lipid profile, HDL-C and TG were positively correlated with TAS grade (*P*-value for trend: $P = 0.021$ and $P = 0.028$, respectively); however, other lipid parameters (TC and LDL-C) showed no statistical significance. In addition, serum creatinine also tended to be lower according to TAS grade; however, the difference was very slight. Each parameter of glucose metabolism showed no statistical significance between the four quartiles of TAS.

With regard to physical measurements, TAS was negatively associated with waist circumference. BMI and hip circumference also tended to be associated with TAS grade, but without statistical significance.

Cognitive function, as determined by MMSE score, was higher according to increasing TAS grade. TMIG index as instrumental ADL also showed a similar positive association; however, Barthel index as basic ADL did not (data not shown). In addition, GDS-15 score as

Table 1 Baseline characteristics of study subjects according to total physical activity score category

	All ($n = 938$)	TAS category				*P*-values for linear trend
		Quartile 1 ($n = 232$)	Quartile 2 ($n = 229$)	Quartile 3 ($n = 230$)	Quartile 4 ($n = 247$)	
Sex (male)*	447 (47.7)	110 (47.4)	109 (47.6)	115 (50.0)	113 (45.7)	0.841
Age at baseline (years)†	71.9 (4.7)	72.7 (4.8)	72.1 (4.8)	72.1 (4.7)	70.8 (4.2)	<.0001
TAS (total)	7.7 (3.0)	3.6 (1.4)	6.6 (0.6)	9.0 (0.9)	11.3 (0.6)	<.0001
WAS (work)	2.1 (1.6)	1.1 (1.4)	2.1 (1.7)	1.7 (1.5)	3.3 (0.4)	<.0001
SS (sports)	2.8 (2.3)	0.1 (0.5)	1.8 (2.2)	4.5 (0.9)	4.8 (0.3)	<.0001
LTS (leisure-time)	2.8 (0.6)	2.4 (0.5)	2.7 (0.4)	2.9 (0.6)	3.2 (0.4)	<.0001
SBP (mmHg)†	137.1 (16.3)	137.8 (15.8)	137.2 (17)	137.2 (16.1)	136.2 (16.2)	0.310
DBP (mmHg)†	75.0 (9.9)	75.2 (10.4)	75.1 (10.1)	74.8 (10.0)	75.0 (9.1)	0.765
PP (mmHg)†	62.1 (13.6)	62.6 (14.1)	62.3 (13.5)	62.3 (13.7)	61.2 (13.2)	0.291
T-chol (mg/dL)†	203.3 (34.7)	202.4 (35.4)	205.7 (37.3)	202.8 (30.1)	202.4 (35.6)	0.770
HDL-C (mg/dL)†	56.4 (17.9)	53.3 (15.9)	56.8 (17.8)	56.3 (19.3)	58.9 (18.2)	0.002
LDL-C (mg/dL)†	121.0 (30.6)	120.8 (31.5)	123.3 (31.8)	120.9 (28.0)	119.1 (31.0)	0.393
TG (mg/dL)†	133.4 (94.1)	143.3 (86.8)	135.2 (128.9)	130.6 (79)	124.9 (72.6)	0.028
sCr (mg/dL)†	0.8 (0.3)	0.9 (0.4)	0.8 (0.4)	0.8 (0.3)	0.8 (0.2)	<.0001
FBS (mg/dL)†	167.4 (50.6)	172.9 (56.4)	168 (51.3)	168.4 (50.0)	161.1 (44.1)	0.019
FIRI (mg/dL)†	10.3 (10.4)	12.8 (13.9)	10.5 (10.2)	9.2 (8.3)	9.2 (8.3)	0.001
HbA1c (%)†	8.5 (1.3)	8.4 (1.2)	8.5 (1.3)	8.4 (1.3)	8.5 (1.2)	0.767
BMI (kg/m^2)†	23.9 (3.5)	24.5 (3.8)	24 (3.5)	23.6 (3.4)	23.5 (3.1)	0.002
Waist circumference (cm)†	84 (10.3)	86 (10.7)	84.2 (9.6)	83.4 (10.6)	82.6 (9.9)	0.0002
Hip circumference (cm)†	93.9 (8.1)	94.9 (8.5)	94.1 (7.8)	93.2 (7.9)	93.4 (7.9)	0.022
W/H ratio†	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.001
MMSE†	27.9 (2.6)	27.4 (3.3)	27.8 (2.4)	28.1 (2.4)	28.5 (2.1)	<.0001
Barthel index†‡	19.8 (1.1)	19.6 (1.7)	19.8 (1.2)	19.8 (0.6)	19.9 (0.3)	0.004
TMIG index†‡	11.6 (2.2)	10.5 (3.1)	11.6 (2.0)	11.9 (1.7)	12.3 (1.3)	<.0001
GDS-15†‡	4.1 (3.2)	5.3 (3.4)	4.4 (3.2)	3.8 (3.0)	3.1 (2.8)	<.0001
Previous CHD*	154 (16.4)	33 (14.2)	44 (19.2)	42 (18.3)	35 (14.2)	0.005
Previous CVD*	123 (13.1)	38 (16.4)	33 (14.4)	34 (14.8)	18 (7.3)	0.005

*n (%), †Mean (SD), ‡Mini-Mental State Examination (MMSE), Barthel index, Tokyo Metropolitan Institute of Gerontology (TMIG) index, and Geriatric Depression Scale (GDS)-15 are on a scale of 0 to 30, 0 to 20, 0 to 13, and 0 to 15, respectively. *P*-value for sex, previous coronary heart disease (CHD), and previous cerebrovascular disease (CVD) were calculated based on the Cochran-Armitage trend test, and others were based on the linear contrast test. BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood glucose; FIRI, fasting insulin resistance index; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LTS, leisure-time activity score; PP, pulse pressure; SBP, systolic blood pressure; sCr, serum creatinine; SS, sports score; TAS, total activity score; T-chol, total cholesterol; TG, triglyceride; W/H ratio, waist-to-hip circumference ratio; WAS, work activity score.

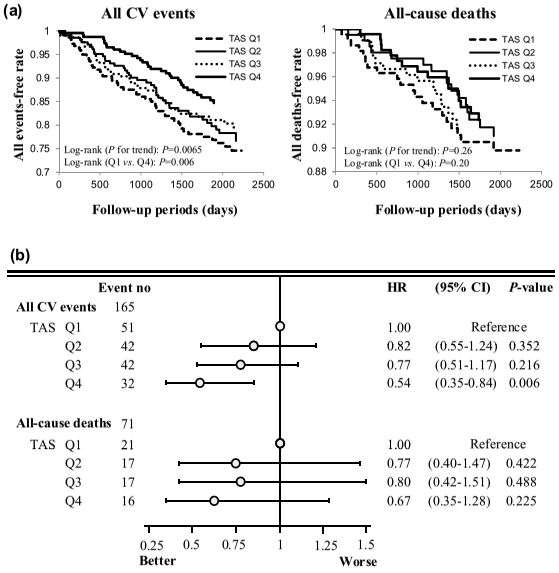

Figure 1 Kaplan–Meier analysis of incidence of all cardiovascular (CV) events and all-cause deaths, and significant risk reduction by higher total activity score (TAS) grade. (a) Kaplan–Meier analysis shows the incidence of all CV events and all-cause deaths. Few primary events of statistical significance were found in the higher TAS group. In contrast to all CV events, all-cause deaths gradually decreased according to TAS grade; however, no statistical significance was found. (b) Before adjustment, hazard ratios (HR) for all CV events and all-cause deaths using a Cox proportional hazards model showed a significant risk reduction with higher TAS grade. Q, quartile.

mood status showed an inverse association with TAS grade, suggesting an association between lower activity and depressive mood.

Regarding previous CHD, there was no significant difference among the groups. In contrast, previous CVD was less frequent in the TAS Q4 group.

Incidence of events during follow-up period

During the follow-up period of approximately 6 years (average 65.2 months), 165 all-CV events and 71 deaths in total occurred. All CV events, defined as a first event, included 45 CHD events (10 fatal and 35 non-fatal), 52 CVD events (4 fatal and 48 non-fatal), 29 diabetes-related events (9 fatal and 20 non-fatal) other than CHD and CVD, and 39 fatal diabetes-independent events. All-deaths included 11 deaths from CHD, four deaths from CVD, 11 diabetes-related deaths and 45 diabetes-independent deaths.

According to TAS grade, the incidence of these events was evaluated in all participants. As shown in Figure 1a, few all-CV events were found in the higher TAS group with statistical significance (log–rank test; $P = 0.0065$). In contrast to all-CV events, all-cause deaths gradually decreased according to TAS grade; however, no statistical significance was found. In analysis without adjustment, HR of each TAS grade were 0.82, 0.77 and 0.54 in Q2, Q3 and Q4, respectively, compared with Q1 as reference (P-value for trend; $P = 0.006$; Fig. 1b). In comparison between the lowest group (Q1) and highest group (Q4), a significant difference in incidence of first events was found from the early phase after randomization (log–rank test [Q1 *vs* Q4]; $P = 0.006$).

To determine how several parameters or TAS contributed to the reduction in all events, we carried out additional analysis after adjustment for several variables as potential confounders (Table 2). Among some variables except TAS, statistical significance was found for HbA1c, age and sex (female). Strikingly, TAS showed strong predictive power for all CV events. HR of each TAS grade were 0.74, 0.77 and 0.62 in Q2, Q3 and Q4, respectively, compared with Q1 as reference, and Q4 group statistically showed a significance ($P = 0.037$). However, variables including TAS except age and sex (female) were not associated with all-cause deaths. After addition of each of previous CVD or CHD to these adjusting variables, HR was 1.52 in previous CVD (95% CI 1.06–2.41, $P = 0.1006$) and HR was 1.45 in previous CHD (95% CI 1.90–2.33, $P = 0.1236$), and HR of TAS Q4 was reduced HR 0.64 (95% CI 0.35–1.17, $P = 0.1447$). In addition, in case of adjustment using previous CVD or CHD, its presence of each previous vascular event showed statistical significance (HR 1.52, 95% CI 1.06–2.41, $P = 0.1006$). Unfortunately, HR of TAS Q4 was similarly reduced HR 0.65 (95% CI 0.35–1.18, $P = 0.1549$).

Table 2 Hazard ratios of all cardiovascular events and all-cause deaths after multivariate adjustment: Impact of total activity score as a strong predictor

Variants	All CV Events HR (95% CI)	*P*-value	All-Cause Deaths HR (95% CI)	*P*-VALUE
TAS				
Q1	1.00 Reference		1.00 Reference	
Q2	0.74 (0.49–1.13)	0.164	0.65 (0.33–1.29)	0.223
Q3	0.77 (0.51–1.17)	0.226	0.81 (0.43–1.54)	0.523
Q4	0.62 (0.40–0.97)	0.037	0.8 (0.41–1.56)	0.513
SBP	1.01 (1.00–1.02)	0.074	1.0 (0.99–1.02)	0.912
HbA1c	1.17 (1.00–1.38)	0.048	1.12 (0.87–1.43)	0.382
T-chol	1.01 (1.00–1.01)	0.056	1.0 (0.99–1.01)	0.886
HDL-C	0.99 (0.98–1.01)	0.333	1.0 (0.98–1.01)	0.699
TG	1.0 (1.00–1.00)	0.947	1.0 (1.00–1.00)	0.999
Age	1.06 (1.03–1.10)	0.0003	1.1 (1.05–1.16)	0.0002
Female	0.51 (0.36–0.71)	<.0001	0.53 (0.32–0.89)	0.016

CI, confidence interval; CV, cardiovascular; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; Q, quartile; SBP, systolic blood pressure; TAS, total activity score; T-chol, total cholesterol; TG, triglyceride.

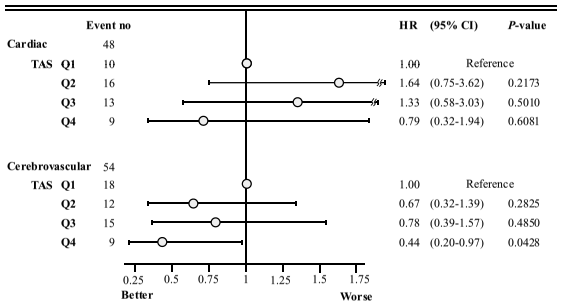

Figure 2 Predictive power for cardiac events and cerebrovascular events according to total activity score (TAS) category. HR, hazard ratio; Q, quartile.

Significant correlation of TAS with cerebrovascular events compared with cardiac events

The association of TAS with cerebrovascular events and cardiac events (AP, MI, coronary revascularization and heart failure) was evaluated. TAS was significantly associated with cerebrovascular disease including both fatal and non-fatal events, although there was no significant association between cardiac events and TAS (Fig. 2).

Next, we compared the predictive power of TAS according to sex and age (young-elderly aged 65–74 years and old-elderly patients aged ≥75 years; Table 3). First, with regard to sex, the predictive power of TAS for all CV events was stronger in women than in men. In addition, TAS in the young-elderly significantly predicted all CV events. In the old-elderly, a similar tendency was observed; however, the association did not reach statistical significance.

Comparison of predictive power of each component in TAS

As described in the Methods section, TAS consists of three components: work activity, sports activity and non-sporting leisure-time activity. Subanalysis clearly

Table 3 Predictive power of total activity score for all cardiovascular events and all-cause death according to sex and age

	Male HR (95% CI)	*P*-value	Female HR (95% CI)	*P*-value
All CV events				
TAS				
Q1	1 Reference		1 Reference	
Q2	0.8 (0.46–1.39)	0.429	0.84 (0.45–1.56)	0.584
Q3	0.95 (0.56–1.61)	0.857	0.50 (0.25–1.03)	0.062
Q4	0.6 (0.34–1.08)	0.087	0.47 (0.24–0.93)	0.030
All-cause deaths				
Q1	1 Reference		1 Reference	
Q2	0.79 (0.33–1.91)	0.606	0.73 (0.28–1.92)	0.527
Q3	1.08 (0.48–2.41)	0.856	0.42 (0.13–1.35)	0.148
Q4	0.74 (0.31–1.78)	0.496	0.60 (0.23–1.58)	0.304
	Young-Elderly HR (95% CI)	*P*-value	Old-Elderly HR (95% CI)	*P*-value
All CV events				
TAS				
Q1	1 Reference		1 Reference	
Q2	0.70 (0.41–1.21)	0.204	1.07 (0.57–2.00)	0.839
Q3	0.81 (0.48–1.35)	0.414	0.73 (0.36–1.49)	0.387
Q4	0.58 (0.34–0.98)	0.042	0.54 (0.23–1.27)	0.158
All-cause deaths				
Q1	1 Reference		1 Reference	
Q2	0.74 (0.31–1.76)	0.498	0.8 (0.3–2.14)	0.653
Q3	0.74 (0.32–1.71)	0.478	0.95 (0.35–2.55)	0.916
Q4	0.73 (0.33–1.63)	0.448	0.68 (0.21–2.22)	0.527

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; Q, quartile; TAS, total activity score.

showed that the predictive power of "work activity" for all CV events was stronger than that of the other components (log–rank test; $P = 0.0003$) (Table 4). After adjustment, its power remained. The risk reduction of work activity was also significant, even in all-cause mortality (log–rank test; $P = 0.004$; data not shown). There was no statistical significance for sports activity. Regarding leisure-time activity, the risk reduction of it for all CV events in Q3 was strongest; however, statistical analysis did not show significance (log–rank test; $P = 0.11$).

Changes in each parameter during follow-up period

To explore which parameter contributed to the risk reduction of all primary events, the changes in values (from baseline to the end of the follow-up period) of each parameter were calculated according to TAS grade (Table 5). Among the parameters, the differences in laboratory data, including lipid parameters and glucose metabolism, BP, physical measurements, cognitive function and depression scale, between TAS grades were not significant, suggesting that a higher level of physical activity itself was important in the risk reduction of events in elderly patients with T2DM.

Discussion

Physical activity has been shown to reduce the risk of CV events; however, the biological mechanisms underlying this finding are still unclear. In the present study, the association of physical activity, as determined by TAS at baseline, with all CV events and all-cause mortality was evaluated in the J-EDIT study.

Higher TAS grade was significantly associated with a risk reduction in non-fatal all CV events; however, the association with all-cause mortality was not significant. In addition, among the three components of TAS, the predictive power of "work activity" was stronger than that of the other components – sports and leisure-time

Table 4 Comparison of predictive power for all cardiovascular events according to each component of physical activity

Component	Unadjusted HR	95% CI	*P*-value	Adjusted* HR	95% CI	*P*-value
Work						
None	1 Reference			1 Reference		
Low	0.57 (0.4–0.83)		0.0029	0.72 (0.49–1.06)		0.0972
High	0.53 (0.37–0.76)		0.0007	0.68 (0.46–1.01)		0.0538
Sports						
Low	1 Reference			1 Reference		
High	0.84 (0.62–1.13)		0.2455	0.8 (0.59–1.08)		0.1425
Leisure-time						
Q1	1 Reference			1 Reference		
Q2	0.73 (0.49–1.09)		0.1236	0.75 (0.49–1.13)		0.1633
Q3	0.53 (0.33–0.83)		0.0062	0.6 (0.37–0.95)		0.0304
Q4	0.75 (0.5–1.11)		0.1502	0.79 (0.52–1.19)		0.2534

*Simultaneously adjusted for age, sex, systolic blood pressure, glycated hemoglobin A1c, total cholesterol, triglyceride, and high-density lipoprotein cholesterol at baseline. CI, confidence interval; HR, hazard ratio.

Table 5 Changes in each parameter throughout follow-up period according to total activity score category

Variables	TAS category Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for trend
FBS (mg/dL)	−21.2 (4.0)	−5.7 (4.4)	−11.7 (4.2)	−10.8 (3.8)	0.0649
HbA1c (%)	−0.6 (0.1)	−0.6 (0.1)	−0.5 (0.1)	−0.6 (0.1)	0.8537
T-chol (mg/dL)	−12.2 (2.5)	−16.7 (2.5)	−7.9 (2.4)	−11.3 (2.5)	0.0979
LDL-C (mg/dL)	−6.6 (2.2)	−11.3 (2.4)	−4.1 (2.3)	−7.1 (2.4)	0.1744
HDL-C (mg/dL)	−0.1 (2)	−2.4 (1)	−2.0 (1)	−1.8 (1)	0.6101
TG (mg/dL)	−15.5 (5.3)	−17.4 (7.9)	−5.2 (5)	−9.0 (4.7)	0.4164
SBP (mmHg)	−2.5 (1.1)	−1.7 (1.3)	−2.4 (1.3)	−2.2 (1.3)	0.9673
DBP (mmHg)	−4.0 (0.8)	−3.8 (0.8)	−2.6 (0.8)	−3.0 (0.7)	0.5372
PP (mmHg)	1.6 (1.0)	2.0 (1.1)	0.0 (1.1)	0.9 (1.1)	0.573
BMI (kg/m^2)	−0.2 (0.8)	−0.4 (0.2)	−0.6 (0.2)	−0.6 (0.2)	0.9353
Waist circumference (cm)	−0.8 (0.3)	−0.1 (0.4)	0.6 (0.5)	−0.1 (0.3)	0.1608
Hip circumference (cm)	0.5 (0.4)	0.0 (0.4)	0.4 (0.4)	−0.1 (0.4)	0.6398
W/H ratio	0.0 (0.0)	0.6 (0.5)	0.5 (0.5)	0.5 (0.5)	0.7671
MMSE	−0.3 (0.1)	−0.4 (0.1)	−0.4 (0.1)	−0.4 (0.1)	0.8441
GDS15	0.0 (0.1)	0.1 (0.1)	0.0 (0.1)	0.3 (0.1)	0.1087

BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood glucose; GDS, Geriatric Depression Scale; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; PP, pulse pressure; SBP, systolic blood pressure; sCr, serum creatinine; SS, sports score; TAS, total activity score; T-chol, total cholesterol; TG, triglyceride; W/H ratio, waist-to-hip circumference ratio; WAS, work activity score.

activity. There was no significant difference in the change in almost all parameters among TAS grades throughout the follow-up period in the present trial. Therefore, we emphasize the following conclusion: (i) our data provide evidence that lower physical activity is a strong and independent predictor of CV events in the elderly with T2DM beyond traditional risk factors; (ii) in addition to routine strict management of laboratory data in clinical practice, engagement with patients to enhance and/or maintain physical activity in their lifestyle is also important. In fact, the elderly have retired from their routine jobs. The results of the present study show that they should do at least slight work routinely in their daily life, such as cooking or gardening. It might be meaningful for them to carry out some activity and continue it by themselves.

Physical activity is a well-established approach to reducing the risk of many chronic diseases. Most studies have shown a significant relative reduction in the incidence of CV events in physically active participants; however, the range of benefit showed considerable variation. For example, Myers *et al.* reported a marked reduction in all-cause mortality of 72% between active and inactive male participants during 6 years of follow up,[21] whereas Lee *et al.* found a risk reduction of just 13%.[22] It is clear that the risk reduction might vary depending on adjustment for important covariables, such as BP and profiles of lipid and glucose metabolism. With regard to adjustment for several relevant risk factors, a meta-analysis handling a total of 33 studies with 883 372 participants (follow-up period from 4 years to over 20 years) clearly showed an important correlation of higher physical activity with a risk reduction in CV mortality of 35% (95% CI 30–40%).[23] In addition, all-cause mortality was also reduced by 33% (95% CI 28–37%). This systematic review by meta-analysis emphasized that physical activity was associated with a marked decrease in CV and all-cause mortality in both sexes, even after adjusting for other relevant risk factors. In the present study, there was a good correlation between TAS and all CV events. However, after adjustment of previous atherosclerotic diseases, its presence of previous CVD or CHD showed a significant association with CV events during the follow-up period. Consequently, the predictive power of TAS against all CV events was slightly decreased. These observations might suggest a high risk of recurrence of CV events in T2DM patients beyond TAS grade at the baseline. Therefore, further subanalysis to simply evaluate the predictive power of TAS as primary prevention against CV events using elderly patients without both previous CVD and CHD is required. In addition, regarding all-cause mortality, TAS tended to show an association with it; however, no statistical significance was reached. One of the hypotheses to explain the relationship and discrepancy is that the sample size was relatively small and non-fatal CV events rather than fatal events might be frequently observed in all participants with T2DM at the baseline.

Next, we focused on cognitive function and depressive mood. The presence of geriatric syndrome including cognitive dysfunction has been shown to be a major factor in decline in physical activity level in the older elderly. Besides traditional risk factors, it has been clearly shown that "depressive mood" readily causes a decline in physical activity, leading to increased risk of CV disease.[24] In addition, patients with depression had a worse prognosis than those without depression after a myocardial infarction.[25,26] Prospective studies have shown that depressed people develop a more sedentary lifestyle and become less physically active.[27,28] In fact, the GDS score was higher in the lower TAS group in the present study as well. Therefore, this evidence that the importance of physical activity in the risk reduction of CV events is also associated with depressive mood is consistent with previous reports. However, the average GDS score was not so high (range 3–5 points). In addition, depressive score did not decrease, even in the lowest TAS group (Q1), throughout the follow-up period. In subanalysis, the inverse correlation between GDS and TAS was more clearly found in young-elderly patients, compared with old-elderly patients. In view of these results, especially in young-elderly patients, detailed assessment of the patient's mentality, including depressive mood, should be considered more aggressively and routinely.

The predictive power of TAS was compared between CHD and CVD. The relative risk of CVD decreased with increasing TAS, with statistical significance; however, no significance was found for CHD. In fact, we found some evidence regarding this discrepancy. Although the incidence of CHD among physically active elderly men in the Honolulu Heart Program study was less than half that in more sedentary men,[29] no clear association was observed in the Established Populations for Epidemiologic Studies of the Elderly study.[30] Compared with CHD, the correlation of physical activity with stroke has not been extensively examined for any age group.[31] However, a meta-analysis handling five epidemiological case–control studies has reported that all studies had consistent evidence showing a large advantage of higher physical activity in reducing the risk of stroke.[32]

As another interest in our data, "work activity" was the most potent predictor of first events among the three components. This suggests that, even if the patient's age is over 65 years, the fact that they are motivated to routinely try to do at least any slight work might enhance their total physical activity.

The present analysis was based on the physical activity score measured once at enrolment in the J-EDIT study. However, during the follow-up period of this trial, some patients showed a gradual decline in TAS. It is notable that new development or progression of diabetic complications, such as neuropathy and retinopathy, readily leads to a decline in physical activity. Therefore, further investigation to evaluate which factor mainly caused the decline in TAS throughout the follow-up period is necessary. This could provide supportive information on the cause–effect relationship of the associations found in this trial.

In addition, the current associations might not be extended to all populations, because the enrolled participants in the present trial were patients with T2DM. Whether the observed associations can be generalized to populations of much older ages and populations without T2DM is unknown.

This prospective follow-up study confirmed that lower physical activity is a strong independent predictor

of onset of CV events, even in Japanese elderly with T2DM. The data in the present study suggest the potential of activity to enhance overall health and well-being with aging. Ultimately, the key is to aggressively translate these findings into public health efforts.

The majority of elderly patients still have a primarily sedentary life. Numerous studies have already addressed the importance of physical activity in health management; however, unfortunately, medical staff might not have been educated about how to promote and augment the level of physical activity in elderly patients. Therefore, as well as strict management of each atherosclerotic risk factor, we should aggressively assess physical activity (especially working) and encourage elderly patients to increase or maintain their level of physical activity.

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Conflict of interest

There is no conflict of interest. The J-EDIT Study Group has not cleared any potential conflicts.

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ORIGINAL ARTICLE

Lower physical activity, but not excessive calorie intake, is associated with metabolic syndrome in elderly with type 2 diabetes mellitus: The Japanese elderly diabetes intervention trial

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Aim: A decline in physical activity has been shown to be associated with metabolic syndrome (MetS), leading to cardiovascular events. However, this is difficult to manage well in the elderly with multiple atherosclerotic risk factors. In this study, we investigated the correlation between physical activity and clinical parameters in the presence and absence of MetS in Japanese elderly subjects with type 2 diabetes mellitus (T2DM). In addition, we determined which factor, calorie intake or physical activity, mainly contributes to the prevalence of MetS.

Methods: Cross-sectional analysis of 846 consecutive Japanese elderly (408 men and 438 women, mean age 68.7 years) was carried out at the time of enrolment (2000–2002) in the Japanese Elderly Diabetes Intervention Trial. Their level of physical activity was evaluated using the Baecke questionnaire, consisting of three components: work, sports and leisure. Total activity score (TAS) as the sum of each activity score was divided into four quartiles (Q1 to Q4).

Results: After adjustment for age and sex, there was a positive association of TAS with high-density lipoprotein cholesterol, although no significant correlation between other lipid parameters and TAS was found. In addition, fasting plasma glucose, insulin level and physical measurements, such as waist circumference, waist/hip ratio and body mass index, were inversely associated with TAS. Although no correlation between TAS and cognitive function Mini-Mental State Examination was found, TAS was positively associated with instrumental ADL and negatively associated with geriatric depression score (GDS), suggesting that a decline in physical activity in the elderly is associated with depressed mood rather than a decline of cognitive function. Total calorie intake appeared to increase according to TAS; however, this did not reach statistical significance. In a subanalysis comparing the presence and absence of MetS, the TAS grade in the MetS group was significantly lower than that in the non-MetS group, although there was no significant difference in total calorie intake between the groups.

Conclusion: These results showed that lower physical activity, but not excessive calorie intake, is independently associated with the prevalence of MetS in the elderly with T2DM. In our routine work, encouraging physical activity might contribute to preventing MetS and subsequent atherosclerotic disease in the elderly, rather than strict management of abnormal laboratory parameters using multiple drugs. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 68–76.**

Keywords: depression, elderly, excessive calorie intake, Japanese Elderly Diabetes Intervention Trial study, metabolic syndrome, physical activity, work activity.

Background

Type 2 diabetes mellitus (T2DM) is an age-related disease with an estimated prevalence in Japan of more than 5% of the population.[1] The setting of treatment goals in medical care, especially in elderly patients, has been believed to be difficult because of several factors. In concrete terms, the purpose of treatment is not only to simply improve glucose intolerance, but also to maintain a higher quality of life (QOL) and prolong healthy longevity in parallel with prevention of diabetic complications. Several prospective intervention studies have recently shown some evidence that intensive glycemic control effectively slows the onset and progression of diabetic vascular complications associated with T2DM.[2,3] However, these epidemiological investigations did not consider the various associations with physical activity in elderly diabetic patients.

Physical activity promotes health and longevity.[4] Excess bodyweight and a sedentary lifestyle are well-established risk factors for not only T2DM, but also cardiovascular disease (CVD). Randomized trials have shown that a combination of weight loss and increased physical activity can reduce the incidence of T2DM and CVD.[5–7] In developed countries, 80% of all deaths from CVD occur in people aged 65 years and older.[8] The Framingham Heart Study has shown an inverse association between physical activity and CVD mortality risk, even in 285 elderly individuals.[9] However, this did not reach statistical significance, possibly as a result of the limited number of events. However, the precise mechanisms whereby physical activity lowers CVD risk are not well understood. In addition, it is possible that a decline in physical activity might lead to several undesirable conditions, including cognitive decline, in the elderly.

Metabolic syndrome (MetS) is loosely defined as a cluster of CVD risk factors, including disturbed insulin and glucose metabolism, hypertension, abdominal obesity and dyslipidemia. A low level of physical activity is believed to be an important determinant of this cluster of metabolic risk factors. Thus far, little is known about the association between physical activity and MetS in Japanese elderly patients with T2DM. To clarify which factors are mainly associated with the prevalence of metabolic syndrome (MetS) in the elderly with T2DM, we carried out a large-scale prospective study, the Japanese Elderly Diabetes Intervention Trial (J-EDIT), which was started in 2001.[10] To address how elderly patients with T2DM should be treated, a randomized controlled intervention study in Japanese elderly patients with diabetes has been carried out.

In the J-EDIT study, we investigated the correlation between physical activity and MetS in the elderly with T2DM. In particular, we focused on the association of oral calorie intake with physical inactivity in the presence or absence of MetS.

Methods

Study population

Participants were enrolled in the J-EDIT, which is a recently completed trial of intensive or standard treatment for diabetes in the primary prevention of CVD in the elderly. J-EDIT included 1173 diabetic patients who were aged 65 years or older (mean age 71.8 ± 4.6 years) and whose serum glycated hemoglobin A1c (HbA1c)

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level was >7.4% from 39 institutes and hospitals (Tokyo University Hospital, Kobe University Hospital, Nagoya University Hospital and Tokyo Metropolitan Geriatric Hospital etc.) in Japan. Patients with chronic renal failure (serum creatinine > 1.5 mg/dL), severe heart failure or symptomatic cerebral infarction were also excluded from the present study. Written informed consent was obtained from all patients.

From these patients enrolled in the J-EDIT, we selected 846 patients with T2DM (mean age 71.9 ± 4.6 years, 408 men (mean age 71.5 ± 4.5 years) and 438 women (mean age 72.2 ± 4.7 years) in whom complete data on baseline physical activity (Baecke questionnaire) and nutritional survey were obtained at entry. We excluded patients who had difficulties in communicating, dementia or serious deterioration of activities of daily life from the present study.

Physical activity assessed by Baecke questionnaire

At enrolment in the present study, physical activity was evaluated by a self-administered validated Baecke physical activity questionnaire, as previously reported.[11] Baecke physical activity score is classified into three domains: work activity, sports activity and non-sporting leisure activity. These three components consisted of items on the frequency, duration, and pace of walking and bicycling during the previous week, the average amount of time spent weekly on hobbies and gardening, and the average amount of time spent monthly on odd jobs and sports. Types of odd jobs, sports and hobbies (e.g. dancing or fishing) were also assessed. Many previous reports have confirmed the reliability of this score in many individuals, suggesting that it might be a useful monitoring tool for assessing the association of multiple domains of physical activity with MetS in elderly patients with T2DM, with acceptable reliability and validity. In analyses, total activity score (TAS; maximum 15 points) was divided into four quartiles (Q1 to Q4) as follows; Q1: <5.7, Q2: ≥5.7 and <7.7, Q3: ≥7.7 and <10.5, Q4: ≥10.5.

Comprehensive geriatric assessment

To perform comprehensive geriatric assessment (CGA), we carried out several evaluations. Mini-Mental State Examination (MMSE) was used to assess cognitive function.[10] Geriatric Depression Scale (GDS) was used to assess depression status. We also checked basic activities of daily life (bADL) and instrumental activities of daily life (iADL), as determined by the Tokyo Metropolitan Institute of Gerontology (TMIG) index of competence.[12]

Physical measurements

Height, weight, waist circumference and hip circumference were measured at enrolment. Body mass index (BMI) and waist-to-hip ratio (W/H ratio) were calculated using these parameters.

Nutritional assessment of dietary calorie intake

Calorie intake was assessed using a self-reported questionnaire that has been previously shown to be valid and reliable.[13] Nutritional habit was evaluated every trimester through 7-day food records. Each energy intake, such as protein, carbohydrate and fat, and total calorie intake were calculated in all patients.

Laboratory measurements and blood pressure

Blood samples were obtained at the time of enrolment and stored in vapor-phase liquid nitrogen (–170°C). Glycemic metabolism, such as fasting plasma glucose and HbA1c; lipid parameters, such as total, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG); and renal function, such as serum creatinine, were measured. Blood pressure (BP) was measured in the non-dominant arm after 5 min of sitting quietly in accordance with the current recommendations for clinic blood pressure of each hospital.

Metabolic risk factor criteria

In the present study, MetS was defined according to the criteria proposed by the Japanese Society of Internal Medicine (JSIM), the International Diabetes Federation (IDF) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).[13–16]

Statistical analysis

Analyses of covariance (ANCOVA) was used to assess independent associations between our two indices of habitual physical activity (daily step count and daily duration of activity at an intensity >3 MetS) and the presence or absence of MetS and five individual diagnostic criteria (BMI, TG, HDL-C, systolic BP and/or diastolic BP, and glucose and/or HbA1c), after controlling for age and sex. We divided the patients arbitrarily into four quartiles of physical activity (Q1: lowest group to Q4: highest group). In addition, pre-existing illness (such as cerebrovascular disease, ischemic heart disease, diabetes and retinopathy) at baseline was also considered. The χ^2-test for linear trends was used to analyze independent associations between habitual physical activity and the metabolic syndrome in adjusted models. Data are presented as mean ± standard deviation (SD), with all statistical comparisons made at the 0.05 level of significance.

Results

Comparison of parameters according to physical activity

Cross-sectional analysis of 846 consecutive Japanese elderly (408 men and 438 women; mean age 68.7 years) was carried out at the time of enrolment (2000–2002) in the J-EDIT study, a randomized, double-blind, recently completed trial of intensive or standard treatment for the prevention of CVD in elderly diabetics.

An index of physical activity was calculated using the Baecke score, including three components (work, sports and leisure). TAS was divided into four quartiles (Q1 to Q4). The baseline characteristics of patients according to their TAS grade are shown in Table 1. Regarding lipid parameters, HDL-C was positively associated with TAS, although there was no significant correlation between other lipid parameters and TAS. A negative correlation of fasting plasma glucose and plasma insulin level with TAS was found. Regarding the association between BP and TAS, no significant tendency was found.

There was a negative association between TAS and physical measurements, such as BMI, waist circumference, hip circumference and W/H ratio. In particular, high significance was observed especially in the young elderly (data not shown). However, there was no significant association with each component of TAS.

Comparison of CGA according to physical activity

Regarding comprehensive geriatric assessment (CGA), TAS was positively associated with TMIG index as instrumental ADL and negatively associated with geriatric depression score (GDS; Table 1). In contrast, there was no significant correlation between TAS and cognitive function, as determined by MMSE. These results suggest that a decline in physical activity in the elderly is associated with a depressive tendency rather than cognitive dysfunction.

Comparison of calorie intake according to physical activity

Next, we measured oral calorie intake. The calorie intake from protein and lipid were positively associated with TAS; however, there was no correlation with calorie intake from carbohydrate (Table 1). Total calorie intake tended to increase according to TAS grade, but the tendency did not reach statistical significance. Next, the total calorie intake was compared according to TAS grade in each group, divided by sex and age (Fig. 1). There was no significant difference between total calorie intake and TAS in all subgroups.

There was no significant difference between both sexes (Fig. 2a). TAS in the old elderly was significantly lower than that in the young elderly in both sexes. Comparing pre-existing illness, there was a correlation between TAS grade and cerebrovascular disease, but not coronary heart disease or diabetic retinopathy (Fig. 2b).

Impact of lower physical activity, but not excessive calorie intake, in elderly with MetS

It is well known that there is a correlation between a sedentary lifestyle and obesity. Even in the elderly, it is possible that the prevalence of MetS is associated with not only excessive calorie intake, but also their behavior. Therefore, next, we examined which factor, excessive calorie intake or physical inactivity, mainly contributes to the prevalence of MetS. First, we divided all the patients into two groups, MetS and non-MetS, using the definition of MetS of the Japanese Society of Internal Medicine (JSIM).

First, calorie intake from several types of food was compared between MetS and non-MetS (Table 2). Calorie intake from protein and fat in MetS was higher than that in non-MetS. However, for carbohydrate-derived and total calorie intake, no significant difference was found between both groups. Furthermore, in addition to the JSIM criteria, we divided the patients into two groups, MetS and non-MetS, using other clinical definitions, IDF and NCEP-ATP III. Even with each definition, TAS grade in the MetS group was lower than that in the non-MetS group (Fig. 3a). Interestingly, there was no significant difference in total calorie intake between both groups. Among the three components of TAS, work activity showed a more significant correlation with the prevalence of MetS than the other components, sports or leisure activity (Fig. 3b).

Discussion

The present study analyzed the possible association between lower physical activity and prevalence of MetS in Japanese elderly patients with T2DM who were enrolled in the J-EDIT study. The present study had two aims: (i) to evaluate the association between TAS as total physical activity and clinical parameters in the diabetic elderly; and (ii) to determine which factor, total calorie intake or physical activity, mainly contributes to the presence of MetS in the elderly with T2DM. In the present study, physical activity was assessed by the Baecke questionnaire,[11] because this is an easy, fast and valid tool for the assessment of physical activity in epidemiological studies concerning elderly populations.

The present study showed several results, as follows: TAS grade as total physical activity level in the young elderly was higher than that in the old elderly. No significant difference in TAS was found between both sexes. The presence of cerebrovascular disease in the

Table 1 Baseline characteristics: Comparison of each parameter according to four quartiles of total physical activity score

Parameters	All	TAS category				*P*-value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
n (male/female)	846 (408/438)	130 (69/61)	295 (134/161)	104 (64/40)	317 (141/176)	0.0101
Age (years)	71.9 ± 4.6	73.5 ± 4.8	72.1 ± 4.6	72.0 ± 4.6	71.0 ± 4.4	<.0001
HbA1c (%)	8.5 ± 1.3	8.4 ± 1.2	8.4 ± 1.3	8.4 ± 1.3	8.5 ± 1.3	0.4467
FBS (mg/dL)	166 ± 49	170 ± 48	171 ± 52	164 ± 40	162 ± 49	0.0423
FRI (mg/dL)	10.1 ± 10.1	12.4 ± 13.6	10.6 ± 11.0	8.3 ± 5.5	9.5 ± 8.8	0.0206
TC (mg/dL)	203 ± 35	198 ± 33	205 ± 37	203 ± 34	203 ± 35	0.6871
TG (mg/dL)	133 ± 96	146 ± 80	129 ± 67	152 ± 190	125 ± 76	0.105
HDL (mg/dL)	56 ± 18	51 ± 15	57 ± 18	55 ± 20	59 ± 18	0.0012
LDL (mg/dL)	121 ± 31	117 ± 32	124 ± 32	120 ± 27	120 ± 31	0.7604
sCre (mg/dL)	0.89 ± 0.97	1.00 ± 0.96	0.85 ± 0.41	0.83 ± 0.26	0.91 ± 1.41	0.9329
SBP (mmHg)	137 ± 16	138 ± 18	138 ± 15	136 ± 16	136 ± 16	0.3507
DBP (mmHg)	75 ± 10	75 ± 11	76 ± 10	74 ± 10	75 ± 9	0.28
Pulse pressure (mmHg)	62 ± 14	62 ± 16	62 ± 13	62 ± 15	61 ± 13	0.7543
BMI (kg/m2)	23.8 ± 3.5	24.8 ± 4.1	23.9 ± 3.4	23.4 ± 3.3	23.6 ± 3.4	0.0017
Waist circumference (cm)	84.0 ± 10.2	86.9 ± 11.1	84.3 ± 9.3	83.9 ± 10.5	82.5 ± 10.2	0.0003
Hip circumference (cm)	94.0 ± 7.9	95.5 ± 8.6	93.8 ± 7.6	94.3 ± 7.3	93.4 ± 7.9	0.0553
W/H circumference ratio	0.89 ± 0.07	0.91 ± 0.07	0.91 ± 0.07	0.89 ± 0.07	0.88 ± 0.07	0.0011
MMSE	28.0 ± 2.7	26.8 ± 3.9	28.0 ± 2.3	27.9 ± 2.4	28.5 ± 2.2	0.1815
GDS-15	4.1 ± 3.2	5.6 ± 3.3	4.4 ± 3.2	4.3 ± 3.1	3.2 ± 2.9	<.0001
TMIG index	11.6 ± 2.2	9.9 ± 3.5	11.6 ± 1.8	11.7 ± 1.9	12.2 ± 1.5	<.0001
Protein intake (g/day)	66.7 ± 19.3	60.4 ± 19.1	67.4 ± 17.9	67.9 ± 18.9	68.3 ± 20.3	0.0023
Fat intake (g/day)	50.0 ± 18.0	46.0 ± 21.2	48.8 ± 16.7	49.2 ± 17.3	51.3 ± 18.7	0.0237
Carbohydrate intake (g/day)	244.7 ± 54.4	240.2 ± 65.1	246.0 ± 52.5	246.0 ± 52.5	244.7 ± 49.0	0.476
Total calorie intake (kcal/day)	1735.5 ± 417.4	1661.6 ± 489.0	1747.5 ± 397.4	1747.4 ± 407.1	1751.4 ± 405.4	0.0697

BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood glucose; FRI, fasting insulin resistance index; GDS, Geriatric Depression Scale; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LTS, leisure-time activity score; MMSE, Mini-Mental State Examination; PP, pulse pressure; SBP, systolic blood pressure; sCr, serum creatinine; SS, sports score; TAS, total activity score; TC, total cholesterol; TG, triglyceride; TMIG, Tokyo Metropolian Institute of Gerontology; W/H, waist-to-hip; WAS, work activity score. MMSE, Barthel index, TMIG index, and GDS-15 are on a scale of 0 to 30, 0 to 20, 0 to 13, and 0 to 15, respectively.

Figure 1 Total calorie intake according to total physical activity score at baseline. NS, not significant.

Figure 2 Total physical activity score according to sex, age and pre-existing illness at baseline. TAS, total activity score.

but not excessive calorie intake, is independently associated with the prevalence of MetS in the elderly with T2DM.

An inverse association between physical inactivity and MetS has been shown in several cohorts; however, there have been very few studies specifically in the elderly. In addition, one advantage of the J-EDIT study is that it obtained information on both physical activity and calorie intake. Many epidemiological observational investigations have shown a consistent inverse association between physical activity and the risk of new cardiovascular events.[17] Even in the elderly, it has been shown that maintaining a higher level of physical activity confers a reduction in coronary heart disease.[18,19] Therefore, we should encourage physical activity in elderly patients in our routine work. The protective potential of physical activity against cardiovascular events might be related to its beneficial effects on not only physical parameters (i.e. bodyweight, BP and other metabolic parameters), but also improvement of depressed mood.

In our analyses regarding CGA, TAS was strongly associated with depression scale. In contrast, no association was found between physical activity and cognitive function (MMSE score). This suggests that impairment of psychological health, especially depression and anxiety, is mainly dependent on physical activity in elderly individuals if cognitive function is not impaired. It appears that, besides traditional risk factors, depressive symptoms are associated with increased risk of CVD, leading to a worse prognosis. Recent reports elderly was associated with a decline in TAS; however, the presence of ischemic heart disease or retinopathy did not contribute to the decline in TAS. Although no significant difference in total calorie intake from dietary food was found between MetS and non-MetS, TAS grade in the MetS group was significantly lower than that in the non-MetS group. Based on these results, we could conclude that a decline in physical activity,

Table 2 Dietary calorie intake according to presence or absence of metabolic syndrome at baseline

	Male			Female		
	MetS (–)	MetS (+)		MetS (–)	MetS (+)	
Age (years)	70.9 ± 4.2	71.9 ± 4.8	NS	71.7 ± 4.5	73.0 ± 4.6	NS
Total calorie intake (kcal/day)	1814 ± 410	1856 ± 479	NS	1639 ± 367	1664 ± 328	NS
Protein (g/day)	70 ± 19	69 ± 20	NS	65 ± 20	63 ± 16	NS
Fat (g/day)	53 ± 18	54 ± 22	NS	48 ± 17	49 ± 15	NS
Carbohydrate (g/day)	253 ± 56	257 ± 65	NS	235 ± 49	237 ± 38	NS
Protein-to-energy ratio (%)	15.3 ± 2.1	149 ± 2.3	NS	15.6 ± 2.2	15.2 ± 2.0	NS
Fat-to-energy ratio (%)	25.7 ± 4.8	25.8 ± 5.4	NS	25.8 ± 4.6	26.0 ± 4.6	NS
Carbohydrate-to energy Ratio (%)	59.0 ± 6.0	59.2 ± 6.6	NS	58.6 ± 6.0	58.8 ± 5.5	NS

MetS, metabolic syndrome; NS, not significant.

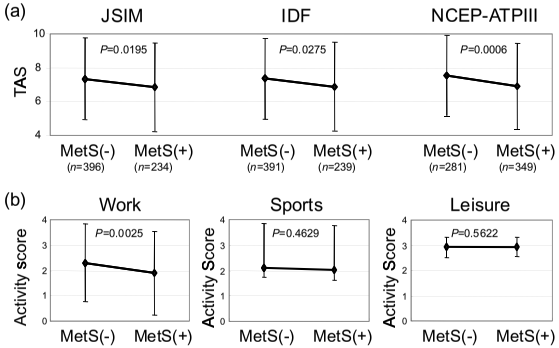

Figure 3 Decline in total physical activity score in elderly patients with metabolic syndrome (MetS). Comparison of total activity score according to each definition and impact of work activity. IDF, International Diabetes Federation; JSIM, Japanese Society of Internal Medicine; NCEP-ATPIII, National Cholesterol Education Program Adult Treatment Panel III.

showed that depression not only leads to a poor outcome in patients with established CVD, but also increases the risk of CVD in apparently healthy persons.[20–22] In addition, prospective studies have shown that depressed persons develop a more sedentary lifestyle.[23,24] Therefore, in the elderly in particular, it is clear that a depressed mood readily leads to a decline in physical activity, resulting in a sedentary lifestyle and eventually MetS. Patients with lower TAS as a result of a markedly depressed mood might have a higher incidence of future CVD.

How can we prevent and treat MetS in the elderly? The proportion of elderly Japanese persons with BMI ≥ 25 kg/m^2 (the insulin resistance threshold proposed by the World Health Organization Western Pacific Region) has risen progressively to a current level of 31% in men and 30% in women.[25] Diseases associated with inactivity are now an important global public health problem, with 11.7% of deaths in developed countries being linked to obesity and MetS.[26,27] Therefore, this is becoming even more significant, considering the problem of the high prevalence of physical inactivity, obesity and MetS. In fact, relatively few investigations have assessed the crucial correlation of physical activity with MetS in elderly patients. In middle age, numerous clinical trials have shown the importance of lifestyle modification, including moderate-intensity physical activity for at least for 30 min a day, most days of the week, and a bodyweight loss of 5–7%, to improve the individual components of MetS. However, the question of whether medical staff should have a similar therapeutic strategy even in elderly patients has been raised. Therefore, in the present study, we focused on the correlation between TAS and the presence of MetS, which is characterized by central obesity, dyslipidemia, hyperglycemia and hypertension.[28] Of note, our analyses showed evidence that inadequate physical activity, but not excessive calorie intake, might be a major reason for MetS in the elderly. In particular, among the three components in physical activity, we found a significant correlation of "work activity", but not sports or leisure activity, with MetS.

Recently, many clinical studies have been carried out to determine the influence of primary care counseling on the level of physical activity and the maintenance of changes in behavior regarding physical activity. Most of the studies have shown that recommending physical activity can achieve an increase in weekly energy expenditure, even in the elderly.[29–31] In the present study, our obtained data might imply that the patients might not have been aware of the importance of physical activity. Therefore, we emphasize the advice that a higher physical activity level in elderly patients is indispensable to maintain healthy condition.

Several limitations of the present study warrant consideration. Physical activity and several of the risk factors were assessed by self-reporting. It is possible that more precise assessment of these factors might have shown a different contribution of these variables to the reduction in CVD risk. In addition, the present data were obtained by cross-sectional analysis at enrolment in the J-EDIT study. Therefore, the present study does not allow any assessment of the cause–effect relationship for the associations found. Further investigation to elucidate how lower physical activity in elderly T2DM patients finally affects the outcome of cardiovascular events by longitudinal follow up is necessary.

The present study showed that lower physical activity, but not excessive calorie intake, is independently associated with the prevalence of MetS in the elderly with T2DM. In our routine work, encouraging physical activity in the elderly might contribute to the prevention of MetS and subsequent atherosclerotic disease, rather than strict management of abnormal laboratory parameters using multiple drugs.

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Conflict of interest

There is no conflict of interest. The J-EDIT Study Group has not cleared any potential conflicts.

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速報論文

Short Paper

高齢者におけるウェアラブル血圧センサーの臨床応用：～認知機能およびストレス感受性からみた血圧短期変動評価への有用性の検討～

Validity and Usefulness of 'Wearable Blood Pressure Sensing' for Detection of Inappropriate Short-Term Blood Pressure Variability in the Elderly: Impact of Cognitive Function and Stress Response

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Keywords: elderly, short-term blood pressure (BP) variability, continuous BP monitoring, cognitive function, lifestyle-related diseases

Summary

An increase in short-term blood pressure (BP) variability is a characteristic feature in the elderly. It makes the management of hemodynamics more difficult, because it is frequently seen disturbed baro-reflex function and increased arterial stiffness, leading to isolated systolic hypertension. Large BP variability aggravates hypertensive target organ damage and is an independent risk factor for the cardiovascular (CV) events in elderly hypertensive patients. Therefore, appropriate control in BP is indispensable to manage lifestyle-related diseases and to prevent subsequent CV events. In addition, accumulating recent reports show that excessive BP variability is also associated with a decline in cognitive function and fall in the elderly. In the clinical settings, we usually evaluate their health condition, mainly with single point BP measurement using cuff inflation. However, unfortunately we are not able to find the close changes in BP by the

traditional way. Here, we can show our advantageous approach of continuous BP monitoring using newly developing device 'wearable BP sensing' without a cuff stress in the elderly. The new device could reflect systolic BP and its detailed changes, in consistent with cuff-based BP measurement. Our new challenge suggests new possibility of its clinical application with high accuracy.

1. はじめに

未曾有の高齢化が進む中で，高齢者の慢性疾患管理が重要になっている．なかでも高血圧罹患率は非常に高く，高血圧を基盤とする様々な疾病を予防するには普段からの厳格な管理が必要となる．その厳格な管理を達成するためには，まず高齢者高血圧の特徴を熟知する必要がある．高齢者は大動脈から中小の筋性動脈を中心に「動脈壁硬化」を呈する．いわゆる血管老化と考えられる現象である．その背景には石灰沈着，過剰なコラーゲン沈着，そして弾性線維の主成分であるエラスチンの脱落・変性・断片化など，様々な変化が起こっている．この動脈壁硬化がより進むことによりWindkessel（ふいご）機能が低下し，孤立性収縮期高血圧を呈しやすくなってくる[Iijima 09]．その結果，拡張期血圧はあまり高値を示さず，ある症例では冠動脈還流圧の低下が惹起される．また，もう一つの特徴として，圧受容器反射機能の低下などにより血圧の自動調節が破綻し，著明な血圧変動を起こしやすくなってくる．その過度の血圧変動が脳心血管疾患の発症や相対的臓器虚血を惹起し，特に相対的脳虚血の場合には立ちくらみやめまい，ひいては転倒リスクにまでつながる．これらの現象は高齢者本人の生活の幅や質（いわゆる日常生活活動度）を大きく損ねるきっかけにもなり得る．よって，「いかに高齢者の血圧変動をより詳細に（連続的に），かつ簡便に評価し，そして臨床診療における高齢者の健康管理に活用するのか」ということが今後の大きな課題となる．

さて，本論文では，大量かつ連続のヘルスケアデータ（血圧データ）を扱う．カフ血圧が，現在の絶対的な医療基準であるため，これまで血圧変動は離散的にしか扱われてこなかったものである．今までにない情報なので，まずはデータをとってみることが重要である．大量に蓄積した血圧の結果を分析すれば，アラートを出すべき状態変化の議論につながるであろう．血圧の超短期変動のように，意味のある情報については，機械学習により自動検出ができるようアルゴリズムを組んで，実際のヘルスケアサービスにつながることを期待している．よって，連続的に血圧変動をモニタリングできるセンサーを用いて，実際の患者から連続データを大量に取得し，重要な血圧変動を描出することができたことを報告する．

2. 高齢者の高血圧と血圧変動

高齢者の高血圧における様々な特徴を表1に列挙する．まず加齢に伴い血管壁硬化が進み，Windkessel 機能が低下することにより，脈圧増大を伴う収縮期高血圧を呈しやすくなる．また，塩分摂取量や降圧薬の服薬管理状況にも大きく影響を受けやすい．さらに，高齢者の血圧管理を行う上で，単なる血圧値だけではなく，数多くの計測によるその血圧変動を十分考慮に入れた管理をしなければならない．いわゆる血圧変動には，交感神経活性や環境因子など様々な要因が考えられるが，なかでも24時間自由行動下自動血圧測定（ambulatory blood pressure monitoring: ABPM）から判定される「日内変動」と，本人が自宅において自動血圧計にて連日測定する「日間変動」の重要性が注目されている．

健常者は夜間就寝中においては（昼間に比べて）生理的に約 10～20%の降圧を示す．高齢者ではその生理的な夜間降圧のパターンが破綻しやすく，Non-dipper 型や Riser 型を呈する症例が少なくない．これらは脳・心血管系疾患のハイリスク群と位置づけされている．また，逆に夜間の過度降圧（Extreme-dipper）を呈する症例も数多く，通常の外来診療における単回の血圧測定による病態把握に限界が生じてくる．これらの日内変動や日間変動が大きいほど，脳・心血管系疾患発症のリスクが高いことは数多くの臨床研究によって報告されている[Kikuya 08]．

また，高齢者における短時間内の血圧変動として，起立性低血圧や食後低血圧が代表的である．図1に ABPM により高齢者高血圧の特徴を捕えられた症例を示す．夜間の血圧は相対的に Extreme-dipper 型を呈し，起床前後の時間帯は典型的な Morning surge を示している．そして，食後に急激な血圧低下も起こっていることが ABPM によって描出されている．

この結果からも，高齢者の血圧はかなり短時間の中でも劇的な変動を示しており，ある症例ではこの過度な血圧変動が相対的脳虚血を惹起し，いわゆるめまい・立ちくらみなどの症状を訴えやすくなり，最終的に易転倒性につながる．

表 1 高齢者高血圧の特徴

1. 血管壁硬化（Windkessel（ふいご）機能の低下）
   収縮期高血圧，脈圧の増大（→冠動脈還流圧の低下）
2. 血圧の動揺性
   白衣高血圧，仮面高血圧
   起立性低血圧，食後低血圧
   （圧受容器時反射の低下，自律神経機能低下と関連）
3. 血圧変動の増加（日内変動・日間変動）
   早朝高血圧（Morning surge）や生理的夜間血圧の破綻
   ・夜間非降圧型（Non-dipper）/夜間上昇型（Riser）
   ・夜間の過度降圧（Extreme-dipper）
4. 降圧や血圧変動に伴う臓器血流の低下（脳，心，腎臓）
5. 食塩感受性（体液量依存性）が高い
6. 服薬状況の安定性が低い（コンプライアンス不良）

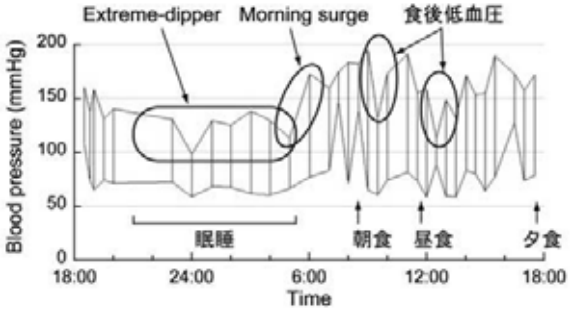

図 1 ある高齢者の 24 時間自由行動下血圧（ABPM）の推移

さらに，高齢者では高血圧と認知機能との関連も無視できない．近年の報告では，認知症の発症・進展には高血圧も含めた生活習慣病との関連も注目されていることから，より幅広い病態把握が必要である[Sakakura 07]．高血圧の管理不良や過度の血圧変動は，急性の脳血管障害だけでなく，慢性の脳虚血所見（ラクナ梗塞や白質病変）も大きく増大させることから，認知症予防という観点からも高血圧管理，ひいては血圧変動の管理が必要になってくることは間違いない．それらを予防するためには，「個人差の大きい高齢者の血圧管理において，短時間内に起こる過度な血圧変動をいかに簡易に評価できるか」が大きな鍵となってくる．

3. ウェアラブル血圧センサーの高齢者への応用

従来のカフ式血圧測定では頻回な測定にも限界があり，同時にカフ圧迫という患者への負担も増える．実際の臨床現場では，医療機関における外来受診時の単回測定によって評価されており，個々の血圧変動の状態を把握することができていない現実がある．また，一般的にカフ式血圧測定が始まると被験者は行動を中断して安静にしなければならないという測定上の制限も出てくる．

東京大学大学院工学系研究科・山田一郎研究室はカフを必要とせずに脈波伝播速度を用いて連続的に血圧をモニタできる血圧計を開発し，臨床への応用を進めているところである[Labat 11]．この原理は脈波伝播速度を元に血圧を推定する方法を採用している[Lopez 10]．脈波伝播速度法では，心電の R 波と脈波の立ち上がり点の時間差である脈波伝達時間(Pulse Arrival Time: PAT)から，収縮期血圧値を算出することで血圧推定を行っている．脈波の計測部位としては，体動による変化を最低限に抑えられる目的で耳たぶを選択している．上記の基本計測原理の検証のため，エルゴメータを用いた自転車こぎ運動による評価実験に行い，医師によるカフ式手動血圧計での聴診法による測定結果と比較して，大きな乖離のない結果が得られている．

今回，我々は開発中であるカフレスで連続的に収縮期血圧を測定できるウェアラブル血圧センサーを用いて，高齢者での短期変動に注目し臨床実験を行った．特に，様々な負荷に対する短時間での昇圧変化，および起立などの急な降圧など，『超』短期変動に焦点を合わせウェアラブル血圧センサーの有用性を検討した．なお，ウェアラブルセンサーの詳細については，既報の論文[Lopez 10, Labat 11]を参照していただくこととして，本稿では詳細を省略する．

4. 実験方法

具体的には，高齢者の『超』短期変動を評価する目的で，表 2 に示すような様々な負荷（メンタル，歩行，立位など）を行い従来のカフ式血圧計（血圧モニタリング）も並行して測定し，ウェアラブル血圧センサーによるデータと比較した．カフ測定間隔に関しては高齢の対象者へのカフ圧迫による負担を軽減させることに配慮しながら，3～5 分間隔で測定した．装置は，通常 1 時間ごとに測定されるカフ式の自動血圧計（NIHON KOHDEN ベッドサイドモニタ BSM2301，OMRON デジタル自動血圧計 HEM-711 ファジィ，またはフクダ電子 FM-800）を用いたが，測定は手動で行った．

対象は東京大学附属病院・老年病科に生活習慣病の慢性管理目的もしくは物忘れを主訴の一つとして入院された 60 歳以上の症例とし，悪性腫瘍や急性疾患を持ち合わせる症例は除外した．すべての症例に同意書を取得した．

5. 結果および考察

5.1 メンタル・ストレス反応性の血圧変動の結果

この『超』短期変動に焦点を合わせ，現在までに 50 症例（平均年齢 80 歳±5.8 歳：男性 16 例，女性 34 例）に対してデータ収集を行った．メンタル・ストレス負荷の中で「2つの物語に対する暗記（復唱）」負荷に対してウェアラブル血圧センサーにより昇圧が認められた症例は 50 例中 20 例（40%），「計算（暗算）」負荷による昇圧を示した者は 50 例中 24 例（48%）であった．また，歩行負荷による昇圧は 50 例中 33 例（66%）であり，この血圧センサーにより比較的多くの症例に超短期血圧変動を感知することができた．

それらの症例の中で，ストレス反応性昇圧に対してウェア

表 2 実験プロトコールの概要

【1】メンタル・ストレス負荷による昇圧
（Mental stress-induced BP elevation）
①「2つの物語に対する暗記（復唱）」負荷
②「計算（暗算）」負荷
1）100 から 7 を連続的に引き算していく
2）3597-59, 1703-17, などの暗算
【2】歩行負荷中の昇圧
（Physical stress-induced BP elevation）
【3】起立による血圧の変化
（Orthostatic hypotension）

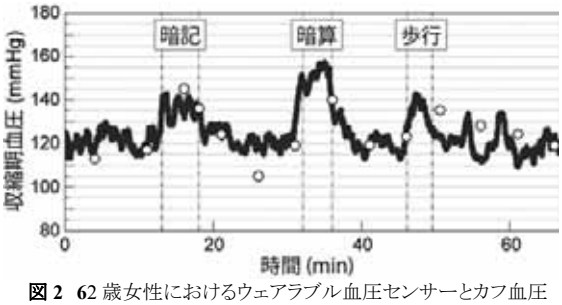

図 2 62 歳女性におけるウェアラブル血圧センサーとカフ血圧
～ストレス反応性昇圧に対する有用性が確認された一例～

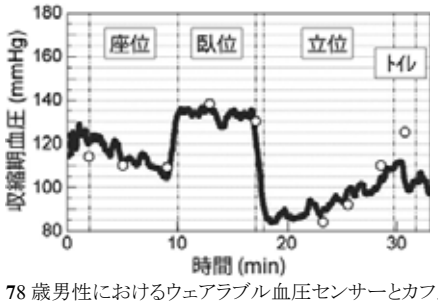

図 3 78 歳男性におけるウェアラブル血圧センサーとカフ血圧
～起立性低血圧に対する有用性が確認された一例～

ラブル血圧センサーの有用性が確認された代表的な症例の血圧測定結果を図2に示す.

カフ血圧測定の収縮期血圧を○印で示す. ウェアラブル血圧センサーによる収縮期血圧の推移は60 beats medianにて表示してある. この症例は認知機能評価としてMini-Mental State Examination (MMSE) 24/30点, Revised Hasegawa Dementia Scale (HDS-R) 26/30点であり, 患者本人の物忘れに対する訴えはあるものの認知機能評価としては軽度認知機能低下(mild cognitive impairment:MCI)のレベルである. 暗記や暗算によるメンタル・ストレス負荷に対して, カフ血圧値は少なくとも20 mmHg以上昇圧していることが分かる. 一方, ウェアラブル血圧センサーによる収縮期血圧の推移を見てみると, そのストレスによる昇圧を再現でき, さらにその昇圧の程度もカフ血圧からの昇圧度から比較するとはるかに大きいことが分かる. 具体的には暗記ストレスによる昇圧はほぼカフ血圧での昇圧の程度と同じであったが, 暗算ストレスにおいては血圧センサーでは約40 mmHg以上上昇していた. 前述したように, カフを用いた血圧測定にはある一定の間隔(ブランク)が必要となる. この結果から見ると, 従来カフ血圧にて連続して測定していても, その間に今までに見えていなかった急峻な血圧上昇や『超』短期変動が存在していた可能性がある.

実際, 認知機能の程度によりカフ血圧の昇圧レベルに差が存在することも報告されており[Kawashima 07], 軽度認知機能低下の傾向にある症例においてはストレスに対して大きな負荷と認識し, 結果的に大きな昇圧が惹起されていることが想定される. 以上より, 生活習慣病としてのリスクを持ち合わせていない高齢者であっても, 従来のカフ血圧測定で描出することができていなかった血圧変動の程度が「認知機能レベル」に大きく依存していることも示唆される. よって, 今後に向けて, この関係を解明すべく症例を重ね検証をすすめていく予定である.

5.2 フィジカル・ストレス反応性の血圧変動の結果

歩行負荷においても, 図2の例においてウェアラブル血圧センサーにより急峻な昇圧(約30 mmHg以上)が確認し得た. カフ測定では歩行中には事実上測定することが不可能である. 特に下半身の筋力低下や脳卒中による麻痺などを持ち合わせている高齢者では, 歩行自体の活動が身体的ストレスになる. その意味でも, 高齢者における身体活動時の血圧変動を確認する上でこのウェアラブル血圧センサーの有用性が伺える. さらに, 収縮期血圧と心拍数から計算されるDouble Productは心負荷レベルを反映しているとされ, 高齢者の歩行リハビリテーションを遂行するにあたり, 過度な心負荷を避ける目的としても良い目安になり得ることが期待される.

また, 認知症に加え起立性低血圧を伴う症例に対して, ウェアラブル血圧センサーにより詳細な血圧変動を同定できた代表的症例を図3に示す.

この症例は認知機能低下に加え自律神経障害も持ち合わせ, 起立性低血圧によりめまい・立ちくらみ, そして転倒を繰り返している症例である. 明らかな脳血管障害は認めないものの, これらの問題に対する恐怖心も併存して, 日常生活における行動範囲が非常に狭められてしまっている. 今回, 起立性の血圧低下に対してウェアラブル血圧センサーを装着し精査を行った. 座位から臥位への体位変換を行っただけでも約20 mmHg以上の血圧上昇がみられ, さらに能動的起立(すなわちSchellong試験)を行ったところ, その起立動作に移っている途中段階から劇的な血圧低下が確認され, 最終的に収縮期血圧が約90 mmHgまで低下した. その後は, ごくわずかな血圧回復を示した.

起立性低血圧をチェックするために, 臨床診療においてはカフ血圧測定を用いてTilt-up試験(受動的起立)やSchellong試験(能動的起立)がよく行われている. この結果から考えると, 測定間隔のあいたカフ血圧値よりも, このウェアラブル血圧センサーによって描出できる詳細な血圧変動の方が高齢者独特の病態を反映する可能性が示唆される.

5.3 考察

以上より, 開発したウェアラブル血圧センサーを血管壁硬化の進んでいる高齢者において臨床応用したところ, 非侵襲的に鋭敏な『超』短期変動を捕えることができた. このウェアラブル血圧センサーをより臨床の場で活用することにより, 従来のカフ圧迫による頻回な苦痛を与えることなく, 様々な環境の変化やストレス下における高齢者の血圧の『超』短期変動を捕えることができると考えられる. 結果に示したように, メンタル・ストレス負荷においてこのセンサーにより昇圧が認められた症例はそれぞれ暗記負荷と暗算負荷で40%と48%であり, また歩行負荷では66%であった. 昇圧が全ての症例において確認されなかった理由として, この50症例には物忘れを主訴とする症例も多く含まれており, 認知機能の低下に応じてメンタル・ストレス負荷が十分かからない症例も存在する可能性が高い. また, 同時にこの対象群には下肢筋力低下も持ち合わせる症例も含まれており, 歩行という動作においては十分な負荷を与えることが限界であった症例も含まれる. 平均年齢80歳の高齢対象者だからこそ, 様々な認知機能や下肢筋力のレベルが存在するが, 認知機能の低下が軽度で留まっている者や歩行が円滑に行える症例においては, 少なくともこの血圧センサーにより超短期血圧変動を感知することができた.

今回の臨床実験を通じて, この血圧センサーを用いての収縮期血圧の絶対値の決定にはキャリブレーションの問題が重要である. 特に血管特性(動脈壁の硬化度など)の個人差が非常に大きな高齢者の場合には, 今回のキャリブレーションの方法ではまだ不完全な部分が残されている. 今後, 同一症例における再現性やbaPWV (brachial-ankle Pulse Wave Velocity)を代表とする動脈壁硬化度とウェアラブル血圧センサーによるデータの相関などの基礎的検討を加えながら, さらに幅広い臨床病態への応用として, 認知機能レベルによるストレス昇圧の反応性の差異, 易転倒性の症例における血圧低下の関与のレベル, さらには高齢者の様々なリハビリテーション時における血圧モニタリングに対するウェアラブル血圧センサーの有用性を検討していく予定である.

カフレスで連続的に血圧を測るセンサーに関して, 脈波伝播速度法を応用した同種の事例がMITより発表されている[McCombie 07]. 一般に測定部の高さが変わると, 水頭圧分の補正が必要になる. このデバイスに関しては, 手首および指でセンスしており, 腕の動作による影響は避けられない. 特に, 歩行中や食事中などの活動状態の際に大きく問題となる可能性があり, 加速度センサーによりこれを補正しようとする論文である. 一方, 本論文で用いた血圧センサーの場合には, 耳たぶという場所を選択しており, 可能な限り体動

の影響を少なくできると考えており，体動の補正なしでも議論が可能である．なお，頭部（耳たぶ）で測ることによる水頭圧の補正は，算出パラメータに含まれるので無視できる．

さて，どちらのセンサーを用いるとしても，臨床の場での十分な活用までにはいくつかの問題を含んでいる．まず1つ目には高齢患者さまご自身の装着感である．現時点でこのウェアラブル血圧センサーを装着した高齢者に聞き取りを行うと，基本的には耳たぶへのセンサーの装着感には大きな問題を訴えてはいない．とはいえ，歩行障害や手指の動作に支障をきたしている高齢者において，いかに身軽な装着として感じることができ，そして体動の影響をいかに少なくできるかが課題であろう．また 2 つ目に，センシング後に算出した血圧値を幅広い医療関係者が見やすい形としていかにリアルタイムに表示できるかも大きな課題である．そこに患者さま側へのデータのフィードバックにも配慮を必要とする．過度な『超』短期変動を捕えることができた時に，その異常をより迅速に診療内容に応用でき，そして患者さま側にも分かりやすい形でデータを共有できるかをさらに検討する必要がある．

6. おわりに

今回，東京大学附属病院・老年病科における高齢症例に対してウェアラブル血圧センサーの有用性を証明すべく，特に『超』短期変動に焦点を合わせて検討した．メンタル・ストレス反応性の昇圧に対しても，そして起立性血圧低下に対しても，カフ血圧値と比較し安定した収縮期血圧の推移を算出することができた．今後，高齢者において，脳・心血管系疾患の発症予防にも「厳格な血圧変動管理」という視点での有用性が期待できるだけではなく，さらに転倒既往や転倒リスクを持ち合わせている高齢者に対しても「過度な血圧変動や過降圧による相対的脳虚血の可能性をチェック」する視点においても非常に有用である．このウェアラブル血圧センサーから得られる情報を臨床診療に活用することにより，最終的には高齢者の日常生活活動度を維持させることにつながることが期待される．

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Geriatrics Gerontology International 1st Impact Factor in June 2010 Medline Indexed

Geriatr Gerontol Int 2011; **11:** *525–526*

LETTER TO THE EDITOR

Actions of the Japan Geriatric Society in response to the 2011 off the Pacific Coast of Tohoku Earthquake: First report

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Dear Editor,

A huge earthquake occurred in Japan on March 11, 2011 at 2:46 PM (Japanese standard time). The Japan Meteorological Agency officially announced that this earthquake was named the "Off the Pacific Coast of Tohoku Earthquake" and had a magnitude of 9.0. This disaster presented several unique characteristics compared to previous earthquakes in Japan, including the great Hanshin-Awaji earthquake, because it brought about a large tsunami, resulting in exceptional damage in the northeast-east areas of Japan and destruction of many coastal cities.[1] According to the report by the National Police Agency of Japan, 15 413 people died as of June 11, approximately 90% of them drowned. In addition, the huge tsunami disaster took an unexpected turn, with 8069 persons still missing. This terrible disaster shows the uniqueness of this earthquake. Approximately 470 000 people had to be evacuated to shelters as a result of unavoidable circumstances at the peak (on 14th March), and around 100 000 people are still living in shelters. In addition, the huge tsunami unexpectedly resulted, not only in widespread destruction of communities, but also in nuclear power plant accidents in Fukushima, leading to the collapse of daily life of many residents.

The Japan Geriatric Society (JGS) immediately formed the Disaster Supportive Center on 18th March 2011 and took several steps to deal with this huge disaster. First, the JGS grappled with the issue of geriatric medicine in the disaster, in cooperation with the Study Group of the "Guidelines Regarding the First Steps and Emergency Triage to Manage Elderly Evacuees". In the case of elderly victims, even after their safe evacuation to a refuge, it is possible that they may suffer from disaster-related illnesses, including the deterioration of pre-existing illnesses, cerebro-cardiovascular disease, infectious disease, and mental stress. In general, these disaster-related illnesses are induced by numerous factors, such as psychological distress, dehydration, and sympathetic nerve hyperactivation, and can lead to fatal and non-fatal conditions. Simultaneously with establishing the guidelines, the Study Group and JGS also made a manual for non-medical care providers (NMCP; e.g. public health nurses and certified social workers). The aim of this simple manual was to help NMCP and/or the families of the elderly to quickly identify illnesses in elderly evacuees. The booklets were distributed to a widespread stricken area, mainly Iwate, Miyagi, and Fukushima prefectures, by JGS members and Japan Medical Association Teams in each prefecture. Therefore, our mission in the JGS, using both the guidelines and the manual, was to extend life-saving medical help to as many elderly evacuees as possible via the reduction of susceptibility to disaster-related illnesses and death.

Next, the JGS Supportive Center immediately decided to dispatch a medical support team to a refuge in Soma City, Fukushima, as well as visit Ishinomaki and Higashi-Matsushima, Miyagi, to investigate the damage situation for elderly victims. In addition, the JGS also sent a support team of physicians to Mitsuke, Niigata, which shares a border with Fukushima prefecture. Mitsuke City, with 42 500 residents, accommodated around 500 refugees in three shelters. Most of the refugees were from Minami-Soma City where it had been recommended that people evacuate because of the nuclear power plant accidents. Since Mitsuke City itself has been struck by natural disasters twice in the last 10 years, but had no damage from the earthquake this time, the quality of support to refugees here was quite different from that in the center of the area struck by the earthquake and tsunami (Abe Y *et al.*, unpubl. data. manuscript in preparation).

Now, beyond the chronic phase, elderly evacuees are being gradually shifted from shelters to temporary housing. However, it is possible that they may have serious new problems, they might lose stimulation from the outside world and become miserable (e.g. survival guilt and nightmares). These emotional changes may lead to a decline in cognitive function and disused muscle atrophy of their extremities while in temporary housing. Another goal of JGS is to prevent a decline in the cognitive and functional abilities of the elderly in the long term through multidisciplinary support. The JGS needs to carry out a longitudinal investigation to clearly address the psychological distress and somatic symptoms in elderly victims based on posttraumatic emotional stress with exposure to disastrous conditions. In addition, the development of a national disaster plan for mental health in the elderly may also be required.

Acknowledgement

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Geriatrics Gerontology International 1st Impact Factor in June 2010 Medline Indexed

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COMMISSION REPORT

Guidelines for non-medical care providers to manage the first steps of emergency triage of elderly evacuees

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On 11 March 2011, a strong earthquake occurred off of Japan's Pacific coast and hit northeastern Japan. The earthquake was followed by huge tsunamis, which destroyed many coastal cities. As a result, the Study Group on Guidelines for the First Steps and Emergency Triage to Manage Elderly Evacuees quickly established guidelines enabling non-medical care providers (e.g. volunteer, helpers, and family members taking care of elderly relatives), public health nurses, or certified social workers to rapidly detect illnesses in elderly evacuees, and 20 000 booklets were distributed to care providers in Iwate, Miyagi, and Fukushima prefectures. The aim of this publication is to reduce susceptibility to disaster-related illnesses (i.e. infectious diseases, exacerbation of underlying illnesses, and mental stress) and deaths in elderly evacuees. **Geriatr Gerontol Int 2011; 11: 383–394.**

Keywords: earthquake, elderly evacuee, emergency triage, guidelines, non-medical care provider.

Background

Japanese people have already experienced a variety of natural disasters including earthquakes,[1] typhoons,[2] tsunamis,[3] and others. It is very important to manage the medical care of elderly evacuees in the wake of disasters because: (i) elderly subjects (especially those needing to live in shelters) may suffer excessive mental and/or physical stress under the altered environment; and (ii) it is difficult to maintain medical management of chronic illnesses (e.g. hypertension, diabetes mellitus, cerebrovascular or cardiac disease) when care has already been started at local medical institutions. It was reported that acute risk factors possibly triggered cardiovascular events in hypertensive elderly patients after the Hanshin-Awaji earthquake.[4] Increased incidence of transient left ventricular apical ballooning (takotsubo cardiomyopathy) was also described after the Mid Niigata Prefecture Earthquake of 2004.[5]

In April 2010, the Study Group on "Guidelines for the First Steps and Emergency Triage to Manage Elderly Evacuees" was formed, with funding from Japan's Ministry of Health, Labour and Welfare, to conduct comprehensive research on aging and health. The study group aimed to complete and revise the guidelines based on external reviews by expert medical doctors by March 2012.

By collaborating with the Japan Geriatrics Society after the 2011 earthquake off the Pacific coast of Tohoku, we have quickly published two tentative guidelines to manage elderly evacuees: one for medical care providers and another for non-medical care providers (NMCP), including volunteer, helpers, and family members who are taking care of the elderly, public health nurses (PHN), or certified social workers (CSW). A total of 20 000 guideline booklets have been distributed by members of the Japan Geriatrics Society and the Japan Medical Association Team to NMCP, PHN, or CSW working in Iwate, Miyagi, and Fukushima prefectures (Fig. 1). The Japan Medical Association Team's mission is to provide medical assistance at hospitals or clinics in disaster-affected areas and to provide ongoing medical treatment that was started before the disaster.[6]

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Authors' contributions: Shigeto Morimoto and Takashi Takahashi contributed to the study concept and design. Masafumi Kuzuya, Hideyuki Hattori, and Koichi Yokono performed acquisition of data. Katsuya Iijima and Shigeto Morimoto analyzed and interpreted the data. Takashi Takahashi and Shigeto Morimoto prepared the manuscript.

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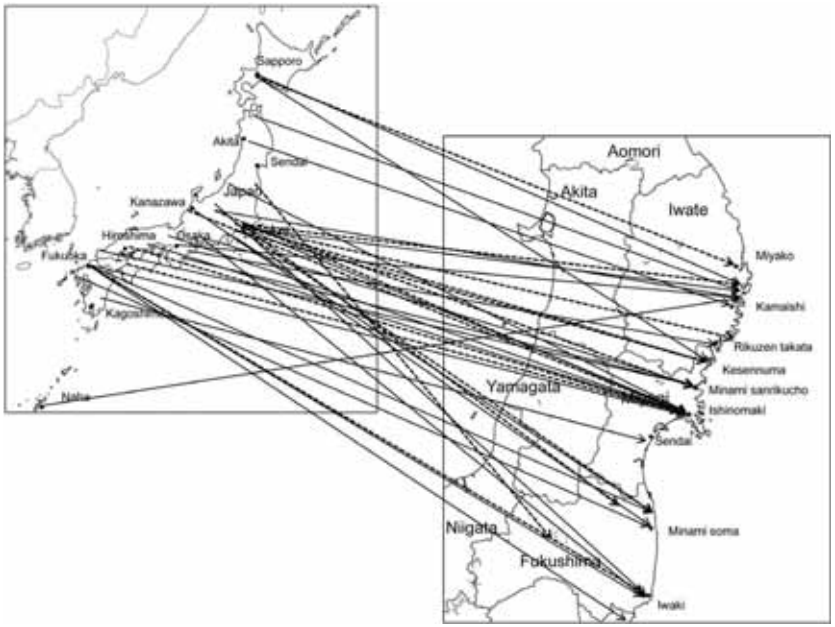

Figure 1 One week after the 2011 Tohoku earthquake, 20 000 booklets for non-medical care providers were distributed by members of the Japan Geriatrics Society (dotted lines) and Japan Medical Association Team (straight lines), to evacuation centers located in Iwate, Miyagi, and Fukushima prefectures.

Preface

The guidelines for NMCP, PHN, and CSW have three chapters: (i) Features and prevention of critical diseases in elderly in evacuation areas; (ii) Signs of acute diseases in elderly; and (iii) Symptoms of anxiety in elderly in shelters. Ideally, NMCP, PHN, or CSW will use the booklets to rapidly detect illnesses in the elderly in shelters or homes. NMCP, PHN, or CSW should immediately inform attending medical staff when those with the signs or symptoms are detected.

Guidelines

I. Features and prevention of critical diseases in elderly in evacuation areas

1–1). Heart attack. This condition includes angina pectoris, myocardial infarction, and other illnesses due to myocardial ischemia, a lack of blood flow in arteries.

Signs and symptoms of a heart attack

Location of symptoms	Central chest to left side of chest
	Apart from chest discomfort, anginal pain in the upper central abdomen, back, neck, jaw, or shoulders
Detailed symptoms	Worsening ("crescendo") chest pain, specifically crushing, burning, or choking sensation
	Onset of severe oppression or worsening oppression
Duration of symptoms	Infrequent or lasting less than 10 min
	Lasting more than 15 min, suggesting unstable condition

Note: Caution is needed because silent or mild symptoms frequently occur in the elderly, especially in those with diabetes. In addition, elderly people sometimes present with atypical symptoms, including breathlessness, nausea, discomfort in the upper central abdomen, or burping.

Measures to prevent heart attack in shelters

- NMCP, PHN, or CSW should be aware of elderly who normally take medication for cardiac disease and/or hypertension.
- NMCP, PHN, or CSW should check on the elderly.
- NMCP, PHN, or CSW should ensure that the elderly drink plenty of fluid, including water, to prevent dehydration. They should also advise that the elderly consume a low-salt diet and not smoke.
- If the elderly have any of the above symptoms, medical staff should be alerted.

Tips to treat cardiopulmonary arrest in shelters

- NMCP, PHN, or CSW should perform CPR, pushing the central chest strongly and quickly (100 times per minute) and alert medical staff immediately.

1–2). Hypertension. Awareness of blood pressure (BP) and its variability in the elderly is necessary because they may have excessive mental and/or physical stress, especially if in an emergency evacuation area or first-aid station, relative to their day-to-day lives before the disaster.

Measures to deal with elderly receiving antihypertensive drugs

- First, elderly people who are usually prescribed antihypertensive drugs should be reported to medical staff. NMCP, PHN, or CSW should check on the elderly.
- Elderly people who have been diagnosed as hypertensive should also be checked by medical staff, NMCP, PHN, or CSW.
- BP should be measured frequently. If possible, it is better to measure it daily using an automatic BP machine. In high-risk patients, it is recommended that BP be measured in both the morning and evening.
- If the elderly person's medication is not known because the prescription record is lost, a doctor or medical staff should be consulted.
- If an elderly person has a headache, palpitations, chest symptoms, and/or flushing, BP should be measured immediately and medical staff consulted.
- No smoking and a low-salt diet are also recommended. Endeavors must be made to ensure the elderly maintain physical activity (e.g. any exercise for at least 30 minutes a day).

2. Stroke/cerebrovascular disease (CVD)

Cerebrovascular accidents occur suddenly due to a disturbance in the blood supply to the brain and lead to a loss of cerebral function.

Signs and symptoms of stroke/CVD

If elderly people have any of the following symptoms, it is possible that they may have suffered a stroke/CVD. Consult medical staff immediately, because these situations may become medical emergencies.

- Symptoms starting suddenly and lasting from a few seconds to minutes
- Headache (mild to severe)
- Vertigo and/or dizziness (with nausea/vomiting on occasion)
- Disturbance of consciousness (snoring-like breathing, semiconscious state/coma)
- Motor disturbance including hemiparesis/hemiplegia/numbness, exhaustion, muscle weakness of the face (central facial palsy), drooling from one corner of the mouth, eyelid drooping (ptosis)
- Aphasia (difficulty with verbal expression, auditory comprehension)
- Sensory or vibratory disturbance (on one side)
- Visual field defect/hemianopia, double vision/polyopia
- Loss of balance when sitting, standing, or walking; loss of coordination.

Measures to prevent stroke/CVD in shelters

- First, medical staff and people around should be aware of elderly people who usually take medication for atherosclerotic diseases and/or lifestyle-related diseases (e.g. hypertension, diabetes, dyslipidemia, and cardiac diseases including atrial fibrillation).
- Also, people around should check on the elderly.

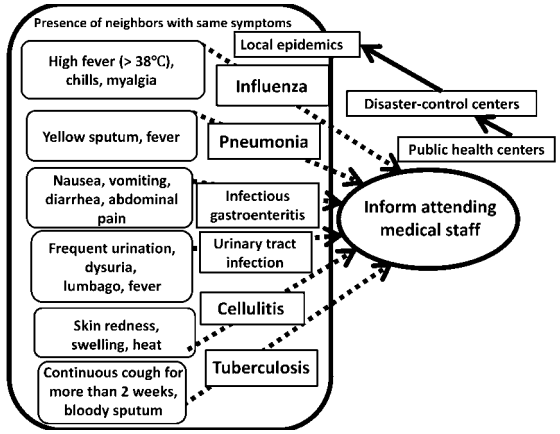

Figure 2 Measures to rapidly detect infectious diseases.

- Continue usual drugs including anticoagulation drugs if possible.
- In cases of unidentified medical conditions because of loss of an elderly person's prescription record, medical staff should be consulted.
- Anticoagulation drugs are generally essential. However, it is better to consult medical staff because it is necessary to check for external wounds or bleeding from the gastrointestinal tract, including stress-induced ulcer.
- CVD is strongly associated with hypertension. Measure BP regularly.
- No smoking is strongly recommended.
- Drink any fluid, including a lot of water, to prevent dehydration.
- A low-salt diet is strongly recommended. Endeavor to take dietary fiber in vegetables including seaweed and mushrooms.
- Endeavor to do any type of exercise or walk for at least 30 minutes a day regularly.
- Prevent constipation.
- Be careful about changes in temperature, especially in winter.

3. Infectious diseases

Signs and symptoms of infectious diseases

It is useful to have information on epidemics of infectious diseases in stricken areas before and after disasters, in order to quickly detect illness. In particular, this measure is beneficial for diseases, such as influenza, food poisoning and viral gastroenteritis, with a short incubation time from infection to the onset of symptoms (i.e. several hours up to 3 days). Pay special attention to elderly persons with these symptoms and immediately inform medical staff if there is suspicion that an elderly person has such an illness. In relation to this point, it is important to collect epidemiological information from district public health centers through disaster-control centers (Fig. 2).

In fact, many evacuees in shelters developed vomiting and diarrhea after the 2007 Noto Peninsula Earthquake. It was possible to immediately predict an outbreak of norovirus gastroenteritis among evacuees since a local epidemic of this infectious disease had already been observed in the Noto area before the quake.

However, local epidemics are not always useful for detecting infectious diseases, particularly those with a long incubation period (i.e. several months up to 2 years) such as pulmonary tuberculosis.

Measures to prevent transmission of infectious agents in shelters

- The environment in shelters induces an increased risk for outbreaks of infectious diseases because many evacuees are living together in a very limited space.
- It is very important to wash hands and gargle as standard precautions. Please apply hand disinfectant when it is not possible to use water. It is essential to wash hands or use hand disinfectant after using the toilet.
- NMCP, PHN, or CSW should not directly touch human bodily fluids (e.g. blood, urine, feces, nasal discharge, and sputum) with their hands because the fluids may include infectious microorganisms.

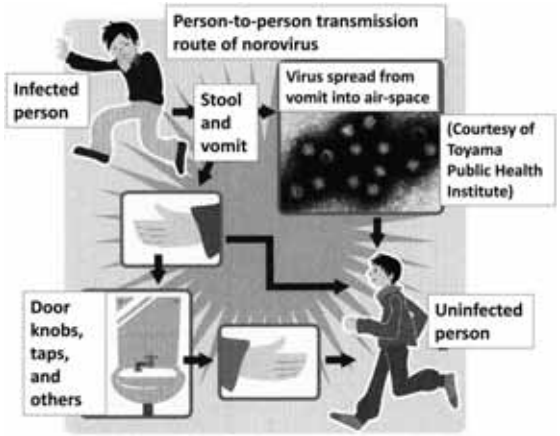

Figure 3 Person-to-person transmission route of norovirus.

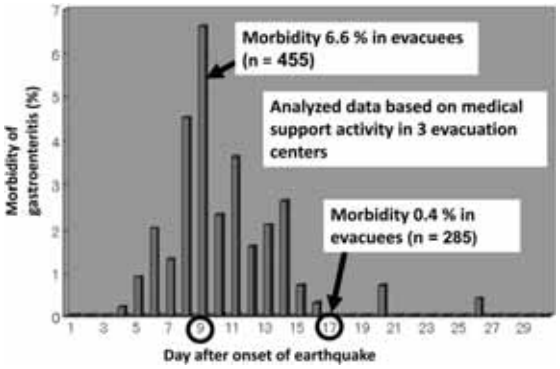

Figure 4 Morbidity of gastroenteritis in evacuees in shelters after the 2007 Noto Peninsula Earthquake.

If NMCP, PHN, or CSW are aware that the environment (floors in shelters, portable toilets, and temporary water-suppliers) has been contaminated with vomitus or diarrheal matter, contact medical staff. Do not clean the contaminated environment yourself. The staff can deal with this using 0.1% sodium hypochlorite disinfectant.

- Norovirus can spread via person-to-person transmission and lead to gastroenteritis outbreaks (Fig. 3).[7] However, it is unnecessary to isolate subjects with gastroenteritis from the stricken areas. The outbreak in shelters after the Noto quake was quelled after one week of interventions including personal hand hygiene, gargling, and the use of disinfectant on environmental surfaces (Fig. 4).[8]

In addition, respiratory hygiene (cough etiquette) is recommended to prevent respiratory infections.[9] With respect to coughing, rhinorrhea, sneezing, and sputum, please instruct evacuees to behave as follows: (i) use a tissue to cover your mouth and nose when you cough or sneeze (Fig. 5); (ii) drop used tissuew in a special waste basket; and (iii) wash your hands with soap and warm

Figure 5 Respiratory hygiene (cough etiquette).

water or clean with alcohol gel or wipes since your hands may be contaminated with secretions (Fig. 5). Elderly people who frequently cough or sneeze should be asked to wear a surgical mask provided by medical staff. Please keep a distance of more than 1 m between symptomatic subjects and others.

4. Dehydration

Signs and symptoms of dehydration

If an elderly person has some of the more severe symptoms of dehydration listed below, call medical staff immediately.

- Muscle weakness
- Physical fatigue
- Increased body temperature
- Decreased urine production
- Dry skin, even under the armpits.

Measures to prevent dehydration in shelters

- When elderly people feel thirsty, they are already dehydrated, so do not restrict water intake.
- To prevent dehydration, an elderly person without particular illness such as heart failure or kidney failure simply needs to replenish fluids with at least one liter of water per day.
- When elderly people have any of the risks for dehydration listed in Table 1, they should be carefully assessed by a doctor for dehydration.

Table 1 Risks for dehydration in the elderly

Inability to feed oneself
Appetite loss (decrease in food intake)
Swallowing problems
Diarrhea or vomiting
Thirsty or dry mouth
Taking a diuretic
Increased body temperature
Decreased urination
No air conditioning/not using air conditioning
Limitation of water intake to avoid frequent urination

5. Malnutrition

Signs and symptoms of malnutrition

When an elderly person has any of the risks for malnutrition listed below, the person should be carefully assessed by medical staff.

- Consumed less than half the usual dietary intake for at least 1 week
- Diarrhea or vomiting for more than 2 or 3 days
- Decrease in body weight of more than 5% for 2 weeks
- Insufficient intake or dysphagia due to inadequate food
- Receiving enteral or parenteral nutrition.

Measures to prevent malnutrition in shelters

The following general precautions to prevent malnutrition should be considered:

- Adequate food supply
- Adequate types of food consumed
- Adequate feeding assistance
- Dental issues such as gum disease, cavities, and poorly fitting dentures
- Regular assessment of nutritional status and weight loss.

6. Gastrointestinal disorders

Signs and symptoms of gastrointestinal disorders

When elderly evacuees have any of the signs and symptoms of gastrointestinal disorders listed below, they should be carefully assessed by medical staff.

- Upper central abdominal pain after meals (on suspicion of stomach ulcer)
- Upper central abdominal pain when hungry (on suspicion of duodenal ulcer)
- Gastric discomfort

- Appetite loss
- Heartburn
- Tarry (black) stool or blood in the stool.

Measures to prevent gastrointestinal disorders in shelters

The following general precautions to prevent gastrointestinal disorders should be considered:

- Avoid psychological stress.
- Eat substantial meals at regular mealtimes.
- Wash hands, gargle, and disinfect cooking utensils to prevent infectious enteritis.
- Flush or discard any vomit, and change diapers with rubber gloves while wearing a flu mask. Thoroughly clean and disinfect contaminated surfaces with a bleach-based household cleaner immediately after an episode of illness.
- Drink sufficient liquid and take a lot of exercise to avoid constipation.
- Do not ignore the urge to defecate and maintain a regular bowel habit.

7. Diabetes mellitus (DM)

7–1). Hyperglycemia

Signs and symptoms of exacerbation of DM

If elderly people have any of the symptoms described below, their DM might be worsening. Please contact medical staff if any of the following symptoms are detected:

- Frequent urination
- Increasing incontinence
- Thirst
- Fatigue
- Not looking well.

Measures to prevent exacerbation of DM in shelters

- Eat meals regularly and take medication with meals.
- Patients with DM type 1 should not skip basal insulin injections.
- Drink enough water to prevent dehydration.
- If someone has a fever or little appetite, monitor blood glucose more frequently than usual or consult a doctor promptly.

7–2). Hypoglycemia. In addition, if elderly evacuees are taking hypoglycemic medication, be alert for symptoms of hypoglycemia.

Signs and symptoms of hypoglycemia

The symptoms described below might be caused by hypoglycemia. Please contact medical staff if any of the following symptoms are detected:

- Strong feeling of hunger
- Cold sweats
- Palpitations
- Weakness
- Sleepiness
- Slurred speech
- Blurred vision
- Convulsion.

Measures to prevent hypoglycemia in shelters

- Elderly people should avoid exercise or working when hungry.
- Eat meals regularly.
- Eat carbohydrates (e.g. rice, bread, noodles, or potatoes).
- If people cannot eat a meal, they should reduce or skip their hypoglycemic medication.
- Set a higher goal of glucose control (150–200 mg/dL) than usual.

Tips to treat hypoglycemia in shelters

- NMCP, PHN, or CSW should ask those with the above symptoms to take a glucose tablet.

8. Bronchial asthma

Signs and symptoms of exacerbation of bronchial asthma

If elderly people have any of the following symptoms, bronchial asthma might be worsening. Please contact medical staff if the following symptoms are detected:

- Paroxysmal wheezing or coughing, or reoccurrence of these symptoms
- Breathlessness during the night
- Breathlessness when moving, speaking, or lying down
- Cyanosis or edema
- Drowsiness.

Measures to prevent exacerbation of bronchial asthma in shelters

- Let NMCP, PHN, CSW, or medical staff know that if an elderly person is taking medication.
- Continue taking medicine.
- Wash your hands and gargle regularly, wear a mask if available, and be careful about infectious diseases such as colds.
- Keep warm.

9. Chronic obstructive pulmonary disease (COPD)

Signs and symptoms of exacerbation of COPD

If an elderly person has any of the following symptoms, COPD might be worsening. Please contact medical staff if the following symptoms are detected:

- Increased respiratory rate and shortness of breath
- Worsening of dyspnea on exertion or at rest
- Increased frequency or severity of cough and excessive sputum production
- Mucopurulent sputum (change in sputum character)
- Cyanosis or edema
- Drowsiness.

Measures to prevent exacerbation of COPD in shelters

Figure 6 Ares where pain occurs due to urinary tract diseases.

- Let NMCP, PHN, CSW, or medical staff know if an elderly person is taking medication.
- Continue taking medication and inhaling bronchodilators.
- Avoid exposure to smoke and dust.
- Try to wash your hands and gargle regularly.
- Keep warm and do not stay in the cold.

10. Chronic kidney disease (CKD)

Signs and symptoms of CKD

If elderly evacuees have any of the following symptoms, CKD might be worsening. Please contact medical staff if the following symptoms are detected:

- Inactivity, fatigue, or weakness
- Edema
- Appetite loss
- Nausea and/or vomiting
- Pruritus.

Measures to prevent CKD in shelters

- Let NMCP, PHN, CSW, or medical staff know if an elderly person is taking medication.
- Continue taking medicine.
- Have regular blood pressure checks.
- Restrict salt intake.
- Drink enough water to prevent dehydration.
- Keep warm.
- Be careful about infectious diseases such as colds.

11. Urinary diseases

Signs and symptoms of urinary diseases

If an elderly person experiences some of the more severe symptoms of urinary diseases listed below, call medical staff immediately.

- Pain on urination
- Lower abdominal pain (Fig. 6)
- Back pain, lumbago (Fig. 6)
- No urination for half a day or longer
- Distention of lower abdomen
- Bloody urine
- Cloudy smelly urine
- Frequent urination
- Incontinence
- High fever (in cases of pyelonephritis, 38°C or higher)
- Limiting water intake in order to avoid frequent urination or incontinence.

Measures to prevent urinary diseases in shelters

- Replenish fluids with at least one liter of water per day in persons without particular illness such as heart failure or kidney failure.
- Do not avoid going to the toilet.

12. Post-traumatic stress disorder (PTSD)

Signs and symptoms of PTSD

Please contact medical staff if an elderly person has any of the following symptoms. Please contact medical staff if the following signs are detected:

- Sudden change in personality
- Absent-mindedness and the inability to respond quickly
- Restlessness
- Frequent hyperventilation
- Frequent palpitations
- Panic attacks.

Measures to prevent PTSD in shelters

- If elderly people feel distressed or pain, they should confide in someone (a medical staff member, NMCP, PHN, or CSW).
- It may be necessary for the elderly to take medication if they cannot sleep or feel distressed and there is no alternative.

13. Depression

Signs and symptoms of depression

It is not unusual for an elderly person to experience grief after suffering from severe stress. Please contact a medical staff member if the following symptoms of depression are detected:

- Cannot help thinking of bad things
- Not knowing what to do despite actually having many things to do
- Feeling too sluggish to move, although the results of a medical checkup and blood tests are normal
- Unable to sleep at night
- Always thinking of dying.

Measures to prevent depression in shelters

- It is important to maintain a routine, including waking up and going to sleep at the same time daily.
- If elderly people feel distressed or pain, they should confide in someone (a medical staff member, NMCP, PHN, or CSW).

- It may be necessary for the elderly to take medication if they cannot sleep or feel distressed and there is no alternative.
- If an elderly person has been attending a clinic for the treatment of depression, please tell a medical staff member. It is important that the person continues to receive treatment.

14. Behavioral and psychological symptoms of dementia (BPSD)

Signs and symptoms of BPSD

Please contact a medical staff member if the following symptoms of dementia are detected:

- Restlessness and speaking in a disjointed manner
- Paranoid or having delusions (e.g. a false idea of being robbed)
- Becoming angry or starting to cry suddenly.

Measures to prevent BPSD in shelters

- Create an environment in which dementia patients can spend time with familiar people.
- Prepare a quiet environment so that dementia patients can get adequate sleep at night.
- Preparations should be made so that a dementia patient can be transferred to a professional medical institute when psychological symptoms or behavioral abnormality is observed.

15. Delirium

Signs and symptoms of delirium

Please contact medical staff if any of the following physical symptoms are detected in elderly persons who had previously been well and not experienced any decrease in cognitive function:

- Speaking or behaving in an erratic manner
- Absent-mindedness or being distracted
- Emotional instability (e.g. becoming angry, starting to cry, or getting excited suddenly).

Measures to prevent delirium in shelters

- Particular attention should be paid to dehydration, infections, and other underlying physical disorders, which can cause delirium in the elderly. Please be aware that elderly people with physical disorders are potential delirium patients.
- Keeping the elderly company and talking to them to provide stimulation are effective for preventing lethargy during the daytime. At night, create a quiet environment to help them achieve a regular sleeping pattern.

16. Dental diseases

Signs and symptoms of dental diseases

If an elderly person is showing some of the more severe symptoms of dental disease listed below, call medical staff immediately.

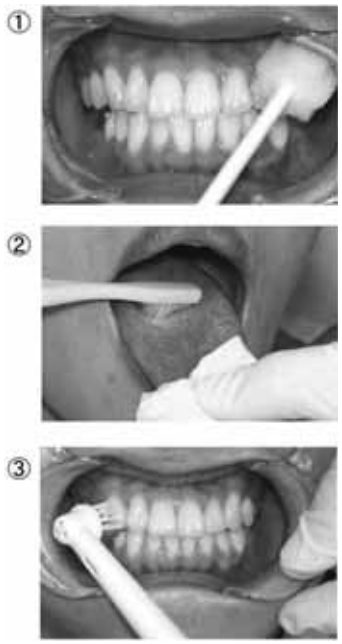

Figure 7 Systematic oral care program.

- Pain from dental caries
- Swelling and bleeding of the gingival
- Severe halitosis
- Fur on the tongue.

Measures to prevent dental diseases in shelters

- Keep cleaning the mouth.
- Brush the teeth every day.
- Those who are unable to do the above independently need to receive a systematic oral care program (Fig. 7)[10]
  1 Remove oral-mucosal and gingival saburra by using an oral care sponge for one minute.
  2 Remove fur from the tongue with a tongue brush for half a minute.
  3 Remove bacterial flora from the tooth surface with an electric toothbrush for 2.5 minutes, if an electric power supply is available.
  4 Rinse the mouth for 1 minute.

17. Functional inactivity

Signs and symptoms of functional inactivity

Elderly people often may not complain of their subjective symptoms accurately, or they may not be aware of a decline in their health. Thus, it is important for NMCP, PHN, or CSW to be aware of elderly persons' health conditions as well as the whereabouts of subjects who require support and/or nursing care.

If an elderly person shows some of the more severe symptoms of functional inactivity listed below, call medical staff and/or shelter staff.

- Being isolated, with no attempt to communicate
- Narrow range of activities and staying indoors
- Lying down all day long

Measures to prevent functional inactivity in shelters

- Encourage subjects to greet each other and make small talk in the shelter.
- Exercise regularly.
- Bend and stretch your arms and legs often, even in the narrow living space in the shelter.
- NMCP, PHN, or CSW should evaluate the reserve capability of elderly subjects with functional inactivity promptly.

18. Decubitus

Signs and symptoms of decubitus

NMCP, PHN, or CSW should actively survey the onset of decubitus ulcer, particularly on the hip, the backbone, the heel, and the back of the head, in bedridden subjects. Since this illness needs long-term management, contact medical staff and arrange transport to the hospital.

Measures to prevent decubitus in shelters

- Change bedridden subjects' position every 2 hours a day.
- Keep the skin clean.

19. Heat stroke

Signs and symptoms of heat stroke

In summer, pay special attention to heat stroke in elderly people in shelters. The main features are hot skin (body temperature ≥ 40°C) without sweat and drowsiness. Call medical staff immediately as this condition will cause fatality.

Measures to prevent heat stroke in shelters

- Keep cooling the neck or under the arms.
- Do not restrict water intake.

II. Signs of acute diseases in elderly

If any of the following symptoms is encountered in the elderly, they may be severely ill due to acute disease. These signs of acute diseases are sensitive enough to rapidly detect a severe state in elderly evacuees. NMCP, PHN, or CSW should consult attending medical staff immediately. Asterisks denote signs indicating the need for emergency transport.

1. Disturbance of Consciousness (Japan Coma Scale [JCS] Scoring)

- Rousable by being spoken to but reverts to previous state if stimulus stops (JCS II-10)
- Rousable with loud voice but reverts to previous state if stimulus stops (JCS II-20)
- Rousable only by repeated mechanical stimuli (JCS II-30)

* Unrousable using any forceful stimuli but responds to avoid the stimuli (JCS III-100 to III-300).

2. Shock

* Anemia (e.g. pallor of lips and/or nails)
* Bleeding due to external injuries
* Disturbance of consciousness (JCS III-100 to III-300)

- Abnormal skin turgor, a physical sign of dehydration
- Dry tongue

* A decline in BP: systolic BP < 90 mmHg
* An increase or decrease in pulse rate (i.e. resting pulse rate of more than 120 beats/minute or less than 50 beats /minute).

3. Dyspnea

- Shallow and rapid respiration, puffing (shallow breathing)
- Shoulder breathing (accessory muscle use)
- Flaring of wings of the nose and dilated nostrils (nasal alar breathing)
- Violet color to lips and nails (cyanosis)
- Wheezing or whistling while breathing (wheeze/stridor)
- Sleeping with the upper body raised in order to breathe (orthopnea)
- Weak breathing, suspended on occasion (apnea)
- Pursing the lips when exhaling (pursed lips breathing)

* Collapse of supraclavicular or intercostal spaces when inhaling (inspiratory retraction)
* Distension of the abdomen/shrinking of the chest when inhaling, and shrinking of the abdomen/ distension of the chest when exhaling (seesaw breathing)
* Obvious asymmetric movement of the chest during respiration
* Respiratory rate less than 10/minute or more than 30/minute.

4. Acute abdomen

* Uncontrollable abdominal pain

* Hematemesis, vomiting blood
* Tarry (black) stool, visibly bloody stools not due to hemorrhoids
* Frequent vomiting
* Abdominal swelling, abdominal distension
* Severe anemia (pallor of face or lips).

5. Neurological abnormalities.

* Motor disturbance including hemiparesis/hemiplegia/numbness, muscle weakness of the face (central facial palsy), eyelid drooping (ptosis)
* Aphasia (difficulty with verbal expression, auditory comprehension)
* Sensory or vibratory disturbance (unilateral)
* Visual field defect/hemianopia, double vision/polyopia
* Loss of balance when sitting, standing, or walking; loss of coordination
* Pupils not isocoric
* Convulsions or cramps.

6. Chest pain

* Chest pain, oppression, burning, or choking sensation in anterior chest
* Increasing frequency and worsening angina attacks compared with 2 weeks earlier
* Chest symptoms even at rest or at night
* Continuation (without improvement) of these symptoms in spite of aspirin or nitroglycerine use
* Duration of chest symptoms: more than 20 minutes.

7. Hypertensive emergency

* Hypertension (systolic BP ≥ 200 mmHg).

8. High fever

- Shivering (shaking chills) coinciding with high fever and potential severe infectious diseases (i.e. bacteremia)
- Burning forehead and poor response to being called.

9. Hematuria

- Red and/or tea-colored urine.

III. Symptoms of anxiety in elderly in shelters

If an elderly person is showing some of the symptoms listed below, immediately ask medical staff to assess the presence of serious diseases.

1. Dysphagia, difficulty in swallowing

- Coughing or breathing in food while swallowing
- Aspiration (i.e. escape of food or liquid into the lungs) or labored breathing while swallowing
- Recurrent pneumonia, respiratory infections, or choking experiences
- Wet vocal quality ("gurgly" voice) after swallowing
- Irritability during feeding or failure to thrive
- Prolonged feeding times (more than one hour)
- Unexplained weight loss.

2. Diarrhea

- Subject has diarrhea and a fever.
- Similar symptoms (diarrhea) are observed in surrounding evacuees.
- If diarrhea persists for two days or more, ask medical staff to assess, in order to avoid dehydration.

3. Constipation

- Change in bowel habit
- Constipation with abdominal pain
- Constipation for 2 or more days.

Discussion

On 11 March 2011, an earthquake with a 9.0 magnitude occurred off of Japan's Pacific coast and hit northeast Japan. The earthquake was followed by huge tsunamis, which destroyed many coastal cities.[11,12] A total of 14 841 people died in these events, and 10 063 persons are still missing as of 6 May 2011.[13] In addition, 109 086 homes were completely or partially destroyed, and 3970 roads were damaged.[13] There are still 119 967 displaced people (down from approximately 470 000 on March 14) living in shelters because of disrupted community utility services and/or health risks related to the nuclear power plant accidents in Fukushima.[13–15] Specifically, 37 482, 35 923, and 25 501 persons took refuge into the 357, 403, and 157 evacuation centers located in Iwate, Miyagi, and Fukushima prefectures, respectively.[13]

There were several reports concerning medical needs following the 2011 earthquake off the Pacific coast of Tohoku. For instance, reports have highlighted the importance of managing the exacerbation of chronic illnesses (e.g. hypertension, cardiac disease, DM, and chronic pulmonary disease) as well as dehydration in elderly evacuees, especially as it was difficult to source enough medication for their chronic illnesses.[16,17] Health workers should pay attention to the possible spread of acute diseases such as gastroenteritis, diarrhea, and other illnesses associated with dirty water.[16] In addition to physical health problems, it is important to rapidly detect long-term mental problems in the elderly (e.g. PTSD, depression, BPSD, and delirium) triggered by the disaster.[16,17] Medical specialists have indicated

that thousands of victims will be in need of long-term counseling to cope with the loss of their relatives, friends, and homes.[16]

There were some cases that previous guidelines failed to cover because of the unexpected phenomena following the Tohoku earthquake. Therefore, it is essential that we are mindful of the difficulties in establishing general guidelines that can cover a wide (and unexpected) range of disasters. Feedback regarding the booklets will need to be collected from NMCP, PHN, or CSW to assess the guidelines' usability. We further need to investigate the morbidity and mortality from disaster-related illnesses among the elderly in order to clarify efficacy of these guidelines.

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Conflict of interest

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TUG groups. The difference in SPMT score at the second follow-up lost significance after additionally controlling for the baseline value.

DISCUSSION

This study found that the gait speed and mobility were associated with global cognitive function after 3 years and were cross-sectionally associated with executive and memory functions. The results could suggest that slowing of mobility can be observed before decline in global function and coinciding with impairment in executive and memory functions in people aged 80 and older. These findings based on octogenarians and nonagenarians in Okinawa, Japan, known for their longevity, give additional generalizability to previous findings.[2,10] This association has potentially important implications for early detection of cognitive impairment in older people.

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COMMENTS/RESPONSES

GUIDELINES FOR NON-MEDICAL CARE PROVIDERS TO DETECT ILLNESSES IN ELDERLY EVACUEES AFTER THE 2011 EARTHQUAKE OFF THE PACIFIC COAST OF TOHOKU

To the Editor: On March 11, 2011, at 2:46 p.m. (JST), a strong earthquake occurred off the Pacific coast of Japan and hit the northeast part of the country. Devastating tsunamis followed that destroyed many coastal cities.[1] The magnitude of this quake according to the Japan Meteorological Agency was Mj9.0. A huge number of aftershocks continued after the quake, even now (May 6, 2011). According to the report by the National Police Agency of Japan, as of May 6, 2011, 14,841 people had died in this disaster, and 10,063 were still missing.[2] In addition, 109,086 homes were completely or partially destroyed, and 3,970 roads were disrupted.[2] As shown in Figure 1A, 119,967 displaced people (peak number approximately 470,000 on March 14, 2011) were still living in shelters supplied by the government as of May 6, 2011, because of disruption of community utility services and health risks of nuclear power plant accidents in Fukushima.[2,3] In particular, 37,482, 35,923, and 25,501 persons took refuge in the 357, 403, and 157 evacuation centers located in Iwate, Miyagi, and Fukushima prefectures, respectively.[2]

Drs. Shigeto Morimoto and Takashi Takahashi reported an outbreak of norovirus gastroenteritis in elderly evacuees after the 2007 Noto Peninsula earthquake in Japan.[4] There were 74 evacuees, including 61 elderly persons, in the shelter where the outbreak occurred.[4] Thirty-one evacuees with gastroenteritis, 29 of whom were aged 65 and older (mean age 76 ± 7), were examined and treated.[4] This experience suggests that elderly victims are more susceptible to disaster-related illnesses (i.e., infectious diseases, exacerbation of underlying illnesses, and mental stress) and disaster-related death. Therefore, a plan to establish guidelines to detect illnesses and perform triage rapidly in elderly evacuees was necessary. In April 2010, the six authors of the current letter formed the Study Group of "Guidelines Regarding the First Steps and Emergency Triage to Manage Elderly Evacuees" under a grant-in-aid for scientific research from the Ministry of Health, Labour, and Welfare of Japan. Two types of guidelines were established: one for medical care providers (MCPs) and the other for non-MCPs (NMCPs, e.g., public health nurses and certified social workers). The guidelines for NMCPs seemed to be more effective

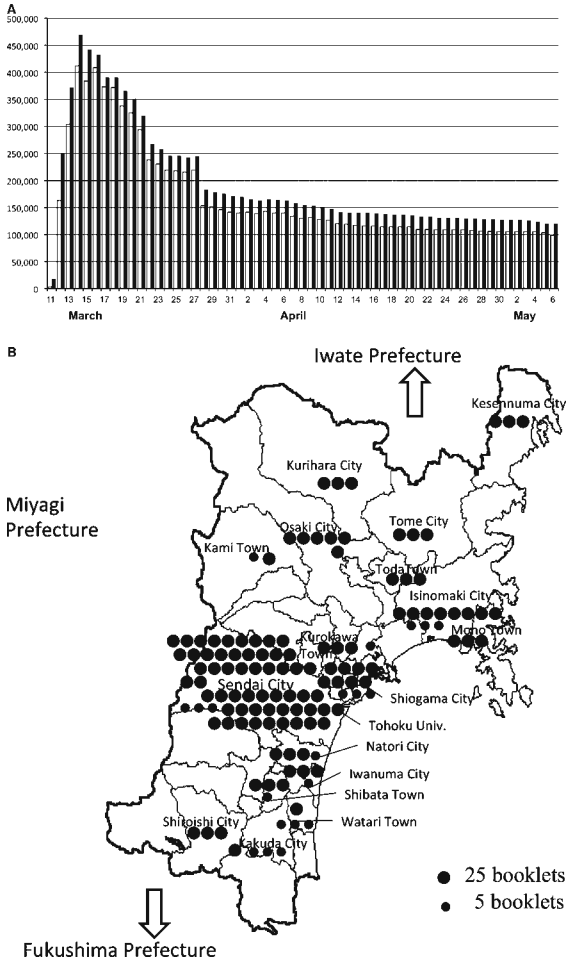

Figure 1. (**A**) Variations in number of evacuees from March 11 to May 6. Black and white bars denote total number of evacuees in Japan and number of persons still evacuated in Iwate, Miyagi, and Fukushima prefectures, respectively. (**B**) Distribution of guideline booklets to detect illnesses in elderly evacuees in Miyagi prefecture. These were distributed in the largest city, Sendai, where most people in this prefecture were living. Large and small closed circles indicate 25 and 5 booklets, respectively.

than those for MCPs, because there were limited MCP resources. The guidelines had three chapters: features of critical illnesses and prevention, acute symptoms, and chronic symptoms in elderly evacuees. For NMCPs to be able to understand the contents easily, it was written concisely.

One week after the 2011 earthquake off the Pacific coast of Tohoku, the guideline booklets were sent through members of the Japan Geriatrics Society (JGS) or the Japan Medical Association Team (JMAT) to NMCPs working in Iwate, Miyagi, and Fukushima. JGS and JMAT members were dispatched to these areas to care for evacuees. NMCP staff used the booklets to detect illnesses rapidly in elderly evacuees in shelters or homes. For example, the booklets were distributed in the largest city, Sendai, where most people in Miyagi were living (Figure 1B). The aim was to reduce morbidity and mortality from disaster-related illnesses in elderly evacuees. An investigation of the differences in morbidity and mortality between areas where the guidelines were and were not applied is planned.

The Japanese people had already experienced another strong quake, the Great Hanshin earthquake, which caused serious damage in the Kobe area on January 17, 1995. This disaster also hit the elderly population of an urban society particularly hard. More than half of the deaths were in those aged 60 and older, and in this age group, female mortality was almost double that of men.[5] Surviving older adults were largely left to their own devices and were marginalized in shelters. Elderly evacuees tended not to complain about their problems, so their suffering tended to be underestimated,[5] and it is therefore important for NMCPs to detect medical conditions quickly in elderly evacuees.

The situation of the recent disaster is different from that of the Great Hanshin quake in terms of the presence of tsunamis and nuclear power plant accidents. The recent quake's epicenter was located beneath the sea and caused huge tsunamis, whereas the Hanshin quake's epicenter was under the land and did not cause tsunamis. Most of the deaths were a result of the tsunamis this time, whereas the victims of the Hanshin quake were related to structure collapses and fires. Moreover, the recent evacuees in Fukushima are at short- and long-term health risks from the nuclear power plant accidents.[3] Therefore, a survey of the morbidity and mortality from disaster-related illnesses in elderly evacuees in Iwate, Miyagi, and Fukushima is needed.

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GAIT VELOCITY VERSUS THE TIMED UP AND GO TEST: WHICH ONE TO USE FOR THE PREDICTION OF FALLS AND OTHER ADVERSE HEALTH OUTCOMES IN PRIMARY CARE?

To the Editor: We read with great interest the recent article by Viccaro and colleagues in which they evaluated the predictive ability of the Timed Up and Go Test (TUG test) and gait velocity (GV) for falls and other adverse health outcomes.[1] Gait velocity predicted most geriatric outcomes, as did the TUG, and GV took less time to complete and demonstrated better prediction in individuals with intermediate (TUG = 12–15 seconds, GV = 0.6–1.0 m/s) and slow test performance (TUG < 12 seconds, GV < 0.6 m/s).

An important consideration when applying mobility measures across the spectrum of older people is the level

災害時高齢者医療の初期対応と救急搬送基準に関するガイドライン作成に関する研究
～高齢者災害時医療における日本老年医学会の役割と今回の東日本大震災への対応～

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研究要旨:

震災列島・日本において、大津波地震とも言えるこの東日本大震災は多くの爪痕を残しただけでなく、災害時高齢者医療における新たな問題点を提起した。災害弱者と言われる高齢者は普段から数多くの疾患やリスクを抱えているからこそ、発災後急性期には「情報をつなぐ医療」を実践しながら、的確な判断が必要とされる。特に循環器疾患管理や対策は非常に重要であり、震災関連死に直結し得る。なかでも高血圧管理は大きな比重を占め、内服薬の中断、避難所生活という急激な環境の変化による脱水や慨日生態リズムの乱れ、肉体的・精神的ストレスによる交感神経の賦活化など、様々な要因が重複する。

また慢性疾患管理に加えて、精神面の管理（サバイバーズ・ギルト、孤独死、閉じこもりなど）も重要になってくる。さらに、要介護高齢者の早期トリアージも重要であり、これらを円滑に行うためには多職種による系列を超えた広域医療連携の構築が必須である。そして復旧する過程で医療だけではなく、社会的支援や見守りも含めた精神面への長期的サポートも欠くことはできない。そこで、普段からどのように震災対応のイメージを共有し、そして自治体を中心とした高齢者に焦点を合わせた防災心への啓発に関する活動を平時から行えるのか、が重要である。そして、そこに日本老年医学会を中心とした高齢者医療に携わっている者が、どのようにコミットできるのかを今後大きな課題として考えていく必要がある。

A. 研究目的

震災列島と言われるわが国・日本は、災害弱者である被災高齢者に対する医療対応は非常に重要である。今回の東日本大震災（マグニチュード 9.0）は言い換えれば「大津波」震災と言っても過言ではない。この未曾有の大震災は発生から1年が経過した現在、大きな爪痕を残していると同時に、慢性期に向けて被災高齢者の様々な管理の難しさとも直面している。具体的には、「避難生活における被災高齢者の潜在的能力の喪失をどう防止するのか」、「災害時高齢者医療における円滑な医療初動のあるべき姿とは」、「大災害発生時に要介護高齢者に対してどう迅速に対応するのか」などである。高齢者災害時医療ガイドライン作成を目的とした本研究を通して、本研究班および日本老年医学会が今までに行ってきた活動を総括し、この大震災から学んだこと、見えてきた数多くの課題を検討・再考する。

B&C. 研究方法および結果

【今回の東日本大震災の特異性】 ～阪神淡路大震災との比較～

今回の東日本大震災の特徴を阪神淡路大震災（1995 年）と比較してみると、その特異性がよく分かる。阪神淡路大震災では8割が圧死・窒息死であり、死者数は 6,434 人に上ったが、逆に行方不明は 3 人のみであった。また Disaster Medical Assistance Team (DMAT)の創設の契機となった。さらに、地震による直接の死因ではなくその後の様々な疾患発症により死亡した方々が 14%に上ったことから、「災害関連死（震災関連死）」が改めて注目された。一方、今回の東日本大震災では死者9割超が水死（溺死・6割が60歳以上）という結果からも、ここ数十年間日本が経験したことのない大震災であったことは間違いない。また、この災害の特徴から今回の DMAT は 2～4 日で解散された。

死者は大震災からちょうど 6 か月経過した 9 月 11 日の時点で 15,782 人に上ると同時に、行方不明が 4,086 人という点が今回の震災の大きな特異性であり、津波地震による大きな影響を物語っている。4 月 11 日までに被災 3 県（岩手県・宮城県・福島県）で検視された 13,135 人の詳細に関する警察庁からの発表を見ると、年齢層別では 80 歳以上（22.1%）、70～79 歳（24.0%）、60～69 歳（19.1%）であり、60 歳以上で全体の 65%超を占めたことになる。

今回の大震災におけるもう一つの大きな特徴は、①被災地は従来から医師不足が問題であった地域であること、②被災地の中核病院自体が数多く被災したことから、カルテなど多くの医療情報が失われてしまったこと、③大規模災害時の通信手段が完全な途絶されてしまったことである。実際に、被災地の大学病院などには最初の数日間は現地からの情報の入手が困難であり、また大学病院の対策本部として怪我をした被災者の殺到を想定していたが、全く想定外の経過をたどった。

【高齢者災害時医療：経時変化から見る特徴】

①急性期（災害発生後 3 日以内）

精神的ストレスが脳心血管疾患の発症を著明に増加させることは明らかであるが、新潟県中越地震（2004 年）では高齢者において地震によるショック死なども多く認めた。さらに、独居高齢者は基本的に自力で行動できるが、従来、地域とのつながりが薄く、緊急事態に関する覚知が遅れやすい。迅速な情報伝達と避難誘導が必要となる。寝たきりの要介護高齢者では自力で移動できないため、避難する際は車椅子やストレッチャー等の補助器具が必要となる。また、認知症高齢者では、記憶が欠損、幻覚や徘徊など、冷静に自己判断できないため、避難誘導の援助も必要となる。すなわち、要介護

高齢者に対する新たなトリアージも必須となる。

②亜急性期（災害発生後 4 日～3 週間）

急性期を免れたにしても、持病としての脳心血管疾患・高血圧・糖尿病などの慢性疾患の悪化、ストレス性胃潰瘍、避難所肺炎を中心とした呼吸器感染症の蔓延、脱水を契機とした脳心血管疾患の発症などが起こりやすく、「震災後関連疾患」とも呼ばれる。高齢者は不慣れな避難所生活を急に余儀なくされ、心身ともに疲弊しやすい。特に血圧異常、発熱、精神症状などは、亜急性期の避難所において恒常的に認められ対応が必要である。ADL の低下した要介護高齢者の避難所生活の困窮や栄養管理の不安定さによる衰弱も大きな問題である。さらに精神的ストレスや生活環境の悪化が助長しやすく、これらによる死亡は「震災関連死」として位置づけられ、震災の死亡者の 1～2割は亜急性期以降に発生することが示されている。以上より、亜急性期における高齢者医療のポイントは、すでに罹患している慢性疾患に対する治療をいかに継続できるか、また、これら疾患の早期発見・早期治療を的確に行える医療体制をいかに迅速に構築するかが、震災関連死を最小限に抑えることにつながる。

③慢性期（災害発生後 4 週間～5 年）

精神面の管理（こころのケア）が非常に重要であり、高齢者の孤独死、孤独・虚無感を背景とした無気力や閉じこもり、潜在的な能力の喪失などが起こりやすい。実際、仮設住宅に入ると現実に戻りやすくなり、悲嘆・絶望に加え、罪責（自分だけが生き残ったこと、家族を救ってあげられなかったこと（すなわち、Survivor's guilt サバイバーズ・ギルト）などの心境に陥りやすく、気力喪失や自殺企図へ向かう場合も少なくない。また、周囲への意識が薄れ無刺激になってしまうことから、認知機能低下や廃用性（生活不活発病）の点も懸念される。精神面の管理をしながら、慎重に自立支援を行っていく必要がある。

【東日本大震災に対する日本老年医学会の対応と今後の課題】

日本老年医学会では震災直後に東日本大震災対策本部を立ち上げ、様々な分野に対して活動が行われた [1]。また、本研究班でも震災直後から打ち合わせを行い、日本老年医学会・震災対策本部との相談の下、下記の活動を行った。

◆『高齢者災害時医療ガイドライン』および『一般救護者向けマニュアル』を公表（図 1）

本ガイドライン（試作版）は震災発生直後に学会ホームページ上で公表し、同時に『一般救護者用・災害時高齢者医療マニュアル』（試作版）も同時に公表した [2,3]。さらに、この一般向けマニュアル（B5 版）の冊子体は、学会会員・代議員の関連施設からの医療支援班や各都道府県の日本医師会医療班（JMAT）による協力も得て約 2 万部が被災地に配布された [4]。

◆『高齢者健康相談』開催

2011 年 9 月 19 日（祝・敬老の日）に宮城県気仙沼市において高齢者健康相談を 6 か所同時開催した（図2）。開催場所は以下のとおりである。（①気仙沼公園住宅集会所、②五右衛門ヶ原運動場・仮設住宅集会所、③面瀬中学校住宅集会所、④大島開発総合センター、⑤気仙沼市保健福祉センター（燦さん館）、⑥小泉中学校校庭仮設住宅集会所）

主催である日本老年医学会に加え、日本老年精神医学会と日本老年歯科医学会が共催として、医師・歯科医師がチームを組んで「体・こころ・歯」の分野に対して健康相談を実施した。

◆ポケット版『高齢者震災カルテ』作成：～情報をつなぐ急性期医療および高齢者に対する防災心の啓発のために～

震災直後に飯島（分担研究者 兼 日本老年医学会震災対策本部）を含む 2 名の医師は、福島県・相馬市の避難所（旧相馬女子高校・廃校舎）にて医療支援を行った。後方医療支援として、被災地福島県から新潟県見附市へ被災高齢者を移送し医療支援を行った。

発災後急性期において、一避難所では具体的に巡回してきた医療班や巡回保健師などの診療行為や注意点がその避難所に記録として残されていないことが少なくない。今回の東日本大震災でもその問題の重要性を改めて認識した。被災地の実地医療が復旧するまでの急性期では、いわゆる「情報をつなぐ医療」が重要になる。そのためには、医師からコメディカル、そしてボランティアまでの多職種にわたる円滑な連携が鍵となる。そこで、本学会はポケット版健康手帳として『高齢者震災カルテ』を作成した（図3）。大災害時には普段のお薬手帳などを持って避難することはなかなか難しい。しかし、高齢者に対して自分自身の医療情報も含めた準備を普段から幅広く啓発し、しっかりとした「防災心」を教育しておく必要もある。

さらに加えて、発災後急性期に巡回医療班が老年症候群（嚥下状態、失禁の有無、筋力の程度、うつ傾向などの気分、転倒リスク、など）にも配慮した形で情報をつないでいく手帳である。避難所生活を通じてでも、いかに認知機能を落とさないようにするか、いかに生活不活発病（廃用性）にさせないか、ということを意識したトータル・サポートが必要であろう。平時から防災袋の中に入れておくよう啓発し、そして震災直後に被災高齢者に携帯させるよう普及に努めたい。

◆要介護高齢者に対する避難誘導システムの確立・啓発・普及

要介護・要支援高齢者の対応も大きな問題である。避難所、福祉避難所、特別養護老人ホームも含めた施設入所、訪問在宅医療、医療機関（大学・病院・診療所）、そして被災地外の後方支援などとの連携が今まで以上に必要とされる（図4）。今後、①要介護高齢者のリスト（在宅高齢者の所在情報の把握）、②どの高齢者をどの施設に円滑に運ぶかということも含めた支援計画の想定、③福祉避難所（二次避難所）のさらなる整備など、平時からの備え・支援体制づくりが必要である。長期的な円滑さを求めて、系列を超えた横の広域医療連携が必須である。

避難所での医療だけでなく、在宅高齢者もいかに守るかが重要である。実際、どうにか杖や歩行器で歩いていた高齢者などが家に閉じこもりになっている現実がある。また自宅でも脱水傾向に陥り、また寝たきりから褥瘡へと向かう。今回の東日本大震災のもう一つの特徴として、被災地の数多くの中核病院も同時に被災してしまったことである。その中でも、ある病院では被災したなか、「訪問診療

と訪問リハビリ」を重視した診療スタイルに移行し、多職種（医師・看護師に加え、理学療法士、作業療法士、言語聴覚士、事務職員など）が訪問チーム診療を行っている。慢性期には『地域に根付いた医療』こそが被災高齢者の管理だけでなく、その家族の安心にまでつながるため、改めて「災害時在宅医療」の原点に立ち返る必要があるであろう。

D. 考察

震災列島・日本における大規模災害被災者の大多数は高齢者であり、災害の急性期から亜急性期、さらには慢性期においても高齢者に様々な疾患や問題が多発し、災害関連死が頻発する。今回の分担研究においては、①高齢者医療に携わる日本老年医学会の震災対策本部の活動、そして②循環器疾患の対策の2つの方向で報告した。

まず、今回の東日本大震災では、東北沿岸地域における大津波による甚大な影響だけでなく、原発問題によっていつまでたっても復興に入れない状況にも置かれた事実も今回の大震災の大きな特徴を物語っている。広域な放射線汚染、被爆への恐怖から惹起されたであろう国内外からの被災地・福島を回避する心理が膨らませた経済的損失や精神的重圧は非常に大きい。今回は高齢化率の高い地域を中心として発災したこともあり、被災高齢者における介護予防の方策とともに、要介護高齢者への支援の在り方についても新たな問題が提起されてくる。

また、過去の大災害での疾患発症や死因を比較すると個々の特徴が見えてくる。阪神淡路大震災での家屋倒壊による圧迫死や今回の東日本大震災での大津波による水死などの直接死因だけでなく、特に脱水による急性心筋梗塞や脳卒中、精神的ストレスからのタコツボ型心筋症などの循環器疾患も数多く報告されている。先の見えない避難所生活の中で過度な心身ストレスが循環動態の不安定さを生み、様々な災害関連死を引き起こす。その背景には、医療機関の機能停止や常用薬の中断など様々な因子も関わる。すなわち高齢者は避難所に収容された後でも大きなリスクと背中合わせなのである。

今回の未曾有の大震災に対して、平成 22 年度から「高齢者災害時医療ガイドライン」を作成していた研究班の一員として、そして日本老年医学会の対策本部の一員として、今回の被災地で活動する中で様々なことが見えてきた。情報をつなぐ急性期医療の重要性と物足りなさ、避難所間の格差、仮設住宅に移ってから新たに生まれてくる問題、高齢者も含めた防災心をどう啓発できてきたのか、などなど。老年医学を志す者として、今後我々に何ができ、逆に何を求められているのか、そして避難生活を通じて被災高齢者の潜在的な能力の喪失をどう防止できるのか、など、恐らく数多くの課題を背負っている。

E. 結論

震災列島であるわが国において高齢者災害時医療に対しては大きな課題がまだ山積みである。医療関係者のみならず、行政や自治体も含めた幅広い広域連携を平時から想定・構築し、そして災害発生後には可及的速やかにそれを実行する必要がある。それらにより、被災高齢者を災害後関連疾患や災害関連死から守り、そして潜在的能力の喪失を予防することにつながる。そこに日本老年医学会を中心とした高齢者医療を担う医療関係者もネットワーク構築に一役担い、またその意義は大きい。

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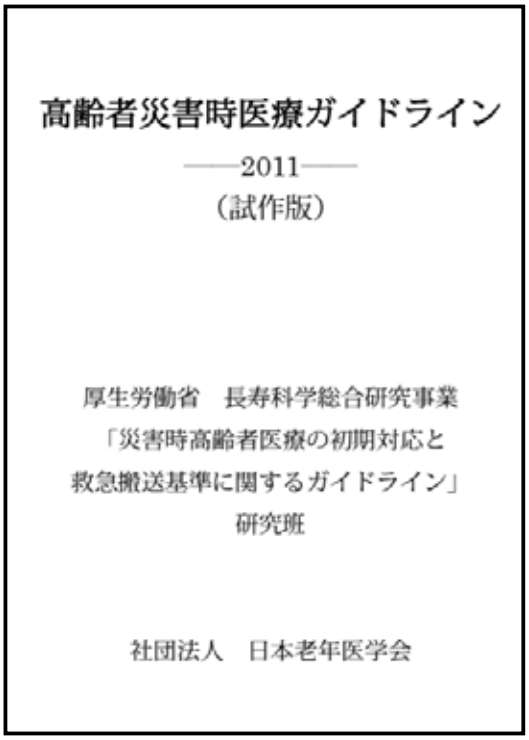
G. 知的財産権の出願・登録状況

なし

H.知的財産権の出願・登録状況 なし

図1.『高齢者災害時医療ガイドライン』および『一般救護者向けマニュアル』を公表

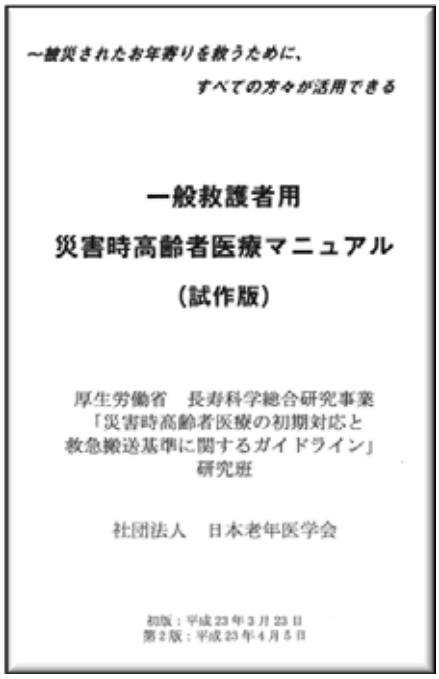

高齢者災害時医療ガイドライン

——2011——

（試作版）

厚生労働省　長寿科学総合研究事業
「災害時高齢者医療の初期対応と
救急搬送基準に関するガイドライン」
研究班

社団法人　日本老年医学会


～被災されたお年寄りを救うために、
すべての方々が活用できる

一般救護者用
災害時高齢者医療マニュアル
（試作版）

厚生労働省　長寿科学総合研究事業
「災害時高齢者医療の初期対応と
救急搬送基準に関するガイドライン」
研究班

社団法人　日本老年医学会

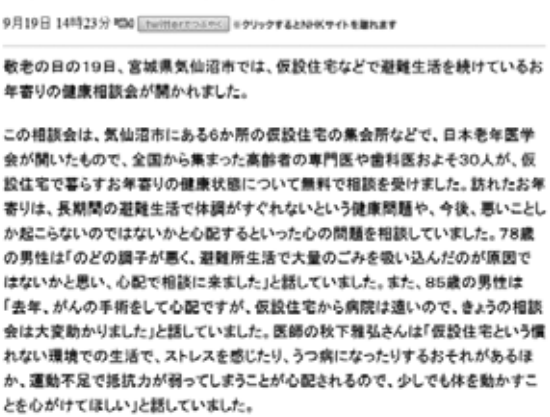
初版：平成23年3月23日
第2版：平成23年4月5日

図2. がんばろう、東北！　敬老の日『高齢者健康相談』開催


がんばろう、東北！
敬老の日
高齢者健康相談
対象：65歳以上の方々すべて（無料）
日時：9月19日（月・祝日）10時～15時
場所：気仙沼地区の集会場など全６か所

①気仙沼公園住宅集会所
②五右衛門ヶ原運動場
仮設住宅集会所
③面瀬中学校住宅集会所
④大島開発総合センター
⑤気仙沼市保健福祉センター
（愛さん館）
⑥小泉中学校校庭仮設住宅集会所

医師・歯科医師が対応いたします。
どなたでもお気軽にご相談下さい。
主催：　日本老年医学会
共催：　日本老年精神医学会、日本老年歯科医学会
後援：　気仙沼市


仮設住宅のお年寄り健康相談

9月19日 14時23分 配信 twitter mixi ※クリックすると2ch(R)サイトを離れます

敬老の日の19日、宮城県気仙沼市では、仮設住宅などで避難生活を続けているお年寄りの健康相談会が開かれました。

この相談会は、気仙沼市にある6か所の仮設住宅の集会所などで、日本老年医学会が開いたもので、全国から集まった高齢者の専門医や歯科医およそ30人が、仮設住宅で暮らすお年寄りの健康状態について無料で相談を受けました。訪れたお年寄りは、長期間の避難生活で体調がすぐれないという健康問題や、今後、悪いことしか起こらないのではないかと心配するといった心の問題を相談していました。78歳の男性は「のどの調子が悪く、避難所生活で大量のごみを吸い込んだのが原因ではないかと思い、心配で相談に来ました」と話していました。また、85歳の男性は「去年、がんの手術をして心配ですが、仮設住宅から病院は遠いので、きょうの相談会は大変助かりました」と話していました。医師の秋下雅弘さんは「仮設住宅という慣れない環境での生活で、ストレスを感じたり、うつ病になったりするおそれがあるほか、運動不足で抵抗力が弱ってしまうことが心配されるので、少しでも体を動かすことを心がけてほしい」と話していました。

図3.『ポケット版　高齢者震災カルテ』

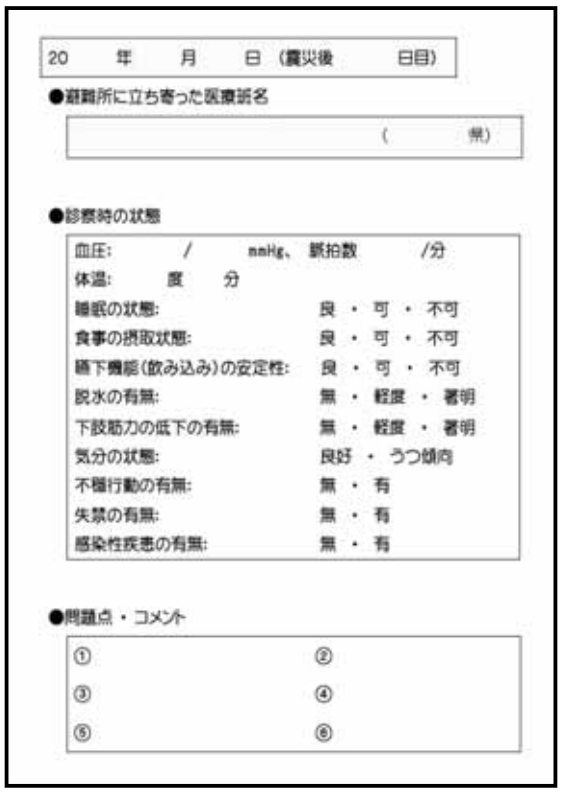
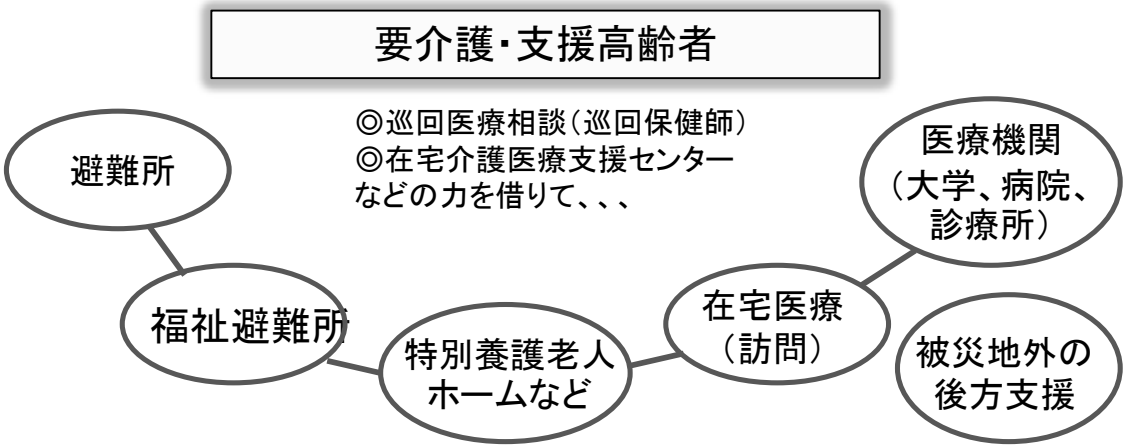


図4. 高齢者避難誘導システムの確立・啓発・普及： 幅広い『防災心』
長期的な円滑さを求めて、『系列を超えた横の広域連携』が必須

☛災害時にはどの高齢者がどの選択肢（施設）に円滑に
運ばれるのかを「あらかじめ事前に」想定しておく必要がある。



災害時高齢者医療の初期対応と救急搬送基準に関するガイドライン作成に関する研究
～ストレス誘発性高血圧への管理を中心とした災害時循環器疾患対策～

飯島　勝矢　　東京大学　高齢社会総合研究機構

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※本報告は平成22年度～23年度にわたる厚生労働科学研究費補助金(長寿科学総合研究事業)による班研究の中の分担研究報告書から引用改変を行った。

研究要旨:

激甚災害は瞬間的に極度のストレス環境におかれ、様々な循環器疾患が誘発されやすく、震災関連死に直結し得る。なかでも高血圧管理は大きな比重を占め、発災後急性期には内服薬の中断、避難所生活という急激な環境の変化による脱水や慨日生態リズムの乱れ、肉体的・精神的ストレスによる交感神経の賦活化、血液凝固能の亢進など、様々な要因が重複する。また、これら急性期の変化だけでなく、慢性期における血圧管理も軽視できない。災害弱者と言われる高齢者は普段から数多くの疾患やリスクを抱えているからこそ、発災後急性期に的確な判断が必要とされる。

実際、過去の大震災を見ても、震災による直接死ではない「震災関連死」も決して少なくないことが分かる。例えば阪神淡路大震災を例にとっても、家屋の倒壊や火災による死亡以外に 900 人以上が避難生活中に死亡している(死者全体の約14%、死者の多くは高齢者であり 60 歳以上が 9 割を占めた)。その死因として、肺炎も含めた感染症だけでなく、持病の悪化による心不全や心筋梗塞などによるものも少なくない。また、新潟県中越地震に多く見られたタコツボ型心筋症やエコノミークラス症候群(深部静脈血栓症)にも代表されるように、過剰な精神的ストレスや脱水・低活動などの状況が疾患発症に大きく関わってしまう。

今回、改めて東日本大震災によって引き起こされた高齢者における循環器系への変化を見直してみると、高齢者災害時医療における急性期から慢性期にかけての阻害要因や問題点が色々と見えてくる。その問題を明確にし、それに対する対策を講じていくことが急務となっている。大震災発災後、約 1 年近くが経過しようとしている今、様々な工夫を凝らして循環器管理を幅広く円滑に進めて行かなければならない。加えて、多職種による系列を超えた広域医療連携による迅速な対応も要求される。また、復旧する過程で医療だけではなく、社会的支援や見守りも含めた精神面への長期的サポートも欠くことはできない。現在、我々は「見守り」の意味合いを兼ねて、血圧遠隔管理を推し進めている。

また、個々人における降圧薬も含めた循環器系作動薬のストックや平時からの情報の備え(お薬手帳など)を心掛けておくべきである。そのためには、自治体レベルで普段からどのように震災対応のイメージを想定・共有し、そして高齢者に目線を合わせた防災心への啓発・教育が重要になってくる。

A. 研究目的

大災害では発災時に多くの生命を奪うだけではなく、その過度なストレスが生物学的にも大きな影響をおよぼし、様々な循環器疾患や感染症、消化器疾患などをひき起こす。その中でも被災高齢者に対する医療対応の中で非常に重要なものに循環器管理がある。今回の未曾有の大震災・東日本大震災(マグニチュード9.0)は言い換えれば「大津波」震災において、急性期における「災害時高齢者医療における円滑な医療初動の中における循環器管理のあるべき姿」を考え直す必要がある。

高齢者は突然起こる災害により劣悪な環境にさらされることから、血圧も含めた循環動態の管理が難しくなる。実際、震災の場合では家屋倒壊による圧迫を介した直接の死因だけでなく、極度の脱水や血圧上昇が大きく関与する循環器疾患の発症および増悪により、病状の悪化、ひいては震災関連死にまで直結するリスクと背中合わせになっている。

今回の東日本大震災における現在の取組に関しても触れながら、改めて本研究を通して、特に災害時急性期における高齢者の循環器疾患管理にどう配慮すべきかを検討する。

B&C. 研究方法および結果

1.　高血圧

◎特徴

・普段から高齢者高血圧の特徴をよく理解しておくことが必要である。

・極度の精神的ストレスも加わるため、正常血圧であった高齢者の一過性血圧上昇が起こりやすい。

・急性ストレス障害や心的外傷後ストレス障害(Post Traumatic Stress Disorder:PTSD)により、通常は管理できていた降圧薬であても血圧管理が不良になってしまうことが推測される。

・震災から2週間以上が経過した後も3～4割の医療機関で診療ができなかったという報告があり、特に降圧薬による血圧管理の中断は非常に大きな問題である。よって、備えとして2週間分のストックを常備しておくことを高齢住民に周知するよう努力する。

【災害時の血圧上昇の機序および急性冠症候群への流れ】

災害時は極度の精神的ストレスも加わるため、従来の高血圧患者の管理がより増悪したり、正常血圧であった高齢者の一過性血圧上昇が起こりやすい。一般的には、極度の精神的ストレス下に置かれるため、交感神経活性の賦活化が生じる。過剰なカテコラミン分泌

はβ1 アドレナリン受容体を刺激し、心拍数や心拍出量を増加させ、さらに血管収縮にも大きく基づき最終的に血圧上昇を惹起する。

発災後急性期には、以下のような様々な現象が惹起されやすく、急性冠症候群が起こりやすい。[1)]

①急性のストレスが交感神経活性を亢進させ、頻脈や血管収縮に基づく血圧上昇を惹起する。同時に、血管壁にかかるストレスも上昇し、不安定プラークの破綻が引き起こされやすい。

②交感神経活性による凝固能の亢進と血小板の活性化により、血栓形成亢進が誘導される。[2)]この機序には、D-dimmer や von Willebrand 因子(vWF)、Tissue Plasminogen Activator (tPA)抗原などの上昇が大きく関わる。実際、ロサンゼルス Northridge 地震では不安定プラークを有する症例が一斉に急性心筋梗塞を発症してしまったため、その結果、ハイリスク症例数が相対的に減少し、地震１ヶ月後からはむしろ急性心筋梗塞の発症が減少した。[3)]

③避難生活においては脱水状態に傾きやすく、血栓形成亢進がより惹起されやい。[4)]

④災害の突然発生により、生体の概日(日内)リズムが撹乱されやすい。

⑤循環器系の慢性疾患に対する通院継続および治療薬の中断にて再発しやすい。

【災害時の血圧管理における精神的影響】

災害時における高齢者高血圧管理をより難しくさせる様々な因子(ストレッサー)を示す(図2)。

＜薬剤の中断＞
・薬剤の紛失
・診療所や医療機関への通院継続の中断(日常生活の破綻)
・医療機関自体の被災
＜身体的要因＞
①厳しい環境(猛暑や寒さ)への暴露
②ライフラインの途絶や肉体的負担の増加
③不眠、疲労
＜心理的要因＞
恐怖、不安、悲しみ、悲嘆・絶望・喪失、怒り、罪責などの不安定な感情が惹起される
①地震の揺れや音、火災などの体感と、その後の断続的に続く余震への恐怖・不安
②悲嘆や絶望(家族の死亡、家屋倒壊、財産の喪失、など)
③目撃による精神的ストレス(死体、火災、家屋の倒壊、人々の混乱、など)
④罪責(自分だけが生き残ったこと、適切に振る舞えなかったこと、などへの反省:いわゆるサバイバーズ・ギルト)
⑤周囲に対する怒り(援助の遅れ、情報の混乱、など)
⑥過失による災害の場合の過失責任機関・責任者に対する怒り
⑦慣れない避難所生活(新しい居住環境や集団生活などへのストレス)
ライフラインの停止・復旧への遅れに対する苛立ち
⑧慢性疾病の増悪や新たな疾病・障害の出現に対する悩み

※ちなみに、水分摂取不足による血管内脱水も血圧管理を難しくさせる。(断水およびプライバシーがない避難所において、トイレを我慢してしまうケースが多い)

※また、東日本大震災の被災地とは関係のない遠方の地域に暮らす高血圧患者でさえも、度重なる余震や計画停電、さらには悲惨な状況を伝える報道などにより、心身両面にわたる影響を受けて血圧管理が不良になった事実も伝えられていることも忘れてはならない。

【治療】

高血圧管理への初期対応における一番重要なポイントは、①緊急性の高い降圧(例えば 180mmHg 以上)の場合の対応、②緊急的な降圧は不要であるが、中断した降圧管理をいかに再開させるか、さらには降圧治療を再開する必要のある高齢者の選別、などが重要であろう。災害後に血圧上昇をみせた場合、多くは一過性であり、大半は 4～5 週間程度で安定する。[5)] また、高齢者は個体差が大きく、慢性疾患の有無でも方針が変わるため、特に個別治療が重要になってくる。

降圧治療のフローチャートを図2に示す。[6)] まずは収縮期血圧 150 mmHg 以下を目安にして、最終的には通常通り収縮期血圧 140 mmHg を目指す。しかし、緊急度、脱水や栄養状態、今までの治療歴など、幅広く全体の情報を把握した上で投薬を開始するかどうか判断する。特に、被災前に降圧治療を受けていた高齢者でも、収縮期血圧 140 mmHg 以下ならば軽々に降圧薬の継続を行わずに、血圧測定を繰り返した上で治療再開の必要性をよく考慮する。そのためにも、自動血圧測定をうまく用いて遠隔管理を行い、現地の医療機関との連携のもと血圧管理不良の被災高齢者をより早く管理するネットワークの構築も今後必要であろう。

◎〈薬物治療〉

緊急性がない限り、①災害前にもともと服用していた降圧薬を可能な限り継続するよう配慮する、②同じ降圧薬を継続できない場合は、速やかに同系統の降圧薬で対応する、この 2 点について配慮する。しかしながら、白衣効果も誘導されやすく、また後期高齢者などでは血圧の短期降圧による相対的臓器虚血を避けるため、降圧薬使用開始の必要性を十分検討する。また、長期的に漫然と投与が継続されることも避けなければならない。そのためにも、少なくとも複数回の血圧測定値で判断し、長期的に継続する。[7)]

高齢者高血圧に対する第一選択薬とされているのは、長時間型カルシウム拮抗薬、アンジオテンシン II 受容体拮抗薬(ARB)/ACE 阻害薬などのレニン・アンジオテンシン系(RA 系)抑制薬、少量の降圧利尿薬である。高血圧性臓器障害や冠動脈狭窄を伴う狭心症の有無などにより降圧薬の選択は変わるが、被災直後の緊急時における降圧したい場合、もしくは従来の降圧薬の内容が不明な場合に関しては、少量のカルシウム拮抗薬(もしくは腎機能に配慮しながら ARB)を用いる。必ず連日にわたり血圧チェックを行う。

また、避難生活において水分摂取が不十分なことによる血管内脱水の高齢者が少なくないため、安易には降圧利尿薬は使用しない。また、飲料水不足や嚥下機能低下などにも考慮し、口腔内崩壊錠も選択肢に入れる。

精神的ストレスにより惹起される高血圧には交感神経遮断薬が有用な場合がある。阪神淡路大震災の時にβ遮断薬を投与されてい

た症例は、非投与症例に比べて平均血圧が有意に抑えられていた。[8] しかし、特に高齢者は交感神経遮断薬により精神症状が悪化してしまう場合もあるため、投与には注意が必要である。実際に降圧目的で使用されたβ遮断薬(メトプロロール)が PTSD 症例のフラッシュバックを惹起したとの報告もある。[9]

◎〈非薬物治療〉
①急激な生活の変化へいかに順応させるか:～いわゆる話を聞いてあげる医療～
災害時のような極限状況を体験した犠牲者にみられるストレス刺激による精神障害により、血圧管理が非常に難しくなる。緊急性を冷静に判断し、短絡的に降圧薬を用いるのではなく、いかに早く順応させ精神的ストレスによる一過性血圧上昇を管理できるよう、精神的緊張を緩和するための対策を積極的に考慮する。そこには、場合により薬物治療および非薬物治療を検討する。また、慣れない避難所生活とはいえ、睡眠を十分取れるような環境作りを心掛ける。
②避難生活における生活習慣の修正
高齢者高血圧は食塩感受性高血圧を示すことが多い。特に非難生活に入ると、今までの食生活が大きく変わり塩分摂取が増加するリスクがあるため、減塩(食塩制限6g/日未満)に心掛ける必要がある。また、心血管病のない高血圧患者には、過度の安静などを予防する意味で、適度な有酸素運動を定期的に行うよう促す。禁煙も徹底させる。

【今後の対策】
①震災から2週間以上が経過した後も3～4割の医療機関で診療ができなかったという報告があり、特に降圧薬による血圧管理の中断は非常に大きな問題である。よって、備えとして2週間分のストックを常備しておくことを高齢住民に周知するよう努力する。
②お薬手帳など常用薬剤の情報を手元に残しておくよう普段から啓発する。
③それらの情報が不明の場合は、短絡的に降圧薬を選択しない。

2. 心血管疾患(虚血性心疾患)

突然の激しい精神的・身体的ストレスや脱水・疲労・環境衛生の不良などが急性冠症候群(Acute Coronary Syndrome: ACS)も含めた心血管疾患を誘発発症機序きっかけ(トリガー)となりやすい。

◎虚血性心疾患の予防と避難所における留意点

①普段の生活よりもストレスが増大するため、禁煙を徹底
②十分な水分摂取
③塩分・糖分・脂肪分を取り過ぎない・バランスのよい食事
④非難場所での適度な運動
⑤動脈硬化関連危険因子(高血圧・糖尿病・脂質異常症など)の基礎疾患や持病の有無を早期チェックおよび薬剤中断の回避
⑥心疾患へのリスクを早期から周知
⑦強い胸痛を感じたら、すぐ医療機関への搬送を
②些細な契機で発症しやすいことを念頭に入れる
③リスク患者は早期から心電図確認を
④非難生活に入る高齢者が、持病として心疾患の指摘をされているかどうか
⑤狭心発作が疑われた場合
⑥治療開始の早さが経過を左右する
⑦急心筋梗塞死亡例の半数以上が「発症から1時間以内に集中している」ことを熟知
⑧高齢被災者に認知機能低下が認められる場合
⑨早急かつ優先的に援助が必要なケース
⑩在宅酸素療法を行っている被災者の場合

◎避難所における重要ポイントと初期対処法

①いかに微細な変化でも疑ってかかる

◎事前対策

①常時の内服薬が中断されないよう多少の余裕を
②普段から心肺蘇生法のトレーニング
③薬の備えについても、かかりつけ医などに相談
④個々の高齢者の医療情報をあらかじめ

3. 脳卒中

避難所では脱水傾向に傾きやすく、また精神的ストレスを背景に血圧上昇、血栓形成亢進などにもなりやすく、高頻度の脳血管障害を引き起こしやすい環境である。

◎災害地でできる診察・検査、災害地でできる治療

・基本的に福祉避難所での対応では不十分であり、高度医療機関への搬送が必要
(・・・救急科・神経内科・放射線科・脳神経外科の連携の良い救急病院への搬送)
・意識レベルの確認、麻痺も含めた上記の症状の確認
・酸素投与
・持続性高血圧や早朝高血圧も脳卒中発症の大きなリスクであるため、降圧薬を服用している高齢者だけでなく、高齢被災者はこまめに血圧測定を行う。

◎意識のない脳卒中患者の応急処置
・・・(トリアージ赤色:緊急治療を要する)

1)適切な場所への移動
・敷物などに乗せ、処置や運び出しがしやすい場所に移す
・原則的には医療機関へ搬送する
・頭をできるだけ動かさない(とくに前に曲げない)
2)気道確保と誤飲の防止
・頭の前屈は禁止 →あえて枕を使用しない
・いびきや呼吸が苦しそうな時 →起動確保が必要
(巻いたバスタオル、座布団などを肩の下に敷き、首を軽く反らせる)
・嘔吐しそうな時 →誤飲や窒息を防ぐため、体ごと横向きに寝かせる(麻痺がある時は、麻痺側を上に向ける)

◎事前対策

・持病に気を配る(高血圧、糖尿病、脂質異常症、心臓病・特に慢性

心房細動)
・日常の注意点:
水分の十分な摂取、血圧のこまめなチェック、塩分制限、普段からの常用薬剤の継続、適度な運動(散歩でも可)、便秘に注意、温度差に注意、禁煙
・個人の医療情報のメモを身に付ける
(通院中の医療機関名、電話番号、診療科と主治医名、常用薬剤名、自宅など緊急連絡先と電話番号など)

D&E. 考察および結論

大災害発災後の急性期には、高齢者や心血管リスクを持ち合わせたハイリスク症例を中心に、様々な生物学的変化が誘発され、最終的に心血管イベント発症につながりやすい。そのイベント発症は特に夜間から早朝にかけて著しく、数カ月以上そのリスクは継続する。この機序として、①震災による恐怖、②環境変化に伴う極度の精神心理ストレス、③睡眠障害、など様々な因子が複合的に影響し合う。これらのストレスは交感神経系亢進や視床下部－副腎皮質系の活性化、サイトカインの増加などを介して、血圧昇圧、血液凝固亢進、炎症反応などが惹起される。

また、復旧する過程で医療だけではなく、社会的支援や見守りも含めた精神面への長期的サポートも欠くことはできない。現在、我々は「見守り」の意味合いを兼ねて、血圧遠隔管理を推し進めている(図3)。①血圧のきめ細やかな管理が達成できる、②「マンスリー・レポート」をご本人へフィードバックすることにより、自分のデータの実感と継続性を持たせることができる、③閉じこもり予防として、「コミュニケーション・ツール」にも活用できる、③遠隔管理しながら、「ご本人への教育・啓発」も可能となる、などの利点がある。実例(マンスリ・レポート)を図4に挙げる。参加者ごとに血圧の管理具合だけでなく、血圧のデータ送信にも差異が認められ、安否確認に加え、送信の状況を把握することを介して見守りにもつながる。

心血管イベント予防のためには、発災時の迅速な救急対応に加えて、ストレスの早期軽減を計ることも最重要課題として掲げ、系列を超えた行政および現場の医療関係者による対応が必要であろう。また、被災高齢者に対応するすべての職種が、前述の特徴を理解した上でのリスク管理が求められる。

E. 結論

震災列島であるわが国において高齢者災害時医療に災害時には，発生直後から心血管イベントが発生し，その増加は数カ月継続する．災害発生時には的確な緊急時の救急対応に加えて，心血管イベントのリスクが増加していることを念頭におき，その後のストレスを最小限にとどめ，心血管リスクを可能な限り早く適切に管理することが重要である．

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G. 知的財産権の出願・登録状況

なし

H.知的財産権の出願・登録状況

なし

図1. 様々な要因により引き起こされる災害後関連疾患および災害関連死

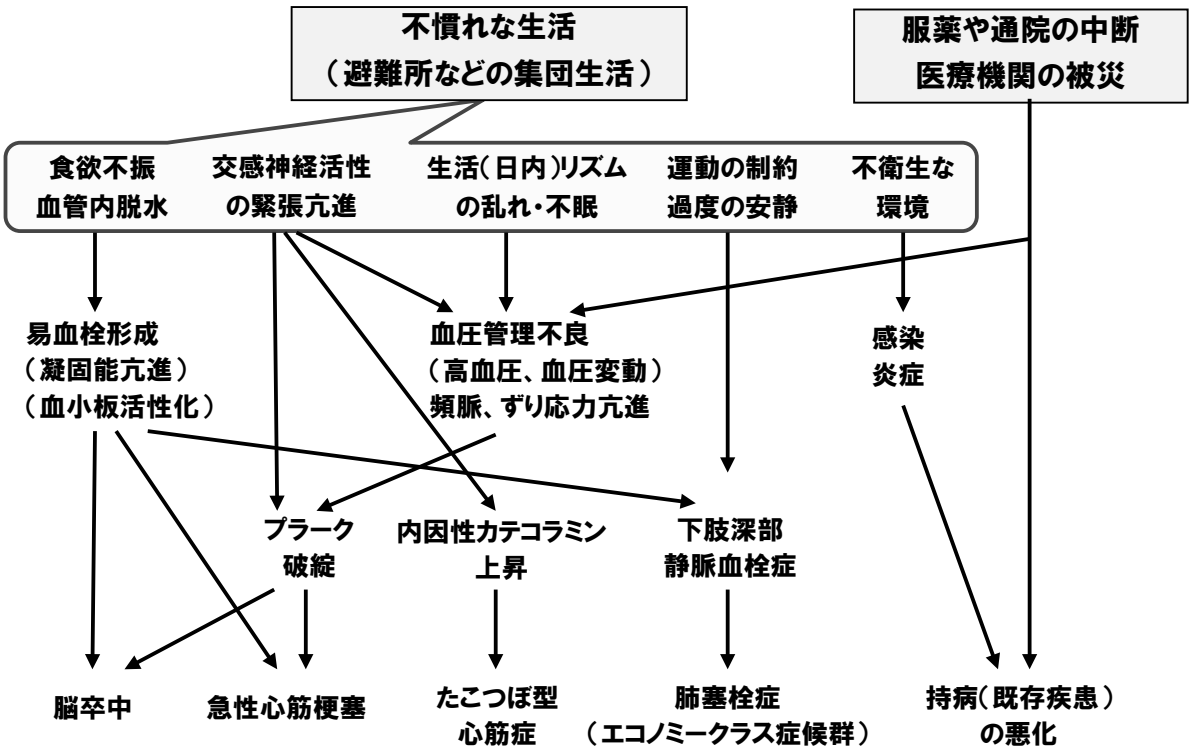


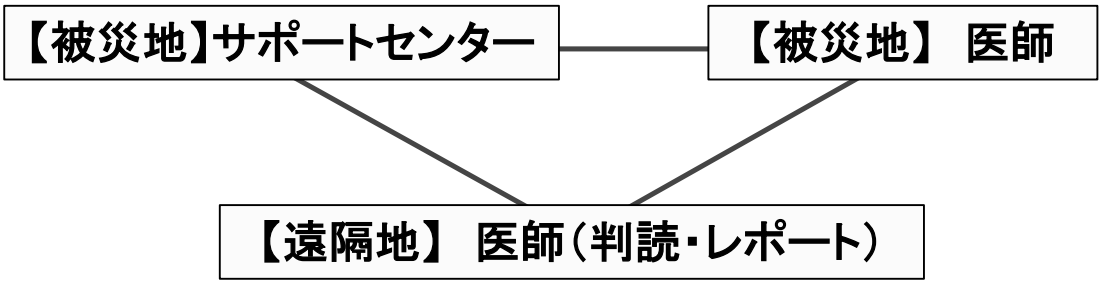
図2. 災害時における高齢者高血圧管理をより難しくさせる因子

●薬剤の紛失による中断
●診療所や医療機関への通院継続の中断・医療機関の被災
（特に今回は300以上の医療機関が休止・中止・廃業）

●身体的要因
①厳しい環境（猛暑や寒さ）への暴露
②身体活動の増加 ・・・過剰労働
③不眠、疲労
④脱水

●心理的要因
①恐怖 ・・・断続的に続く余震への恐怖
②悲しみ ・・・家族の死亡
③絶望 ・・・家屋倒壊、財産の喪失
④不安 ・・・慣れない避難所生活、慢性疾病の増悪など
将来への不安（失業、家計のひっ迫）

図3．被災地の仮設住宅と遠隔地との見守り機能を兼ねた血圧遠隔管理



①血圧のきめ細やかな管理
②「マンスリー・レポート」をご本人へフィードバック
　☛自分のデータの実感と継続性
③閉じこもり⇒「コミュニケーション・ツール」にも活用
③遠隔管理しながら、「ご本人への教育・啓発」も
④いずれ「へき地医療への応用」にも発展
⑤「点」の活動から「線」の活動へ

図4．実際の血圧遠隔管理におけるマンスリーレポート（実例）


管理レポート

ご利用者名	参加者A	サービス利用期間	2011年11月22日から 年 月 日
名称	血圧プロジェクト	担当者名	東京大学病院

血圧・脈拍 推移グラフ 2011年12月23日 より過去1ヶ月 を表示

コメント欄

12月の結果をお知らせします。
毎日きっちりと血圧が測定・送信されており、大変すばらしい健康習慣を続けておられます。

・12月11日まではかなり高めの血圧が続き管理不良でしたが、それ以降は上の血圧値が140～150mmHgで推移しており緊急性はありません。現在、複数の降圧薬を服用されておりますが、現在の治療をすぐ変更する必要はないと思われます。次回、かかりつけの医師先生に受診する際には、このレポートを必ずお見せして相談してみて下さい。
・もし可能でしたら、早朝と就寝前にも測定してみることをお勧めします。
・食事に関して塩分を多く摂りすぎないように心掛けて下さい。減塩でもかなりの効果が期待できます。
・また、お薬を服用し忘れのないよう気をつけて下さい。

【ワンポイント・アドバイス】
薬と生活習慣の改善（減塩、適度な運動、十分な睡眠、など）の両方を組み合わせると、血圧管理にはより効果的です。


管理レポート

ご利用者名	参加者B	サービス利用期間	2011年11月22日から 年 月 日
名称	血圧プロジェクト	担当者名	東京大学病院

血圧・脈拍 推移グラフ 2011年12月24日 より過去1ヶ月 を表示

コメント欄

12月の結果をお知らせします。
測定開始からまだ1か月余ですが、血圧が測定されていない日が見られるようです。今後も定期的に測定および送信を心掛けて下さい。

・添付の血圧推移値の通りに、上の血圧が平均161mmHgと高値であり、特に160mmHg以上の日が多いです。全体的に血圧の管理はあまり良くありません。
・早朝血圧が160mmHg以上と高値の時があります。今後も早朝と就寝前での測定をお勧めします。
・降圧薬の情報が現時点では不明ですので、ご確認をお願い致します。

【ワンポイント・アドバイス】
・薬と生活習慣の改善（減塩、適度な運動、十分な睡眠、など）の両方を組み合わせると、血圧管理にはより効果的です。まずは食事に関して塩分を多く摂りすぎないように心掛けて下さい。減塩でもかなりの効果が期待できます。
・かかりつけの先生がいらっしゃいましたら、受診する際にはこのレポートを必ずお見せしてご相談下さい。

Geriatrics Gerontology International 1st Impact Factor in June 2010 Medline Indexed

Geriatr Gerontol Int 2012; **12 (Suppl. 1):** *7–17*

ORIGINAL ARTICLE

Long-term multiple risk factor interventions in Japanese elderly diabetic patients: The Japanese Elderly Diabetes Intervention Trial – study design, baseline characteristics and effects of intervention

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Aim: To evaluate long-term, multiple risk factor intervention on physical, psychological and mental prognosis, and development of complications and cardiovascular disease in elderly type 2 diabetes patients.

Methods: Our randomized, controlled, multicenter, prospective intervention trial included 1173 elderly type 2 diabetes patients who were enrolled from 39 Japanese institutions and randomized to an intensive or conservative treatment group. Glycemic control, dyslipidemia, hypertension, obesity, diabetic complications and atherosclerotic disease were measured annually. Instrumental activity of daily living, cognitive impairment, depressive symptoms and diabetes burden were assessed at baseline and 3 years.

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Results: There was no significant difference in clinical or cognitive parameters at baseline between the two groups. The prevalence of low activities of daily living, depressive symptoms and cognitive impairment was 13%, 28% and 4%, respectively, and was similar in the two groups. A small, but significant difference in HbA1c between the two groups was observed at 1 year after the start of intervention (7.9% *vs* 8.1%, $P < 0.05$), although this significant difference was not observed after the second year. With the exception of coronary revascularization, there was no significant difference in fatal or non-fatal events between the two groups. Composite events were also similar in the two groups.

Conclusions: This study showed no significant differences in fatal or non-fatal events between intensive and conventional treatment. The present study might clarify whether treatment of risk factors influences function and quality of life in elderly diabetic patients. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 7–17.**

Keywords: diabetes mellitus, elderly, geriatric assessment, intervention, vascular complications.

Introduction

The prevalence of diabetes increases with age, with approximately 15% of elderly people in Japan having the disorder.[1] These patients often suffer from diabetic microvascular and macrovascular complications.[2] Treatment goals in this elderly diabetic population are to maintain functional abilities and quality of life, and to prevent diabetic complications. Physical functional activities[3,4] and cognitive function[5,6] are more impaired in elderly diabetic patients, with depression and low well-being being major concerns.[7,8] It is therefore important to evaluate the effects of clinical interventions on physical, psychological and mental functions, as well as on disease-related variables, such as diabetic complications, atherosclerotic disease and mortality.

The impact of intensive blood glucose, blood pressure or multiple risk factor intervention on diabetic complications in type 2 diabetes has been evaluated in the United Kingdom Prospective Diabetes Study (UKPDS),[9,10] Kumamoto Study[11] and Steno-2 Study.[12] As only a few elderly people were included in these studies, little is known on the effects of multiple risk factor intervention on diabetic complications and functional prognosis.

We therefore carried out a randomized clinical trial to evaluate the efficacy of multiple risk factor intervention on functional prognosis, and development and/or progression of diabetic complications and cardiovascular disease in elderly people with type 2 diabetes. The present study presents baseline demographic and biomedical characteristics, and describes the major outcome variables measured at baseline.

Methods

Participants

The participants recruited for the Japan Elderly Diabetes Intervention Trial (J-EDIT) were diabetic outpatients at 39 representative hospitals in Japan between March 2001 and February 2002. Written informed consent was obtained from all participants before screening, consistent with the Helsinki Declaration and the guidelines of each center's institutional ethical committee.

Initial screening tests included glycated hemoglobin A1c (HbA1c), body mass index (BMI), blood pressure, serum total cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL-C). Inclusion criteria included age 65–85 years, HbA1c ≥ 7.9% or HbA1c ≥ 7.4% with at least one of following criteria: BMI ≥ 25 kg/m^2, blood pressure ≥ 130/85 mmHg, serum total cholesterol ≥ 200 mg/dL (or low-density lipoprotein cholesterol [LDL-C] ≥ 120 mg/dL in participants without coronary heart disease [CHD]) or ≥180 mg/dL (or LDL-C ≥100 mg/dL in participants with CHD), triglycerides ≥ 150 mg/dL and HDL-C < 40 mg/dL. Exclusion criteria included a recent (<6 months) myocardial infarction (MI) or stroke, acute or serious illness, aphasia and severe dementia.

Randomization and intervention

A total of 1173 diabetic outpatients were enrolled and randomly allocated to either the intensive or conventional treatment group. The randomized factors were age, sex, diabetes treatment, HbA1c, total cholesterol, triglycerides, HDL-C, blood pressure, diabetic

Table 1 Treatment goals of multiple risk factor intervention studies in patients with type 2 diabetes

	J-EDIT	UKPDS	Steno-2 Study
Mean age (years)	72	52	55
Range	(65–84)	(25–65)	(40–65)
Treatment goals			
Glucose control			
FPG (mmol/L)		<6.0	
HbA1c (%)	<6.9		<6.5
Blood pressure control (mmHg)	<130/85	<150/85	<140/85 (1993–1999) <130/80 (2000–2001)
Cholesterol (mg/dL)	<200 (<180) if one has CHD	none	<190 (1993–1999) <175 (2000–2001)
Triglycerides (mg/dL)	<150	none	<150
HDL-C (mg/dL)	>40	none	>40
Other interventions	BMI <25		Smoking cession Aspirin use

CHD, coronary heart disease; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol, J-EDIT, Japan Elderly Diabetes Intervention Trial; UKPDS, United Kingdom Prospective Diabetes Study.

microangiopathy, atherosclerotic disease, hypertension, hyperlipidemia and institutions.

The treatment goal in the intensive treatment group was HbA1c < 6.9%, BMI < 25 kg/m^2, systolic blood pressure (SBP) < 130 mmHg, diastolic blood pressure (DBP) < 85 mmHg, HDL-C > 40 mg/dL, serum triglycerides < 150 mg/dL and serum total cholesterol < 180 mg/dL (or LDL-C < 100 mg/dL if patients had CHD) or <200 mg/dL (or LDL-C < 120 mg/dL if patients did not have CHD; Table 1). If HbA1c levels did not reduce to <6.9%, oral hypoglycemic drugs (sulphonylurea, biguanides, α-glucosidase inhibitors and pioglitazone) or insulin therapy was introduced by the physician. If total cholesterol or LDL-C levels did not reach the treatment goal, the physicians were advised to use atorvastatin. Patients with a history of cerebral infarction also had antiplatelet therapy where possible.

The conventional treatment group continued their baseline treatment for diabetes, hypertension or dyslipidemia without a specific treatment goal.

Each participant had a standardized medical history and physical examination at baseline, and then annually. Baseline information included age, sex, medical history, family members with whom they lived, education, employment, height, bodyweight, waist-to-hip ratio, maximum body weight, diabetes duration, family history of diabetes and diabetes treatment. Standardized questionnaires were used to obtain self-reported data on smoking, alcohol, hypoglycemia frequency, nutritional status, dietary habits and adherence, self-efficacy, activities of daily living (ADL), physical activities, comprehensive cognitive function, and psychological status including diabetes burden and depressive symptoms.

Basic ADL was assessed by the Barthel index,[13] whereas functional disabilities were examined by the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence.[14] This index includes 13 items and three subscales: instrumental ADL, intellectual activity and social role. The index is well validated and is widely used to measure functional abilities in community-dwelling or institutionalized elderly subjects.[15]

Physical activities were assessed using the Baecke questionnaire.[16] The Folstein Mini-Mental State Examination (MMSE) was carried out to assess comprehensive cognitive function including orientation, memory recall and calculations.[17]

Depressive symptoms were evaluated using a short form of the Geriatric Depression Scale (15 items, GDS-15),[18] whereas diabetes-specific burden and concerns were examined using the elderly diabetes burden scale (EDBS).[19] EDBS is a short revised version of the elderly diabetes impact scale reported previously,[4] and consists of six subscales: symptom burden (4 items), social burden (5 items), diet restrictions (4 items), concern (4 items), treatment satisfaction (3 items) and burden by tablets or insulin (3 items). Each of the 23 EDBS items was rated on a four-point multiple-choice scale. The elderly diabetes burden score was calculated by reversing the scores of the treatment satisfaction subscale and summing the scores of the six subscales. EDBS has good test–retest reliability, construct validity, convergent validity and satisfactory internal consistency.

The frequency of mild or severe hypoglycemia was assessed using questionnaires (number of hypoglycemic episodes and number of comas or emergency hospital visits or admissions as a result of hypoglycemia in a year, month or week). Mild hypoglycemia episodes included the appearance of or recovery from hypoglycemic symptoms. Severe hypoglycemia episodes were defined as

coma, convulsion or incapacity of the patient sufficient to require the assistance of another person.

Nutritional intake was assessed for 1 week using the Yoshimura food frequency questionnaire[20] that estimated food and total energy intake, carbohydrate-, protein- and fat-to-energy ratios, and intake of cholesterol, salt, iron, calcium, vitamins and dietary fiber from portion sizes (relative to the standard amount) and frequency (intake number for 1 week) of 29 food groups.

Measurements

Venous blood was drawn for determination of blood glucose, HbA1c and serum concentrations of total cholesterol, HDL-C and triglycerides at baseline, and then at least twice a year. Plasma glucose was measured by the glucokinase method, and HbA1c by ion-exchange high-performance liquid chromatography. The Japan Diabetes Society (JDS) has standardized several HbA1c assays with the international standard value adjusted by the equation of HbA1c (JDS) (%) plus 0.4%. Serum insulin was measured by an enzyme immunoassay, and total cholesterol, triglycerides, HDL-C, white blood cells, red blood cells, hematocrit (Ht), blood urea nitrogen (BUN), serum creatinine, uric acid, total protein and albumin by established methods.

Blood pressure was measured with a mercury sphygmomanometer using a cuff of appropriate size. Diastolic blood pressure was determined as Korotkoff phase V. Body mass index was calculated as weight in kilograms / (height in meters)^2.

Microangiopathy (retinopathy, nephropathy and neuropathy), macroangiopathy (ischemic heart disease [IHD]), stroke and peripheral vascular disease [PVD]) were assessed at baseline, and then annually. Funduscopic examinations were carried out on dilated pupils by experienced ophthalmologists using direct ophthalmoscopy. Retinopathy status was assessed by the Japanese Diabetes Complication Study method and classified into five stages: stage 0: no retinopathy; stage 1: dot hemorrhages, hemorrhages or hard exudates; stage 2: soft exudates; stage 3: IRMA or venous deformities; stage 4: neovascularization, preretinal proliferative tissues, vitreous hemorrhages or retinal detachment. Diabetic maculopathy was assessed according to findings of hemorrhages, local edema, hard exudates and diffuse edema at macular areas. Uncorrected and corrected visual acuities, the occurrence of cataract, corneal opacity, glaucoma, age-related macular degeneration, laser photocoagulation, cataract operations and vitrectomy were assessed. Urinary albumin was measured by immunological assay. Mean urinary albumin-to-creatinine ratio (ACR; μg/mg creatinine) in two or three successive urinalyses was used to classify diabetic nephropathy as no nephropathy (ACR < 30), microalbuminuria (30 ≤ ACR < 300) or persistent proteinuria (ACR ≥ 300 or urinary protein ≥30 mg/dL). Diabetic neuropathy was defined as loss of Achilles tendon reflexes and diminished vibration sensation, and/or neuropathic symptoms including paresthesia.

Follow up

The annual examinations included bodyweight, BMI, waist-to-hip ratio, treatment of diabetes, fasting plasma glucose, serum insulin, total cholesterol, triglycerides, HDL-C, lipoprotein(a), white blood cells, red blood cells, Ht, platelet, BUN, serum creatinine, uric acid, total protein, albumin, blood pressure, visual acuity, microalbuminuria, deep tendon reflexes, neuropathic symptoms, resting electrocardiogram (ECG), chest X-ray, and the occurrence of retinopathy, nephropathy, neuropathy, IHD, stroke and PVD. HbA1c and ACR were measured biannually. Basic ADL, functional abilities, cognitive function, depressive symptoms and nutrition were assessed every other year. Use of medications, including insulin and hypoglycemic, antihypertensive, antihyperlipidemic, antiplatelet and anticoagulant drugs, was checked annually.

Data management and analyses

The main database was stored at the data management and statistical analysis center. A data sheet of each patient was mailed from the study institutions to the data management and statistical analysis center each year. The data was validated by range, combinatorial and historical checks of compatibility with previous data. A visual check of the list of abnormalities and information in the data sheets was carried out by trained staff. The study institutions were notified of unexplained abnormalities in the data that were completed or corrected before entry into the main database.

Data are presented as means ± SD or as proportions, unless otherwise specified. Data for analysis was extracted from the main database, and statistical analysis was carried out using the SAS computer programs. For univariate analysis, we used unpaired *t*-test and χ^2-test to compare baseline clinical characteristics in the two treatment groups. $P < 0.05$ was considered statistically significant.

Data security was maintained by exclusion of patient identities, password access and secure output within the data management and statistical analysis center.

End-points

Fatal and non-fatal events during follow up were certified by at least two members of the expert committee, masked to the participants' diagnosis and risk factor status. Death as a result of diabetes was defined as sudden death or death from atherosclerotic CHD (MI or heart failure as a result of ischemia) or stroke, death as

a result of renal failure, hyperglycemia or hypoglycemia. The history of macroangiopathy was obtained from medical records. Ischemic heart disease was classified as present when the patient had (i) a history of MI characterized by a typical clinical picture (chest pain, chest oppression and dyspnea), typical ECG alterations with occurrence of pathological Q waves and/or localized ST variations) and typical enzymatic changes (creatine phosphokinase); and (ii) a history of angina pectoris, positive treadmill ECG test or positive postload cardiac scintigram, confirmed by coronary angiography. Stroke was defined as clinical signs of a focal neurological deficit with rapid onset persisting ≥24 h, confirmed by either brain computed tomography or magnetic resonance imaging. No cases of asymptomatic lesions detected by brain imaging (i.e. silent infarction) were included. PVD was defined as the absence of dorsal pedal artery or posterior tibial artery pulsation and ankle–brachial index <0.8 or the presence of foot gangrene or ulcers.

All events related to diabetes were defined as any complications of cardiovascular events, fatal or non-fatal stroke, sudden death, renal death, diabetic foot complications and heart failure. All events included death unrelated to diabetes, as well as all events related to diabetes.

End-point validation

Possible clinical end-points were noted in the annual data sheets, with the diagnostic criteria for each end-point being predetermined. When an end-point was notified on a data sheet, the administrator requested full information from the data management and statistical analysis center, followed by a review by two clinical assessors of the event assignment committee. Two separate assessments for each end-point were entered on a special data sheet. If there was disagreement on the assessment, a final decision was made after discussions of the committee. The definition of the end-points is shown in the Appendix.

Statistical analysis and criteria for stopping the study

Differences in end-points (deaths or complications) between the two groups were analyzed using the log–rank test. Uni- and multivariate survival analyses were carried out using Cox proportional hazard regression models. All major analyses were according to assigned allocations (intention to treat), without exclusion of protocol deviants.

The Data and Safety Monitoring Committee examine the end-points annually and will stop the study when the difference in diabetes-related deaths or complications (disease) between the two groups becomes significant ($P < 0.001$, log–rank test).

Results

A total of 1173 outpatients with diabetes, aged over 65 years, were registered between March 2001 and February 2002. After randomization, 585 and 588 patients were allocated to intensive or conventional treatment, respectively. There were no significant differences between the two groups for age, sex, diabetes treatment, BMI, HbA1c, SBP and DBP, total cholesterol, triglycerides, HDL-C levels (Table 2), and number of risk factors (data not shown).

At baseline, the proportion of patients with a low ADL (TMIG Index of Competence ≤ 9), depressive symptoms (GDS-15 ≥ 5), or cognitive impairment (MMSE ≤ 23) were 13%, 28% and 4%, respectively. The prevalence of low ADL, depressive state and cognitive impairment was similar in the two groups (Table 2).

The dropout rate after 6 years was 8.9% (104 cases). HbA1c, total cholesterol, triglycerides, blood pressures and BMI at baseline and during follow up are shown in Table 3 and Figures 1–4. A small, but significant difference in HbA1c between the two groups was observed at 1 year after the start of intervention (7.9% *vs* 8.1%, $P < 0.05$), although this significant difference was not observed after the second year. Although SBP and DBP, total cholesterol and triglycerides levels tended to decrease by the sixth year compared with the baseline data in both groups, no significant differences in these variables were observed between the two groups during follow up (Figs 1–4). BMI and HDL-C levels did not change over the follow-up period in either group.

Table 4 shows the fatal and non-fatal events during follow up in the two groups. With the exception of coronary revascularization, there were no significant differences in fatal or non-fatal events between the groups ($P < 0.05$, log-rank test). Composite events (death as a result of diabetes, death unrelated to diabetes, coronary vascular events, stroke, total diabetes-related events and all events) were also similar in the two groups (Table 5).

Discussion

The J-EDIT study has the potential to determine whether multiple risk factor intervention prevents aggravation of complications and quality of life, and reduces mortality in elderly diabetic patients. The study has three characteristics. First, it is a large-scale study of multiple risk factor intervention in elderly diabetic patients. No or very few elderly patients were included in the UKPDS[9,10] or Steno-2 Study.[12] Second, the multiple interventions involved control of blood pressure, serum lipids, bodyweight and blood glucose. The treatment goals in the intensive treatment group were similar

Table 2 Clinical characteristics of the participants at baseline

	Conventional treatment ($n = 588$)	Intensive treatment ($n = 585$)
General characteristics		
Age (years)	71.7 ± 4.7	71.9 ± 4.6
Male (%)	46.3	46.3
Duration of diabetes (years)	18.0 ± 9.9	16.7 ± 8.5
Body mass index (kg/m^2)	24.3 ± 7.3	24.0 ± 3.9
Waist (cm)	83.6 ± 9.9	84.3 ± 10.4
Waist-to-hip ratio	0.89 ± 0.07	0.90 ± 0.07
Smoking (%) (non-/ex-smoker/current smoker)	16:31:53	15:29:56
Smoking (package × years)	848 ± 762	789 ± 601
Family history of diabetes (%)	45.8	39.7
Systolic BP (mmHg)	137 ± 17	137 ± 16
Diastolic BP (mmHg)	75 ± 10	76 ± 10
Clinical status		
Ischemic heart disease (%)	16.3	14.9
Cerebrovascular disease (%)	12.4	13.3
Retinopathy (%)		
Stage 0	53.6	51.7
Stage 1	30.5	31.4
Stage 2	7.8	9.1
Stage 3	3.3	3.4
Stage 4	4.7	4.7
Nephropathy (%) (no/microalbuminuria/persistent proteinuria)	51:30:19	53:30:17
Loss or weakness of ATR (%)	56.8	57.1
Paresthesia (%)	18.5	22.3
Laboratory data		
HbA1c (%)	8.5 ± 0.9	8.4 ± 0.8*
Fasting plasma glucose (mg/dL)	170 ± 53	168 ± 49
Fasting insulin (mIU/mL)	10.9 ± 12.0	10.3 ± 9.6
Total cholesterol (mg/dL)	202 ± 34	203 ± 34
Triglycerides (mg/dL)	131 ± 70	137 ± 110
HDL-C (mg/dL)	56 ± 18	57 ± 19
Uric acid (mg/dL)	5.1 ± 2.0	5.1 ± 1.4
Blood urea nitrogen (mg/dL)	16.9 ± 5.9	17.2 ± 6.1
Creatinine (mg/dL)	0.93 ± 1.2	0.83 ± 0.36
Treatment		
Treatment of diabetes (diet/OHA/insulin)	9.0:60.7:30.3	8.7:61.0:30.3
Sulfonylurea drugs	54.6	56.0
α-Glucosidase inhibitors (%)	30.5	28.0
Biguanides (%)	16.4	15.5
Pioglitazone (%)	4.5	5.2
Glinides (%)	2.3	2.1
Antihypertensive drugs (%)	56.4	57.4
ACE inhibitors (%)	22.9	23.3
ARB (%)	10.1	9.3
Calcium blockers (%)	42.9	41.0
β-Blockers (%)	6.2	5.7
α-Blockers (%)	6.1*	3.4
Diuretics (%)	5.1	7.5
Antihyperlipidemic drugs (%)	40.2	36.8
Statins (%)	30.3	26.5
Fibrates (%)	3.4	3.9
EPA (%)	0.7*	2.7
Nicotinates (%)	1.3	1.4
Probucol	2.2	1.6
Antiplatelet drugs (%)	25.9	27.4
Aspirin (%)	13	15
Geriatric Assessment		
Barthel index (full score: 20)	19.8 ± 0.9	19.8 ± 0.8
Prevalence of any disabilities (%)	11	14
Functional abilities (TMIG index of competence) (full score: 13)	11.6 ± 2.2	11.6 ± 2.2
Geriatric depression scale (full score: 15)	4.3 ± 3.3	4.0 ± 3.2
Depressive symptoms (%) (Geriatric depression scale ≥5)	41	36
MMSE (full score: 30)	28.0 ± 2.4	27.8 ± 3.0
Cognitive impairment (%) (MMSE ≤23)	7	6
Visual impairment (%) (≤0.1)	9	12

ARB, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; ATR, Achilles tendon reflex; BP, blood pressure; EPA, eicosapentenoic acid; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; OHA, oral hypoglycaemic agents; TMIG, Tokyo Metropolitan Institute of Gerontology. *$P < 0.05$.

Table 3 Changes in bodyweights, glycated hemoglobin A1c, serum lipids, and blood pressure at baseline and during the follow-up period

	Conventional treatment							Intensive treatment						
Follow up (years)	0	1	2	3	4	5	6	0	1	2	3	4	5	6
BMI (kg/m^2)	23.6	23.6	23.6	23.4	23.5	23.5	23.4	23.9	23.8	23.8	23.8	23.8	23.7	23.5
HbA1c (%)	8.5	8.1	8.0	7.9	7.9	7.9	7.8	8.4	7.9	7.8	7.8	7.8	7.8	7.7
TC (mg/dL)	202	200	199	195	193	190	190	202	196	198	194	190	188	188
TG (mg/dL)	112	111	109	108	103	101	101	114	110	110	108	110	104	104
HDL-C (mg/dL)	56	56	55	56	55	55	54	57	54	54	55	55	55	55
SBP (mmHg)	137	137	135	135	135	135	134	138	136	136	133	134	136	134
DBP (mg/dL)	75	74	73	72	72	72	71	74	73	74	72	71	71	71

BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 4 Comparison of fatal events and non-fatal events during the 6-year follow-up period in the conventional and intensive treatment groups

		Number	*P*-value
Fatal event	Myocardial infarction	12	0.083
	Sudden death	13	0.993
	Stroke	6	0.656
	Death due to renal failure	3	0.084
	Death due to hyper/hypoglycemia	1	0.322
	Malignancy	37	0.506
	Pneumonia	10	0.525
	Others	13	0.570
	Subtotal	95	0.291
Nonfatal event	Myocardial infarction	17	0.998
	Angina pectoris	21	0.517
	Coronary revascularization	18	0.0282
	Hospitalization due to heart failure	15	0.190
	Stroke	63	0.281
	Diabetic ulcer or gangrene	12	0.564
	Subtotal	146	
Total		241	

Table 5 Comparisons of composite events (death due to diabetes, death unrelated to diabetes, coronary vascular events, stroke, total diabetes-related events and all events) in the conventional and intensive treatment groups

	No. events	*P*-value (log–rank test) Conventional *vs* intensive
Death due to diabetes	35	0.8495
Death not related to diabetes	59	0.2991
Coronary vascular events	55	0.9868
Stroke	67	0.2915
All events related to diabetes	155	0.5573
All events	206	0.2239

Death due to diabetes was defined as sudden death or death from atherosclerotic coronary heart disease (myocardial infarction or heart failure due to ischemia) or stroke, death due to renal failure, hyperglycemia or hypoglycemia. All events related to diabetes were defined as any complications of cardiovascular events, fatal or non-fatal stroke, sudden death, renal death, diabetic foot complications and heart failure. All events included death unrelated to diabetes, as well as all events related to diabetes.

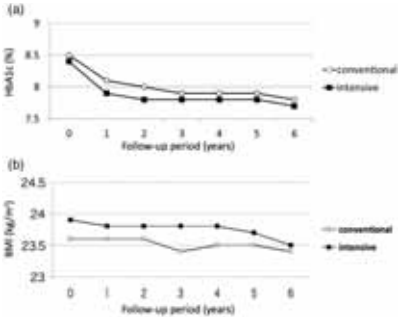

Figure 1 Clinical course of (a) glycated hemoglobin A1c (HbA1c) and (b) body mass index (BMI) in the conventional and intensive treatment groups.

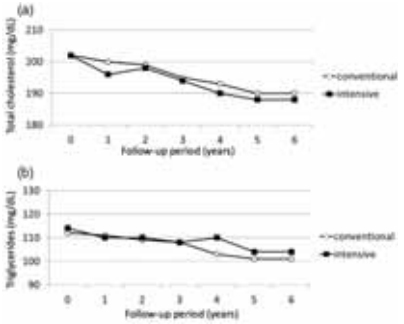

Figure 2 Clinical course of (a) total cholesterol and (b) triglycerides in the conventional and intensive treatment groups.

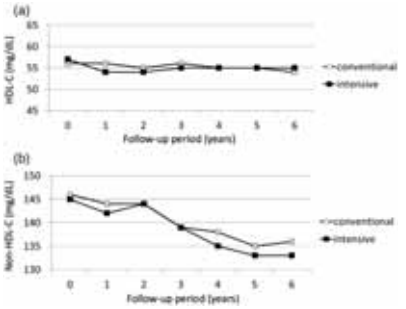

Figure 3 Clinical course of (a) high-density lipoprotein cholesterol (HDL-C) and (b) non-HDL-C in the conventional and intensive treatment groups.

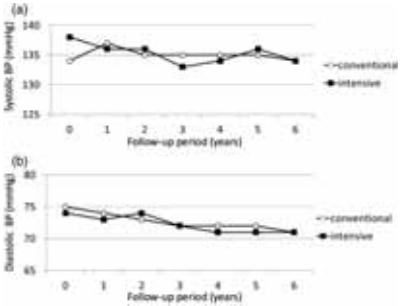

Figure 4 Clinical course of (a) systolic and (b) diastolic blood pressures (BP) in the conventional and intensive treatment groups.

to those in the Steno-2 Study[12] and considerably stricter than those in the UKPDS[9,10] (Table 1). Third, outcome in the study included ADL, cognitive function, depressive mood, well-being and the diabetic-specific psychological state, important components for geriatric assessment of elderly people.

The treatment groups in the study had similar general characteristics, diabetic complications, atherosclerotic disease, blood pressure, metabolic risk factors and prevalence of drug therapy for diabetes, hypertension, and hyperlipidemia, with the prevalence of micro- and macrovascular complications being 50% and 15%, respectively. As patients with poor diabetes control were selected, the prevalence of drug-treated hypertension and hyperlipidemia was high (47% and 65%, respectively). Mean HbA1c level at baseline was 8.5%, lower than that of the UKPDS, but still worthy of improvement. The prevalence of patients with SBP ≥ 130 mmHg (70%), DBP ≥85 mmHg (14%), serum total cholesterol ≥ 200 mg/dL (52%), triglycerides ≥ 150 mg/dL (30%), HDL-C ≤ 40 mg/dL (15%) or BMI ≥ 25 (34%) was also high, showing a need for intervention. The high prevalence and presumably high rate of deterioration of complications and potential risk factors show that the present study had a good chance of determining whether multiple risk factor intervention prevented the development and progression of complications. Therefore, we included both primary and secondary prevention trials.

The oral hypoglycemic drugs differed from those used in previous studies. Oral hypoglycemic drugs might be more beneficial than sulfonylurea drugs for preventing cardiovascular disease in patients with type 2 diabetes. α-Glucosidase inhibitors also prevent cardiovascular disease and progression of carotid atherosclerosis,[21-23] whereas metformin use is associated with lower cardiovascular morbidity and mortality, and attenuated progression of carotid atherosclerosis compared with sulfonylurea therapy.[24,25] Thiazolidinediones attenuate carotid atherosclerosis and restenosis after coronary stent implantation in patients with type 2 diabetes.[26,27]

We did not observe any significant differences in fatal or non-fatal cardiovascular events and composite events, including diabetes-related mortality, between the two treatment groups over the follow-up period. Although we observed significant improvements in HbA1c and LDL-C during the first 2 years in the intensive treatment group, there were no differences in HbA1c, lipid or blood pressure after that time. The similar values in atherosclerotic risk factors in both groups during follow up might account for the same prevalence of events, including cardiovascular and stroke, in the two groups. The results show it is difficult to markedly reduce HbA1c, blood pressure and lipid levels in elderly diabetic patients. The high prevalence of depressive and hypoglycemic symptoms at baseline in our cohort was notable. The intention of physicians to avoid hypoglycemic events and psychological barriers to providing elderly patients with extremely strict glucose control might explain the difficulties associated with aggressive intervention. In fact, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, aggressive glucose control was reported to lead to increased mortality in patients with longstanding diabetes.[28] Cardiovascular autonomic abnormalities, arrhythmia and hypercoagulability as a result of hypoglycemia might be responsible for increasing mortality during aggressive treatment. In addition, elderly patients do not accept the increase in the number of oral drugs or the initiation of insulin therapy.

In conclusion, preliminary analysis in the present study showed no significant differences in fatal or non-fatal events between the intensive and conventional treatment groups. However, as the levels of blood lipids, SBP and HbA1c tended to decrease during the follow-up period, further detailed analysis of the data might clarify to what extent treatment of risk factors influences functions and quality of life in elderly diabetic patients.

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Conflict of interest

There is no conflict of interest. The Japanese Elderly Diabetes Intervention Trial (J-EDIT) Study Group has not cleared any potential conflicts.

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Appendix

1. Atherosclerotic coronary heart disease (CHD) death – either or both of the following categories:

A. Death with consistent underlying or immediate cause plus either of the following:
   (1) Preterminal hospitalization with definite or suspected myocardial infarction (MI).
   (2) Previous definite angina or definite or suspected MI when no cause other than atherosclerotic CHD could be ascribed as the cause of death.

B. Sudden and unexpected death (requires all three characteristics).
   (1) Deaths occurring within 1 h with or without the onset of severe symptoms.
   (2) No known non-atherosclerotic acute or chronic process or event that could have been lethal.
   (3) An unexpected death of a person who was not confined to their home, hospital or other institution as a result of illness within 24 h before death.

2. Criteria for non-fatal MI – any one or more of the following categories using the stated definition:

A. Diagnostic electrocardiogram (ECG) at the time of the event.
B. Ischemic cardiac pain and diagnostic enzyme profile.
C. Ischemic cardiac pain and equivocal enzymes and equivocal ECG.
D. A routine ECG diagnostic for MI while the previous ECG was not.

3. Angina pectoris

The participants must report pain or discomfort with all of the following characteristics:
(1) The site must include the sternum at any level.
(2) It must occur during a form of exertion or stress and must usually last at least 30 s.
(3) It must on most occasions disappear within 10 min or less from the time of resting or decrease the intensity of exertion.
(4) It must usually be relieved in 2–5 min by nitroglycerine (does not apply if participant has never taken nitroglycerine).

In the case of angina pectoris at baseline, chest pain or discomfort should disappear or be controlled at entry. Reappearance or exacerbation of chest pain or discomfort and fulfilling points (1)–(4) were considered as an event. Subjects with uncontrolled angina pectoris at entry were not enrolled in the study.

4. Cerebrovascular disease

A diagnosis required all of the following:
(1) History of recent onset of unequivocal and objective findings of a localizing neurological deficit documented by a physician.
(2) Findings persist longer than 24 h.
(3) The neurological findings were not referable to an extracranial lesion.
(4) Findings of computed tomographic (CT) or magnetic resonance image (MRI) taken within 3 weeks after onset, or autopsy records classifying the cerebrovascular disease into cerebral hemorrhage, cerebral infarction, or subarachnoidal hemorrhage. Cerebral infarction was defined as a stroke accompanied by CT and/or MRI scan(s) that showed an infarct in the expected area, and also on the basis of clinical findings of stroke, for which there was evidence of cerebral infarction at autopsy. Cerebral or subarachnoid hemorrhage was classified on the basis of evidence obtained on CT or MRI scans or at autopsy, excluding hemorrhagic conversion of infarction.

In the case of cerebrovascular disease at baseline, the appearance of new unequivocal and objective findings of a localizing neurological deficit documented by a physician that persisted longer than 24 h was considered as an event and classified on the basis of evidence obtained on CT or MRI scanning or at autopsy. Cerebral infarction without obvious neurological symptoms shown by CT or MRI scans taken incidentally was not considered as an event.

5. Composite events

Death as a result of diabetes was defined as sudden death or death from atherosclerotic CHD (MI or heart failure as a result of ischemia) or stroke, death as a result of renal failure, hyperglycemia or hypoglycemia. All events related to diabetes were defined as any complications of cardiovascular events, fatal or non-fatal stroke, sudden death, renal death, diabetic foot complications and heart failure. All events included death unrelated to diabetes, as well as all events related to diabetes.

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ORIGINAL ARTICLE

Non-high-density lipoprotein cholesterol: An important predictor of stroke and diabetes-related mortality in Japanese elderly diabetic patients

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Aims: To evaluate the association of low-density lipoprotein, high-density lipoprotein and non-high-density lipoprotein cholesterol with the risk of stroke, diabetes-related vascular events and mortality in elderly diabetes patients.

Methods: This study was carried out as a post-hoc landmark analysis of a randomized, controlled, multicenter, prospective intervention trial. We included 1173 elderly type 2 diabetes patients (aged ≥65 years) from 39 Japanese institutions who were enrolled in the Japanese elderly diabetes intervention trial study and who could be followed up for 1 year. A landmark survival analysis was carried out in which follow up was set to start 1 year after the initial time of entry.

Results: During 6 years of follow up, there were 38 cardiovascular events, 50 strokes, 21 diabetes-related deaths and 113 diabetes-related events. High low-density lipoprotein cholesterol was associated with incident cardiovascular events, and high glycated hemoglobin was associated with strokes. After adjustment for possible covariables, non-high-density lipoprotein cholesterol showed a significant association with increased risk of stroke, diabetes-related mortality and total events. The adjusted hazard ratios (95% confidence intervals) of non-high-density lipoprotein cholesterol were 1.010 (1.001–1.018, $P = 0.029$) for stroke, 1.019 (1.007–1.031, $P < 0.001$) for diabetes-related death and 1.008 (1.002–1.014; $P < 0.001$) for total diabetes-related events.

Conclusions: Higher non-high-density lipoprotein cholesterol was associated with an increased risk of stroke, diabetes-related mortality and total events in elderly diabetes patients. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 18–28.**

Keywords: diabetes mellitus, diabetic complications, elderly, non-high-density lipoprotein cholesterol, stroke.

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Introduction

Although the importance of multiple risk factor intervention on type 2 diabetic complications has been shown in the United Kingdom Prospective Diabetes Study,[1,2] Kumamoto Study[3] and Steno-2 Trial,[4] the merits of modifying blood lipid, blood pressure (BP) and hyperglycemia in elderly (>65 years) diabetic patients are unclear. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed that intensive glucose-lowering therapy reduced the risk of non-fatal myocardial infarction in patients with advanced type 2 diabetes and a high risk of cardiovascular disease, but increased the risk of death.[5] Severe hypoglycemia and autonomic neuropathy also predicted cardiovascular mortality in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and ACCORD studies, respectively.[6,7]

Non-high-density lipoprotein cholesterol (non-HDL-C), a major atherogenic lipoprotein, was identified by the National Cholesterol Education Program (NCEP) Expert Panel as a secondary target for preventing coronary heart disease (CHD).[8] Although the associations between non-HDL-C and CHD, ischemic stroke, and mortality are inconsistent,[9–25] the predictive potential of non-HDL-C for CHD or stroke might be similar to or lower than that of low-density-lipoprotein cholesterol (LDL-C) or total cholesterol (TC).[18–23] In elderly diabetes patients, the significance of conventional risk factors including BP, TC, LDL-C and glycated hemoglobin A1c (HbA1c), and non-HDL-C has not been established.

The Japanese Elderly Diabetes Intervention Trial (J-EDIT) is a randomized control trial evaluating the efficacy of multiple risk factor interventions on functional prognosis and development, and/or progression of diabetic complications and cardiovascular disease (CVD) in 1173 elderly type 2 diabetes patients enrolled from 39 Japanese diabetes care institutions. No significant risk reduction in cardiovascular events, stroke or mortality was observed with intensive treatment.[24] Because TC and HbA1c decreased with intensive treatment compared with conventional treatment during the first year,[24] we carried out a landmark analysis 1 year after study entry to evaluate the effects of glucose and lipid control. In particular, we examined whether high non-HDL-C was associated with increased risk of stroke, diabetes-related mortality and total events.

Methods

Participants

J-EDIT was organized between April and December 2000. Participants were recruited from diabetic outpatient departments at 39 representative hospitals in Japan between March 2001 and February 2002. Written informed consent was obtained from all participants before screening as per the Helsinki Declaration.

The initial screening tests included body mass index (BMI), BP, serum HbA1c, TC, triglycerides and HDL-C. Eligibility criteria of the participants were: (i) age 65–85 years; and (ii) HbA1c ≥ 7.9% or HbA1c ≥ 7.4%, unless they met the treatment goals of the study. Major exclusion criteria included a recent myocardial infarction or stroke, acute or serious illness, aphasia, or severe dementia.

Randomization and intervention

A total of 1173 >65 years-of-age diabetic outpatients were registered. Within 1 month, the patients were randomly allocated to intensive or conventional treatment groups, as reported elsewhere.[17] The treatment goal in the intensive treatment group was HbA1c < 6.9%, BMI < 25 kg/m^2, systolic blood pressure < 130 mmHg, diastolic blood pressure < 85 mmHg, HDL-C > 40 mg/dL, serum triglycerides < 150 mg/dL and serum total cholesterol < 180 mg/dL (or LDL-C < 100 mg/dL if patients had CHD) or <200 mg/dL (or LDL-C < 120 mg/dL if patients did not have CHD). If TC or LDL-C treatment goals were not achieved, the physicians were advised to use atorvastatin. The conventional treatment group continued their baseline treatment for diabetes, hypertension or dyslipidemia, without a specific treatment goal.

Each participant had a standardized medical history and physical examination at baseline, and every subsequent year. Standardized questionnaires were used to obtain self-reported data on smoking and alcohol habits, hypoglycemia frequency, nutritional status, dietary habits, dietary adherence, self-efficacy, activities of daily livings, physical activities, comprehensive cognitive function, and psychological status. Functional disabilities were assessed using the Tokyo Metropolitan Institute of Gerontology Index of Competence.[25] Folstein's Mini-Mental State Examination was used to assess comprehensive cognitive function including orientation, memory recall and calculations.[26] Depressive symptoms were evaluated using a short form of the Geriatric Depression Scale 15.[27] The frequency of mild or severe hypoglycemia was assessed using questionnaires with mild hypoglycemia episodes including both appearance and recovery from hypoglycemic symptoms. Episodes of severe hypoglycemia were defined as coma, convulsion or incapacity of the patient sufficient to require another person's assistance.

Measurements

Venous blood was drawn for measurement of serum glucose, HbA1c, TC, HDL-C and triglycerides at baseline, and at least twice a year. Plasma glucose was measured by the glucokinase method, and HbA1c by ion-exchange high-performance liquid chromatography. HbA1c was expressed as the international standard value adjusted by the equation of HbA1c (Japan Diabetes Society [JDS]) (%) plus 0.4%. Serum insulin was measured by an enzyme immunoassay method and TC, triglycerides, HDL-C, blood urea nitrogen, serum creatinine, uric acid, total protein and albumin by established standard methods.

Blood pressure was measured with a mercury sphygmomanometer using a cuff of appropriate size. Diastolic BP was determined as Korotkoff phase V. Body mass index was calculated as weight (kg) / height $(m)^2$.

Microangiopathy and macroangiopathy were assessed at baseline and then annually. Fundoscopic examinations were carried out through dilated pupils by experienced ophthalmologists using direct ophthalmoscopy. Retinopathy status was assessed by the Japanese Diabetes Complication Study method and classified into five stages. According to mean urinary albumin-to-creatinine ratio (ACR; μg/mg creatinine) in two or three successive urinalyses, diabetic nephropathy was classified as no nephropathy (ACR <30), microalbuminuria (ACR 30–300) or persistent proteinuria (ACR ≥ 300 or urinary protein ≥ 30 mg/dL). Diabetic neuropathy was defined as a loss of Achilles tendon reflexes and diminished vibration sensation, and/or neuropathic symptoms including paresthesia.

Ischemic heart disease was diagnosed when the patients had at least one of the following: (i) a history of myocardial infarction (MI) characterized by a typical clinical picture (chest pain, chest oppression and dyspnea), typical electrocardiographic alterations with occurrence of pathological Q waves and/or localized ST variations, and typical enzymatic changes (creatine phosphokinase [CPK] CPK-MB); and (ii) a history of angina pectoris and a positive treadmill electrocardiography or positive postload cardiac scintigraphy confirmed by coronary angiography. Stroke was defined as clinical signs of a focal neurological deficit with rapid onset that persisted ≥24 h, confirmed by either brain computed tomography or magnetic resonance imaging. Peripheral vascular disease was defined as either the absence of dorsalis pedis or posterior tibial artery pulsation and an ankle – brachial index <0.8, or the presence of foot gangrene or ulcers.

End-points

Fatal and non-fatal events identified during the follow-up period were certified by at least two members of the expert committee, blinded to the participants' diagnosis and risk factor status.

Mortality related to diabetes was defined as death from atherosclerotic coronary heart disease (MI or heart failure as a result of ischemia), sudden death, or death as a result of stroke, renal failure, severe hyperglycemia or hypoglycemia. Cardiovascular events were defined as new onset of MI, angina pectoris or coronary revascularization. Stroke included cerebral infarction and bleeding, but not transient ischemic attacks. Total diabetes-related events consisted of cardiovascular events, stroke, sudden death, death as a result of renal failure, diabetic ulcers or gangrene, or heart failure. Information on macroangiopathies was obtained from medical records.

Statistical analyses

Data are presented as means ± SD or as proportions, unless otherwise specified. Data was extracted from the main database and analyzed using the SAS computer program. Unpaired *t*-test and χ^2-test were used to compare the baseline clinical characteristics of the two treatment groups.

Uni- and multivariate survival analyses were carried out using Cox proportional hazard regression models. Landmark analyses were carried out to show the effects of time-dependent factors and comprised a survival analysis in which follow up started at the landmark time 1 year after study entry. Only patients who had survived to the landmark time-point were included. Time-dependent risk factors were evaluated at the landmark time-point and analyzed as fixed variables. $P < 0.05$ was considered statistically significant.

Table 1 Clinical characteristics of participants at the landmark time

	Conventional treatment ($n = 496$)	Intensive treatment ($n = 497$)
General characteristics		
Age at baseline (years)	71.6 ± 4.7	71.8 ± 4.5
Male (number, %)	227 (45.8)	225 (45.3)
Body mass index (kg/m^2)	23.8 ± 3.4	23.6 ± 3.5
HbA1c (%)	7.7 ± 1.1	7.5 ± 1.0*
Systolic BP (mmHg)	137 ± 16	136 ± 15
Diastolic BP (mmHg)	73 ± 9	74 ± 9
TC (mg/dL)	200 ± 34	197 ± 33
Triglycerides (mg/dL)	133 ± 89	131 ± 97
HDL-cholesterol (mg/dL)	54 ± 15	56 ± 17
LDL-cholesterol (mg/dL)	116 ± 29	119 ± 30
Non-HDL-cholesterol (mg/dL)	144 ± 33	143 ± 32
Complications		
Ischemic heart disease (%)	16.3	16.9
Stroke (%)	12.9	14.5
Retinopathy (none : simple : proliferative, %)	52.6:44.0:3.5	51.5:45.1:3.3
Nephropathy (none : microalbuminuria : macroproteinuria : chronic renal failure, %)	51.2:32.4:12.4:4.0	48.3:36.6:10.4:4.6
Diabetes treatment (diet alone : OHA : insulin : combination of OHA and insulin, %)	5.1:60.6:20.8:12.4	5.4:62.5:19.2:12.9
Antihyperlipidemic agents (%)	44.9	40.0
Statin (%)	33.2	26.1
Fibrates (%)	3.4	3.6
Antihypertensive agents (%)	60.0	58.9

*$P < 0.05$ vs conventional treatment group. BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OHA, oral hypoglycaemic agents; TC, total cholesterol.

Results

A total of 1173 >65 years-of age diabetic outpatients were enrolled in the study. At the landmark time, 32 patients had died, 110 had dropped out or had no successive biochemical data and 37 were excluded because of missing or incomplete data. Data of 993 patients (496 conventional treatment and 497 intensive treatment) were used in the landmark analyses. At the landmark time, there were no significant differences in age, sex, diabetes duration, BMI, BP, TC, triglycerides, HDL-C, LDL-C or non-HDL-C (Table 1). As a consequence of the interventions, HbA1c was significantly lower in the intensive treatment group ($P < 0.05$).

The clinical courses of HbA1c, systolic BP (SBP), non-HDL-C, and LDL-C at the landmark time and during follow up in the two treatment groups are shown in Figures 1 and 2. There was a similar decrease in these parameters in both groups during the follow-up period.

During the 6-year follow-up period, there were 38 cardiovascular events, 50 strokes, 21 diabetes-related deaths and 113 diabetes-related events.

Table 2 shows a comparison of cardiovascular event and mortality incidence during the follow-up period in

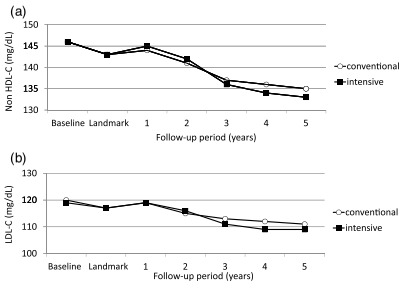

Figure 1 Clinical course of non-high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) in conventional and intensive treatment groups. Non-HDL-C and LDL-C showed similar decreases in both groups during the follow-up period after the landmark time.

groups stratified by age, sex, HbA1c, TC, LDL-C, non-HDL-C and SBP. Increased non-HDL-C was associated with an increased incidence of stroke ($P = 0.059$) and total diabetes-related events ($P = 0.020$), but not

Table 2 Incidence of cardiovascular events, stroke and mortality after the stratification by age, sex, glycated hemoglobin A1c, lipids and blood pressures

	Cardio vascular events	Stroke	Mortality due to diabetes	All events related to diabetes
Age ≥ 75 years *vs* age < 75 years	5.0% *vs* 4.8% 1.16 (0.58–2.34) *P* = 0.673	8.2% *vs* 4.9% 1.06 (0.999–1.12) *P* = 0.054	2.9% *vs* 1.7% 1.80 (0.75–4.35) *P* = 0.190	16.4% *vs* 11.9% 1.49 (1.01–2.21) *P* = 0.044
Men *vs* women	5.6% *vs* 4.3% 0.71 (0.38–1.32) *P* = 0.276	7.2% *vs* 4.6% 0.65 (0.37–1.13) *P* = 0.124	2.6% *vs* 1.6% 0.62 (0.26–1.47) *P* = 0.278	15.5% *vs* 11.1% 0.67 (0.46–0.97) *P* = 0.035
HbA1c ≥ 8.4% *vs* HbA1c < 8.4%	5.8% *vs* 4.6% 1.46 (0.76–2.77) *P* = 0.254	8.1% *vs* 3.6% 2.35 (1.35–4.09) *P* = 0.003	1.9% *vs* 2.2% 0.94 (0.36–2.42) *P* = 0.897	14.5% *vs* 11.5% 1.38 (0.94–2.02) *P* = 0.101
TC ≥ 200 mg/dL *vs* TC < 200 mg/dL	5.9% *vs* 4.2% 1.48 (0.79–2.79) *P* = 0.222	6.3% *vs* 5.3% 1.29 (0.74–2.26) *P* = 0.374	3.3% *vs* 0.8% 3.62 (1.33–9.88) *P* = 0.012	15.1% *vs* 11.5% 1.39 (0.96–2.02) *P* = 0.082
LDL-C ≥ 115 mg/dL *vs* LDL-C < 115 mg/dL	6.4% *vs* 3.3% 2.04 (1.03–4.06) *P* = 0.040	6.4% *vs* 5.2% 1.48 (0.83–2.63) *P* = 0.181	2.9% *vs* 0.8% 3.98 (1.34–11.8) *P* = 0.013	15.6% *vs* 10.9% 1.63 (1.11–2.39) *P* = 0.013
Non-HDL-C ≥ 140 mg/dL *vs* Non-HDL-C < 140 mg/dL	6.0% *vs* 3.9% 1.53 (0.80–2.95) *P* = 0.203	7.1% *vs* 4.4% 1.78 (0.98–3.23) *P* = 0.059	2.8% *vs* 1.3% 2.11 (0.82–5.45) *P* = 0.121	15.8% *vs* 10.5% 1.58 (1.08–2.33) *P* = 0.020
HDL-C < 50 mg/dL *vs* HDL-C ≥ 50 mg/dL	5.8% *vs* 4.5% 1.27 (0.67–2.37) *P* = 0.465	5.0% *vs* 6.5% 0.70 (0.38–1.26) *P* = 0.233	2.3% *vs* 2.0% 1.11 (0.47–2.64) *P* = 0.812	13.8% *vs* 13.2% 1.01 (0.69–1.47) *P* = 0.959
SBP ≥ 140 mmHg *vs* SBP < 140 mmHg	4.5% *vs* 4.8% 1.06 (0.55–2.05) *P* = 0.869	7.5% *vs* 5.0% 1.85 (1.06–3.25) *P* = 0.032	1.7% *vs* 2.1% 0.81 (0.32–2.03) *P* = 0.650	14.0% *vs* 12.8% 1.24 (0.85–1.81) *P* = 0.266
DBP ≥ 75 mmHg *vs* DBP < 75 mmHg	3.4% *vs* 6.0% 0.59 (0.30–1.17) *P* = 0.130	6.2% *vs* 6.0% 1.27 (0.73–2.20) *P* = 0.406	2.1% *vs* 2.0% 1.04 (0.43–2.51) *P* = 0.930	11.6% *vs* 14.9% 0.86 (0.59–1.26) *P* = 0.434

Incidence, hazard ratios, 95% CI and *P*-values in univariate Cox regression analyses are shown. DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure, TC, total cholesterol.

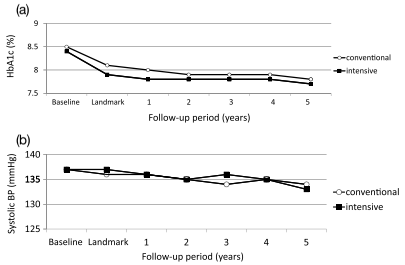

Figure 2 Clinical course of glycated hemoglobin A1c (HbA1c) and systolic blood pressure (BP) in conventional and intensive treatment groups. Decreases in HbA1c and systolic BP were similar in the two groups during the follow-up period after the landmark time.

with cardiovascular events (*P* = 0.203). In contrast, high LDL-C was significantly associated with increased incidence of cardiovascular events (*P* = 0.04), diabetes-related mortality (*P* = 0.013) and total diabetes-related events (*P* = 0.013), but not with stroke (*P* = 0.181). High HbA1c and SBP were also significantly associated with increased incidence of stroke (*P* = 0.003 and *P* = 0.032, respectively).

The patients were divided into quartiles of possible risk factors, and survival curves were compared using age- and sex-adjusted Cox hazard regression models. As shown in Figure 3a, the highest non-HDL-C quartile (≥163 mg/dL) had significantly higher diabetes-related mortality than the lowest (<122 mg/dL; *P* = 0.030) and second highest (143–163 mg/dL; *P* = 0.019) quartiles. Figure 3b shows that the total diabetes-related event was also significantly higher in the highest quartile (≥163 mg/dL) than either the lowest, second

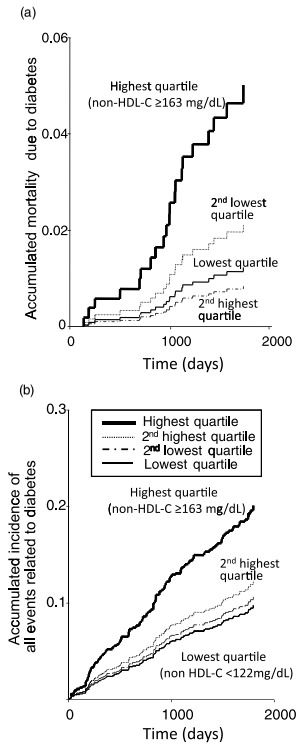

Figure 3 Non-high-density lipoprotein cholesterol (HDL-C) and mortality as a result of diabetes and total diabetes events. The highest non-HDL-C quartile (≥163 mg/dL) had a significantly higher mortality as a result of diabetes than the lowest and second highest quartile (*P* = 0.030 and *P* = 0.019, respectively). The accumulated incidence of total diabetes events was also significantly higher in the highest non-HDL-C quartile (≥163 mg/dL) than the lowest, second lowest and second highest quartiles (*P* = 0.003, *P* = 0.031, and *P* = 0.008, respectively).

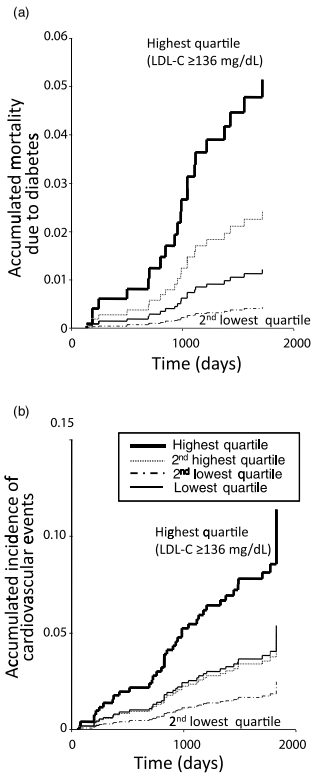

Figure 4 Low-density lipoprotein cholesterol (LDL-C) and mortality as a result of diabetes and incidence of cardiovascular events. The incidence of cardiovascular events or mortality as a result of diabetes was highest in the highest LDL-C quartile (≥136 mg/dL) and lowest in the second lowest LDL-C quartile (99–116 mg/dL). This suggests the existence of a J-curve incidence for stroke according to LDL-C distribution.

lowest or second highest quartiles (*P* = 0.003, *P* = 0.031 and *P* = 0.008, respectively). Stroke incidence tended to be greatest in the highest non-HDL-C quartile (*P* = 0.099; *vs* the lowest quartile, *P* = 0.076; *vs* the second lowest quartile, *P* = 0.080; *vs* the second highest quartile). Similarly, cardiovascular event also tended to be increased in the highest non-HDL quartile compared with the second lowest (*P* = 0.065) and second highest quartiles (*P* = 0.088).

Figure 4a and b show that cardiovascular event or diabetes-related mortality incidence was greatest in the highest LDL-C quartile (≥136 mg/dL) and lowest in the second lowest LDL-C quartile (99–116 mg/dL). This suggested the existence of a J-curve incidence for stroke according to LDL distribution.

Figure 5a and b show that the highest HbA1c quartile (≥8.8%) had a significant increase in the incidence of

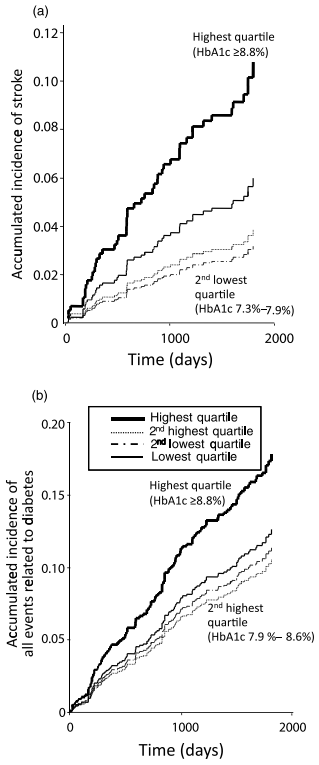

Figure 5 Glycated hemoglobin A1c (HbA1c) and incidence of stroke or all events related to diabetes. The highest HbA1c quartile (≥8.8%) had an increased incidence of stroke compared with the second lowest ($P = 0.003$), second highest ($P = 0.008$) and lowest ($P = 0.092$) quartiles. The incidence of stroke was lowest in the second lowest HbA1c quartile (7.3–7.9%). This suggests the existence of a J-curve incidence of stroke according to HbA1c distribution. The highest HbA1c quartile (≥8.8%) had a significant increase in diabetes-related events compared with the second lowest ($P = 0.031$) and second highest quartiles ($P = 0.058$), but not the lowest quartile group.

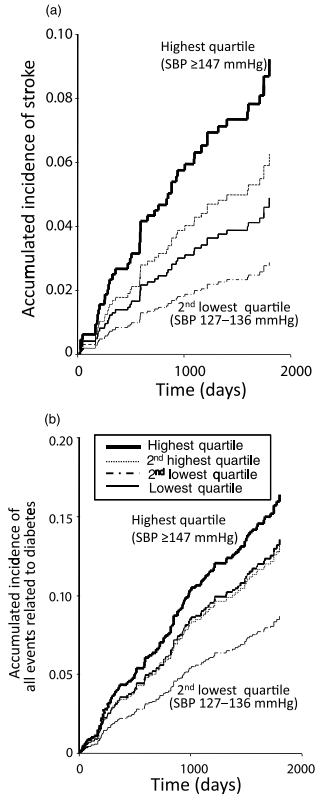

Figure 6 Systolic blood pressure (SBP) and incident of stroke or all events related to diabetes. The highest SBP quartile (≥147 mmHg) had an increased incidence of stroke compared with the second lowest (127–136 mmHg; $P = 0.013$) and lowest (<127 mmHg; $P = 0.083$) quartiles. The incidence of total diabetes events in the highest SBP quartile (≥147 mmHg) was significantly greater than only the second lowest quartile ($P = 0.023$). This suggests the existence of a J-curve incidence of stroke according to SBP distribution.

stroke and total diabetes-related events compared with the second lowest HbA1c quartile ($P = 0.003$ for stroke and $P = 0.031$ for total diabetes events). Interestingly, stroke incidence was lowest in the second lowest HbA1c quartile (7.3–7.9%) compared with the other three quartiles, resulting in a J-curve incidence for stroke according to HbA1c distribution. Similarly, the highest SBP quartile (≥147 mmHg) had an increased incidence of stroke and total diabetes-related events compared with the second lowest SBP quartile (127–136 mmHg; $P = 0.013$ for stroke and $P = 0.023$ for total diabetes-related events; Fig. 6a,b). The incidence of stroke or total diabetes-related events was also lowest in the second lowest SBP quartile, showing a J-curve incidence for stroke according to SBP distribution.

Table 3 Variables associated with incident composite events in multivariate Cox regression analyses after the landmark time

	Number of events	Significant variables	Hazard ratio (95%CI)	Significance
CVE (fatal MI + non-fatal MI + angina pectoris + coronary revascularization)	35	Age	1.028 (0.955–1.107)	0.460
		Sex	0.663 (0.328–1.342)	0.253
		HbA1c	1.182 (0.856–1.631)	0.309
		LDL-C	1.011 (1.000–1.021)	0.045
		HDL-C	0.996 (0.973–1.019)	0.705
		SBP	1.004 (0.983–1.026)	0.706
Stroke	48	Age	1.080 (1.016–1.148)	0.013
		Sex	0.466 (0.255–0.850)	0.013
		HbA1c	1.364 (1.093–1.701)	0.006
		Non-HDL-C	1.010 (1.001–1.018)	0.029
		HDL-C	1.003 (0.985–1.022)	0.734
		SBP	1.017 (0.999–1.035)	0.067
Diabetes-related mortality	21	Age	1.123 (1.023–1.232)	0.015
		Sex	0.471 (0.188–1.180)	0.108
		HbA1c	0.851 (0.516–1.402)	0.526
		Non-HDL-C	1.019 (1.007–1.031)	<0.001
		HDL-C	1.019 (0.991–1.047)	0.183
		SBP	0.994 (0.966–1.023)	0.691
Total diabetes events (CVE + stroke + sudden death + renal death + diabetic foot + heart failure)	108	Age	1.081 (1.038–1.125)	<0.001
		Sex	0.560 (0.376–0.834)	0.004
		HbA1c	1.149 (0.957–1.378)	0.136
		Non-HDL-C	1.008 (1.002–1.014)	0.005
		HDL-C	1.004 (0.991–1.017)	0.532
		SBP	1.008 (0.996–1.019)	0.215

CVE, cardiovascular event; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SBP, systolic blood pressure.

Table 3 shows the variables that were significantly associated with incident composite events. Using six variables (age, sex, HbA1c, SBP, non-HDL-C and HDL-C), non-HDL-C was significantly and independently associated with increased risk of stroke, diabetes-related mortality and total events. The adjusted hazard ratios (95% CI) for non-HDL-C were 1.010 (1.001–1.018, $P = 0.029$) for stroke, 1.019 (1.007–1.031, $P < 0.001$) for diabetes-related mortality and 1.008 (1.002–1.017; $P = 0.005$) for total diabetes-related events. When LDL-C was added to the model for total diabetes-related events, non-HDL-C remained significant ($P = 0.007$), whereas LDL-C did not. The significant association between non-HDL-C and total diabetes-related events persisted after the addition of statin treatment to the model ($P = 0.005$).

High HbA1c was also independently associated with incident stroke. Using six variables (age, sex, HbA1c, SBP, LDL-C and HDL-C), LDL-C was the only significant predictor for cardiovascular events ($P = 0.045$).

Discussion

The significance of several risk factors, such as serum lipid abnormalities and increased HbA1c, for stroke and mortality has not been shown clearly in elderly type 2 diabetes patients. The present study used a landmark analysis to show that non-HDL-C, SBP and HbA1c were independent predictors for stroke development during a 6-year follow-up period. A weak, significant association between non-HDL-C and stroke was found in agreement with several prospective studies.[9,10] In the Emerging Risk Factors Collaboration study on 302 430 people from 68 long-term prospective studies, the hazard ratios for ischemic stroke were 1.12 (95%CI:1.04–1.20) for non-HDL-C and 1.02 (95%CI:0.94–1.11) for triglycerides. However, the hazard ratio for ischemic stroke was approximately fourfold weaker than that for coronary heart disease.[9] The Women's Health Study also showed that compared with the lowest non-HDL-C quintile, the highest quintile had multivariate-adjusted hazard ratios for ischemic stroke of 2.45 (95%CI:1.54–3.91), higher than the ratios for HDL-C or LDL-C[10]. These

findings show non-HDL-C might be an important risk factor for stroke, even in elderly diabetes patients.

We also showed that non-HDL-C predicted diabetes-related mortality and total diabetes-related events. The predictive power of non-HDL-C for mortality was stronger in high-risk CHD patients associated with vascular intervention, chronic renal failure or diabetes mellitus.[11–15] In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators (PROVE IT-TIMI 22) trial on acute coronary syndrome patients receiving either pravastatin 40 mg or atorvastatin 80 mg, non-HDL-C, HDL/TC and Apolipoprotein (Apo) B / Apo A1 predicted death or acute coronary events.[11] In the Bypass Angioplasty Revascularization Investigation (BARI) Study, non-HDL-C was a strong and independent predictor of non-fatal MI and angina pectoris at 5 years compared with LDL-C or triglycerides, even after adjustment for potential covariates in patients undergoing angioplasty revascularization or bypass-surgery.[12] Nishizawa *et al.* showed that non-HDL-C in predialysis serum was a significant and independent predictor of cardiovascular mortality in hemodialysis patients.[13] In the European Community funded Concerted Action Programme into the epidemiology and prevention of diabetes (EURODIAB) Prospective Complication Study, non-HDL-C, age, pulse pressure and waist-to-hip ratio were independent predictors for all-cause mortality in type 1 diabetes patients.[14] Herman *et al.* showed the discriminatory power of non-HDL-C was similar to Apo-B in diabetes patients because of the discriminant ratio and unbiased equation of equivalence.[15] Non-HDL-C was also shown to be a better predictor of CVD mortality or acute myocardial infarction (AMI) than LDL-C or TC.[16–18] In the present study, the predictive potential of non-HDL-C was stronger in diabetic patients who had a residual risk beyond LDL-C.

Our finding in the landmark study that patients with a non-HDL-C > 163 mg/dL had a significantly increased incidence of stroke, diabetes-related death and total events compared with those with a non-HDL-C < 122 mg/dL suggests that lipid lowering with a statin is of considerable importance, even in the elderly diabetes patients. This result is in agreement with a report from the Japanese Circulatory Risk in Communities Study[19] showing an association between non-HDL-C and CHD incidence, with the greatest discriminative power at non-HDL-C > 140 mg/dL. In contrast, in the National cholesterol education program-III (NCEP-III) guidelines, the optimal goal of non-HDL-C in CHD patients was <100 mg/dL.[17] The decrease in non-HDL-C after the landmark time in both our intensive and conventional treatment groups might represent an effect of statin treatment, and might also explain the differences in events described here. In the Collaborative Atorvastatin Diabetes Study, treatment decreased both LDL-C and non-HDL-C, leading to prevention of stroke and cardiovascular events.[28] The present results suggest that even in elderly high-risk diabetes patients, a reduction of non-HDL-C using a statin might be beneficial for preventing CVD, stroke and mortality.[29]

The reason for the lack of significant associations between non-HDL-C and cardiovascular events remains unclear. In contrast, LDL-C was a significant predictor of cardiovascular events in the present study. The differences in predictive power of non-HDL-C and LDL-C for CVD and stroke might reflect variability in the vulnerability of cerebral and coronary arteries to lipoproteins. Non-HDL-C in combination with a Apo-B100, remnant lipoproteins and small, dense lipoproteins might be involved in stroke events as a consequence of biological actions beyond LDL-C. Alternatively, the predictive power of non-HDL might be affected by age,[20] sex,[21,22] ethnicity[23] and lifestyle habits.

The present data showed high HbA1c predicted stroke in elderly people with type 2 diabetes. In a Finnish elderly cohort, HbA1c and fasting, and 2-h glucose predicted stroke events.[30] In the Diabetes among Indian Americans (DIA) study, HbA1c and smoking were predictors for stroke in men without previous stroke, whereas therapy with insulin plus oral agents predicted stroke in men with a history of stroke.[31]

In contrast, stroke incidence in the present study was lowest in the second lowest HbA1c quartile (7.3–7.9%), resulting in a J-curve incidence for stroke according to HbA1c distribution. The study on the UK General Practice Database showed low and high HbA1c were both associated with increased large-vessel disease and all-cause mortality in 27 965 diabetic patients,[32] possibly because of hypoglycemia, leading to arrhythmia, cardiovascular autonomic abnormalities, QT prolongation, and induction of prothrombotic and proinflammatory markers. Moderately abnormal glucose control with HbA1c around 7.5% (JDS, 7.1%) with no hypoglycemia during follow up might have a beneficial effect on stroke in high-risk, elderly diabetic patients.

Similarly, the lowest incidence of stroke and total diabetes events in the second lowest SBP quartile (127–136 mmHg), and the lowest incidence of cardiovascular events and total diabetes events in the second lowest LDL-C quartile (99–116 mg/dL) suggest the existence of a J-curve. The J-curve effect of BP lowering has been reconsidered recently, with recommendation that aggressive BP control should be undertaken carefully in high-risk, older diabetes patients.[33,34] A review of observational studies shows a trend where all-cause mortality was highest when TC was lowest.[35] Only a few randomized control trials have not provided evidence of an effect of lipid-lowering treatment on mortality in ≥80 years-of-age patients.[35] Although it is not possible

to disregard the possibility that comorbidities, such as inflammation and malnutrition, are associated with an increased incidence of stroke in the lowest SBP and LDL-C groups, cautious and comprehensive management of BP and LDL-C is also required in older people with diabetes.

The present study had several limitations. First, our cohort comprised high-risk, elderly Japanese subjects, and therefore our results cannot be generalized to other populations. Second, the study population was limited by a relatively small sample size compared with other published reports, and it is likely that the lack of significant relationships between variables reflects inadequate statistical power rather than a true negative result. Finally, the landmark analysis after 1 year of intervention did not completely reflect the effects of temporal changes in the parameters over the entire follow-up period, although some tracking effects of lipid parameters were observed.

In conclusion, this relatively large-scale prospective study showed non-HDL-C was an important predictor for stroke, diabetes-related mortality and total diabetes events in high-risk, elderly type 2 diabetes patients. Non-HDL-C reflected several pathological lipoproteins, including LDL-C, ApoB, triglycerides, remnant lipoproteins and small, dense lipoproteins.[36] Measurement of non-HDL-C might therefore be useful for evaluating the effects of lipid intervention using statin, fibrates and eicosapentaenoic acid in elderly people with diabetes. However, further studies including sophisticated randomized trials are necessary to elucidate the role of non-HDL-C on vascular events.

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Conflict of interest

There is no conflict of interest. The Japanese Elderly Diabetes Intervention Trial (J-EDIT) Study Group has not cleared any potential conflicts.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Polypharmacy as a risk for fall occurrence in geriatric outpatients

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Objective: To investigate the predictors of falls, such as comorbidity and medication, in geriatric outpatients in a longitudinal observational study.

Methods: A total of 172 outpatients (45 men and 126 women, mean age 76.9 ± 7.0 years) were evaluated. Physical examination, clinical history and medication profile were obtained from each patient at baseline. These patients were followed for up to 2 years and falls were self-reported to their physicians. The factors associated with falls were analyzed statistically.

Results: A total of 32 patients experienced falls within 2 years. On univariate analysis, older age, osteoporosis, number of comorbid conditions and number of drugs were significantly associated with falls within 2 years. On multiple logistic regression analysis, the number of drugs was associated with falls, independent of age, sex, number of comorbid conditions and other factors that were significantly associated in univariate analysis. A receiver–operator curve evaluating the optimal cut-off value for the number of drugs showed that taking five or more drugs was a significant risk.

Conclusion: In geriatric outpatients, polypharmacy is associated with falls. Intervention studies are needed to clarify the causal relationship between polypharmacy, comorbidity and falls. **Geriatr Gerontol Int 2012; 12: 425–430.**

Keywords: bone/musculo-skeletal, elderly, falls, geriatric medicine, internal medicine, polypharmacy.

Introduction

Previous studies have assessed the risk factors for falls in community-dwelling elderly,[1–3] but not in geriatric outpatients, and history of falls, physical ability and living environment were found to be predictors of falls. Outpatients have different characteristics from community-dwelling elderly, and previous studies have not assessed whether medical comorbidity and therapeutic drugs might be risk factors for falls. Falls in patients on medication are complicated, because some drugs, such as aspirin, can cause serious bleeding when they have injurious falls, and others, such as antihypertensive[4] and hypoglycemic[5,6] agents, can cause falls.

Previously, we reported that polypharmacy was associated with the tendency for falls using four indices of fall tendency in a cross-sectional setting in geriatric outpatients,[7] though that study did not evaluate fall occurrences, and also not in a longitudinal manner. Therefore, we aimed at investigating whether polypharmacy was predictive of fall occurrences in a prospective fashion. For this purpose, we followed geriatric outpatients for up to 2 years, and assessed whether polypharmacy is a risk for fall occurrence, together with other risks.

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The validity of two novel indices of fall tendency, the 22 items fall risk index[8] and the 13 points simple screening test,[3] which were used in our previous study, have been confirmed in community-dwelling elderly, but not in geriatric outpatients. Therefore, in the present investigation, the association of these two indices with falls was also evaluated to confirm their validity in geriatric outpatients in a longitudinal study.

Methods

Patients

From 2006 to 2007, a total of 190 consecutive patients aged 65 years or older who were receiving treatment for chronic diseases, such as hypertension, dyslipidemia, diabetes and osteoporosis, who were seen every 2–4 weeks at the outpatient clinic of the Research Institute of Aging Science, Tokyo, were enrolled. All the patients were able to walk independently and their condition was stable. Patients who had acute illness or overt dementia were excluded. Anthropometric and medical information including past history of stroke, myocardial infarction, malignancy and prescribed drugs was obtained from each patient at baseline from the medical chart recorded by the physician in charge. However, 18 patients were excluded, because they were lost to follow up soon after enrolment and the medical information was not fully obtained. All prescribed drugs had not been changed in the included patients for at least 2 months before enrolment. The patients were followed up for 2 years.

Occurrence of falls

During the follow-up period, the patients and their family members responded to the annual questionnaire asking about the occurrence of falls within the past year. The questionnaire was repeated for 2 years.

Indices of fall tendency

After enrolment, the patients were examined for two indices to investigate the fall tendency. These were (i) a questionnaire of the 22 items portable fall risk index;[8] and (ii) the 13 points simple screening test to assess the fall tendency.[3]

Ethical consideration

The present study was approved by the Institutional Review Board of the Research Institute of Aging Science. We obtained written consent from all participants and/or their guardians.

Data analysis and statistical methods

Values are expressed as mean ± standard deviation. In order to analyze the relationship between falls and comorbidity or drugs, variables were compared using Student's *t*-test or χ^2-test as appropriate. Significant factors found in univariate analysis were included in multivariate logistic regression analysis to determine the association of falls with other variables. Receiver–operating curve (ROC) analysis was carried out to identify the optimal cut-off value of the number of drugs for predicting falls within 2 years. The value with the highest sum of sensitivity and specificity was used as the optimal cut-off value. Logistic regression analysis was carried out to assess the validity of the two indices of fall tendency, adjusted by age and sex. *P*-values <0.05 were considered statistically significant. Data were analyzed using JMP version 8.0.1 (SAS Institute, Cary, North Carolina, USA).

Results

Baseline medical information and two indices of fall tendency were evaluated in 172 patients (Table 1). Drugs prescribed in less than 5% of the patients are not shown. Because only patients who were in a stable condition and were able to walk independently were included, patients with Parkinson's disease, severe paresis or painful arthralgia were not included. Calcium channel blockers prescribed in the present study were all long-acting agents, and the prescribed aspirin dosage was 100 mg in all cases. Only a few patients were receiving insulin therapy, sulfonylureas, angiotensin converting enzyme inhibitors, β-blockers, α-blockers, non-steroidal anti-inflammatory drugs or anticoagulants. No patients were taking neuroleptics or antiparkinsonian drugs.

After 1 year, all patients, except for one who died of congestive heart failure, were followed up ($n = 171$, follow-up rate 99.4%). Falls occurred in 22 patients. Only a higher age was associated with falls within 1 year on univariate analysis (non-fallers: 76.4 ± 6.8 years, fallers: 81.0 ± 6.9 years, $P = 0.004$).

After another year (2 years after enrolment), one patient had died of lung cancer, and five patients were lost to follow up. A total of 165 patients were evaluated (follow-up rate 95.9%), and 10 patients had fallen during the second year; thus a total of 32 patients had fallen within 2 years. As shown in Table 2, higher age, osteoporosis, number of comorbid conditions and number of drugs were significant factors associated with falls. To determine the association of falls with these significant factors, multivariate logistic regression analysis was carried out, and as shown in Table 2, the number of drugs was the only factor that was significantly associated with falls within 2 years.

As polypharmacy was assumed to be a risk for falls within 2 years, the cut-off of the number of the drugs was analyzed. Figure 1 shows the ROC curves to define the optimal cut-off point in relation to falls within

Table 1 Characteristics and univariate analysis of association with fallers and non-fallers within 2 years and risk factors

Total		Non-fallers ($n = 133$)	Fallers ($n = 32$)	P-value (Fallers vs. Non-fallers)
Age (years)	77.0 ± 7.0	76.3 ± 6.9	80.0 ± 6.9	0.007
Body mass index (kg/cm^2)	22.7 ± 3.2	22.7 ± 3.3	22.7 ± 3.1	0.98
No. comorbid conditions	1.9 ± 1.1	1.8 ± 1.1	2.3 ± 0.9	0.009
No. drugs	3.2 ± 2.8	2.8 ± 2.7	4.9 ± 2.5	<0.0001
Female ($n = 122$)	–	72.9%	78.1%	0.66
Hypertension ($n = 106$)	–	62.4%	71.8%	0.41
Dyslipidemia ($n = 76$)	–	47.3%	40.6%	0.56
Diabetes ($n = 23$)	–	12.8%	18.8%	0.40
Osteoporosis ($n = 59$)	–	30.8%	56.3%	0.01
History of stroke ($n = 6$)	–	2.3%	9.4%	0.09
History of myocardial infarction ($n = 3$)	–	0.8%	6.3%	0.10
History of cancer ($n = 8$)	–	5.3%	3.1%	0.99
Calcium channel blocker ($n = 59$)	–	33.3%	46.9%	0.16
Angiotensin II receptor blocker ($n = 56$)	–	33.3%	37.5%	0.68
Statin ($n = 40$)	–	23.5%	28.1%	0.65
Aspirin ($n = 31$)	–	19.0%	24.1%	0.61
Bisphosphonate ($n = 9$)	–	4.6%	9.4%	0.38
H2-blocker ($n = 9$)	–	3.8%	12.1%	0.80
Proton pump inhibitor ($n = 11$)	–	5.3%	12.1%	0.23
Hypnotic ($n = 31$)	–	16.7%	28.1%	0.14

Values are expressed as mean ± SD ($n = 165$).

Table 2 Logistic regression analysis of association of falls within 2 years with age, sex, other significant factors found in univariate analysis, and polypharmacy

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/1 year)	1.08 (1.03–1.13)†	1.06 (0.99–1.13)	1.06 (0.99–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.98 (0.29–3.23)	0.75 (0.23–2.38)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)†	2.76 (0.92–7.38)	3.02 (0.96–6.15)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	0.90 (0.55–1.47)	0.99 (0.62–1.56)
No. drugs (/drug)	1.29 (1.12–1.48)‡	1.30 (1.08–1.57)*	–
Five or more drugs ($n = 0$, Y = 1)	5.04 (2.25–11.3)‡	–	4.50 (1.66–12.2)†

*$P < 0.05$, †$P < 0.005$, ‡$P < 0.0005$. CI, confidence interval.

2 years: the area under the ROC was 0.731, and the optimal cut-off value of the number of drugs was five (sensitivity 0.576, specificity 0.788). Logistic regression analysis showed that taking five or more drugs was significantly associated with an increased risk of falls (odds ratio 4.5, 95% CI 1.7–12.2) after adjustment for age, sex, osteoporosis and number of comorbid conditions (Table 2).

Also, the association between falls and two indices of fall tendency was evaluated to confirm the validity of each index in geriatric outpatients. As both indices included the questionnaire asking whether patients were "taking five or more drugs," the number of drugs was excluded from this analysis because of duplication in the statistical model. As shown in Table 3, the 22 items fall risk index showed a tendency towards an association with falls within 2 years, odds ratio 1.12 (95% CI 1.00–1.26; $P = 0.05$), whereas the 13 points screening test was significantly associated with falls after adjustment for age, sex and other factors significantly associated in the univariate analysis. Therefore, these indices are considered to be good predictors of falls in geriatric outpatients, as has been shown in community-dwelling elderly subjects.

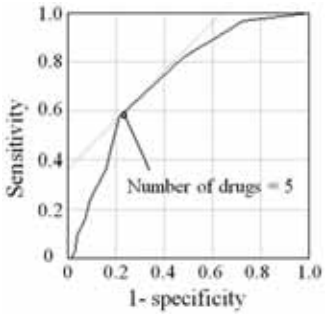

Figure 1 Receiver–operating curves to define optimal cut-off value of number of drugs at baseline in relation to falls within 2 years. Area under the curve was 0.731, optimal cut-off value of the number of drugs was five (sensitivity = 57.6%, specificity = 78.8%).

Discussion

The risk of falls has been assessed in community-dwelling elderly, and history of falls, physical ability and living environment were found to be predictors of falls. Also, in nursing home residents, cognitive function, gait disturbance and urinary incontinence are reported to be risk factors for falls,[9,10] and length of stay, disease condition, surgical procedures and some specific drugs are reported to be risk factors in hospital inpatients.[11,12]

Nevertheless, the risks in geriatric outpatients have not been sufficiently assessed, although assessment of fall risk in geriatric outpatients is important; their medical conditions or drugs might cause falls, and drugs, such as antiplatelet agents or anticoagulants, might cause critical bleeding after a fall. Also, physicians could prevent falls in their patients by giving advice during regular consultations, if risk factors are identified.

In our previous cross-sectional study assessing geriatric outpatients, polypharmacy was significantly correlated with indices of fall tendency, and the present follow-up study of geriatric outpatients showed the impact of polypharmacy on falls within 2 years. Statistical analyses showed that polypharmacy was a risk factor for falls, independent of age, sex and comorbidity.

Besides polypharmacy, several medications and comorbid conditions have been reported as risks for falls.[13–22] Among these, diabetes,[5,6] insomnia,[13] hypnotics,[13–15] antiarrhythmics[22] and antihypertensive agents[14] were not significantly associated with fall risk in the present study. Just 11 patients (45.9% of diabetic patients) were prescribed hypoglycemic agents, such as a sulfonylurea ($n = 8$) or insulin ($n = 3$), and the relatively low rate of prescription of hypoglycemic agents might have affected our result. Neither hypnotics nor antihypertensives were associated with falls. This result might be a result of the small sample size. Anti-arrhythmics were taken by just three patients (digoxin: $n = 2$, class IA anti-arrhythmic drug: $n = 1$). Other drugs, such as major tranquillizers,[14] antidepressants[17,18] and antiparkinsonian agents,[19,22] might increase fall risk; however, no patient used these drugs in the present study. In the present study, most of the patients were in a stable condition throughout the 2 years, though their drugs were changed gradually according to their medical conditions during the observation period. We only used the number of drugs at baseline for statistical analysis; however, the number of drugs increased from 3.2 ± 2.8 to 3.9 ± 3.0 during the 2 years. There were 17 patients whose number of drugs had been decreased, 70 patients not changed and 78 patients increased. The number of drugs after 2 years was also associated with falls ($P < 0.0005$). The optimal cut-off point for the number of drugs was again five (area under ROC curve 0.780, sensitivity 0.576, specificity 0.788). Furthermore, the changes in number of drugs were also associated with falls ($P < 0.05$), and the optimal cut-off point for the change in number of drugs was +1 (area under ROC curve 0.649, sensitivity 0.727, specificity 0.409).

Table 3 Logistic regression analysis of association between 2-year fall occurrences with two indices of fall tendency; 22 items fall risk index and 13 points simple screening test

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age (/year)	1.08 (1.03–1.15)**	1.06 (0.99–1.13)	1.06 (1.00–1.13)
Sex (male = 0, female = 1)	1.39 (0.56–3.48)	0.75 (0.23–2.43)	0.79 (0.24–2.56)
Osteoporosis ($n = 0$, Y = 1)	3.12 (1.43–6.84)**	2.56 (0.96–6.82)	2.61 (0.98–6.95)
No. comorbid conditions (/disease)	1.63 (1.14–2.32)*	1.24 (0.83–1.86)	1.32 (0.88–1.97)
Fall risk index (/item)	1.23 (1.11–1.37)***	1.12 (1.00–1.26)	–
Simple screening test (/point)	1.19 (1.06–1.33)**	–	1.14 (1.01–1.29)*

*$P < 0.05$, **$P < 0.005$, ***$P < 0.0005$. CI, confidence interval.

Consequently, polypharmacy, especially taking five or more drugs, should be considered a risk for falls.

There were several limitations of the present study. First, the falls were self-reported by the patients. Although all the patients had no overt dementia, they might have forgotten the incident of falling. We attempted to count the total fall occurrences in each patient; however, we could not differentiate the repeated falls in the second year from the fall occurrence in the first year. In fact, we asked 22 patients who reported falls in the first year about fall occurrence during the second year, but they did not accurately recall whether they experienced falls in the first or second year. Second, five patients were lost to follow up at 2 years for unknown reasons. The follow-up ratio was acceptable, although some of the patients might have fallen, have been no longer able to come to the clinic and moved to nursing homes. This might have slightly influenced the result. Also, the cause of falls in polypharmacy patients is not explained. Potentially inappropriate medications, which could cause adverse drug reactions, are usually seen in patients with polypharmacy, and falls might be the consequence of adverse drug reactions, such as dizziness, instability and light-headedness. Pathophysiological assessments and drug-reducing interventions are expected to elucidate the causal relationship.

Additionally, we showed that the 22-item fall risk index and its simple screening test were useful to predict falls in geriatric outpatients. Although both indices have been validated in community-dwelling elderly people, the present finding also showed their association with fall risk among geriatric outpatients. The difference of statistical significance between fall risk index and simple screening test might be a result of small sample size or the difference in the contribution of each item to total scores between the two indices. "Taking five or more drugs" accounts for only one item out of the 22-item fall risk index; in contrast, the same questionnaire accounts two points in the 13-point simple screening test. Because polypharmacy was a strong risk factor of falls in elderly outpatients in the present study, the proportion of polypharmacy in the scores might have caused the discrepancy. Taken together, it is likely that 13-point screening test was more suitable to our subjects who were taking several medicines.

In summary, the present study showed that geriatric outpatients with polypharmacy were at a high risk of falls, especially those receiving five or more drugs. Our finding might add new information for pharmacotherapy and geriatric research in elderly patients with chronic diseases. Intervention studies examining the effect of drug reduction for the prevention of falls are required in the future.

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Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Dietary pattern and mortality in Japanese elderly patients with type 2 diabetes mellitus: Does a vegetable- and fish-rich diet improve mortality? An explanatory study

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Aim: To assess the effect of dietary patterns on all deaths and diabetes-related deaths in the Japanese Elderly Diabetes Intervention Trial (J-EDIT).

Methods: We investigated relationships between that of overall mortality and dietary pattern, and diabetes-related deaths and dietary pattern as observed among 912 registered cases of the J-EDIT study, which is a prospective follow-up study of elderly Japanese type 2 diabetic patients.

Results: Factor analysis with the factor number 3 led to deriving three dietary patterns (healthy type, snack type and greasy type). The relationship between these patterns and overall mortality or diabetes-related death was investigated. Although not statistically significant, there was a lower tendency of overall mortality and diabetes-related deaths for the healthy type dietary pattern. When the tendencies of overall mortality were analyzed for "young-old," who are younger than 75 years-of age, and "old-old" of over 75 years-of-age, the mortality rate for the greasy type and healthy type dietary patterns were nearly the same and higher than the snack type dietary pattern in young-old. In contrast, in old-old, a higher mortality rate was reported for the greasy type dietary pattern and a lower mortality rate was reported for the healthy type dietary pattern. The hazard ratio by Cox regression analysis for greasy type to healthy type in old-old was 3.03 ($P = 0.04$, CI 1.07–8.57). Furthermore, in old-old, as vegetable consumption increased, the lower the tendency for overall mortality, and the more fish that was consumed, the overall mortality significantly decreased ($P = 0.020$) in the tertile.

Conclusions: The greasy type dietary pattern with an increased amount of sugar, fat and meat led to poor life prognosis for elderly Japanese type 2 diabetic patients. The healthy type dietary pattern rich in vegetable and fish, which is similar to the Mediterranean diet and Dietary Approach to Stop Hypertension diet, was suggested to improve life prognosis. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 59–67.**

Keywords: dietary pattern, elderly type 2 diabetes mellitus, mortality, sugar- fat- and meat-rich diet, vegetable- and fish-rich diet.

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Introduction

The relationship between diet and health is an ancient interest, and nutritional epidemiology is one of the important branches of epidemiology.[1] In the study of circulatory disease since World War II, "associations between food and disease" has become one of the major research topics, yielding important study results such as the over consumption of salt and saturated fatty acids being risk factors for arteriosclerosis.[2–4]

According to the Vital Statistics Survey, and the National Health and Nutrition Survey by the Japanese Ministry of Health, Labor and Welfare, the disease frequency patterns of modern Japanese are becoming similar to that of Europe and the USA, with the Westernization of diet characterized by increased meat and fat consumption. Studies on Japanese immigrants who moved to the USA and other countries showed that in the younger generations, their dietary and disease patterns resemble that of the general population in the country they live in, as observed in second generation Japanese and, to a greater degree, in the third generation.[5]

The recent research has focused more on dietary patterns to investigate the relationship between disease and diet, rather than the individual food, such as meat and fat or nutrient factors. We have seen favorable results of these approaches, such as the "Mediterranean diet" and "Dietary Approach to Stop Hypertension (DASH) diet," that were reportedly effective in reducing atherosclerosis.[6–11]

Based on these background findings, we have planned an explanatory study on the relationship between dietary pattern and mortality with the cases registered in a randomized comparative study of elderly diabetes patients and healthy life expectancy, the Japanese Elderly Diabetes Intervention Trial (J-EDIT.) We would like to caution that we present this study as an explanatory study based on 1000 participants from J-EDIT; as the majority of reports statistically investigated the effectiveness of dietary pattern had subject populations of tens of thousands to hundreds of thousands, and it was unknown how strongly we were able to hypothetically confirm the results.

Methods

Participants and follow up

The data at study registration and for the events from the subgroup of 912 cases with valid responses to the nutritional survey in J-EDIT were analyzed as the subjects.

The study design and the details of J-EDIT are described in the article by Araki *et al.*[12] in the present issue of the journal, and the details of the questionnaire for the nutritional survey are described in the article by Yoshimura *et al.*[13] and Kamada *et al.*[14] Following is a brief outline of the study: J-EDIT studied elderly type 2 diabetes patients, randomizing them to standard therapy or intensive therapy. It was a prospective randomized controlled trial that followed the patients for 6 years. A total of 39 facilities throughout Japan participated, and 1173 patients were registered from March 2001 to February 2002.

After the sixth year of follow up, the drop-out rate was 8.9%,[12] but considering that the participants are elderly, the follow-up rate is excellent (death is treated as a cut-off in the calculation for the drop-out rate).

Data on diet

For the 912 patients that submitted consent at the start of survey, the nutritional survey was carried out using a questionnaire for the frequency of food intake developed by Yukio Yoshimura *et al.* of Shikoku University.[13] Various data were obtained; however, for the present study, we focused on the data for the amount of food intake that classified the food into 16 classes adjusted for the energy contents (see Table 1).

Clinical measurements and end-points

At the time of patient registration, information such as health history, anthropometric measurements (body

Table 1 Factor analysis of Food Frequency Questionnaire Based On Food Groups data

	Factor pattern		
	Factor1	Factor2	Factor3
Grains	−0.01381	−0.62273	−0.20002
Nuts	−0.00282	0.26514	−0.32125
Potato	0.06179	0.43822	−0.20527
Sugar	0.02085	0.55776	0.04851
Cake	−0.65543	0.46833	−0.09534
Fat	−0.09459	0.21467	0.45972
Beans	0.38596	−0.04934	−0.35434
Fruit	0.00396	0.4124	−0.30199
Vegetables	0.67618	0.2742	0.0019
Other vegetables	0.66522	0.32309	0.03519
Seaweed	0.54044	0.16768	−0.07672
Seasoning	−0.36263	0.18651	−0.16649
Fish	0.40058	−0.04679	−0.3489
Meat	0.11449	−0.0528	0.72903
Egg	0.02962	−0.09866	0.31668
Milk	−0.00566	−0.21447	0.21014

Rotation method: Promax (power = 3). Factor 1 vegetables, other vegetables, seaweed, fish: "healthy". Factor 2 sugar, cake, potato, fruit, less grain: "snack". Factor 3 meat, fat: "greasy".

height, bodyweight, waist and hip circumferences) and blood biochemical examination were obtained. End-points were death as a result of myocardial infarction, cardiac sudden death, cerebrovascular disorders, renal failure, hypoglycemia or hypoglycemia, unexpected accident, malignant neoplasm, pneumonia and other causes. For analysis, we created two groups as follows, which were treated as composite endpoints: (i) all deaths – included nine kinds of all fatal events; and (ii) diabetes-related deaths – out of nine fatal events, five kinds including myocardial infarction, cardiac sudden deaths, cerebrovascular disorders, renal failure and deaths caused by hypoglycemia or hyperglycemia were selected. For analyzing diabetes-related deaths, four kinds of deaths other than diabetes-related deaths (unexpected accident, malignant neoplasm, pneumonia an other causes) were treated as cut-offs.

Statistical analysis

For the nutritional data, the overall tendency was studied by principal component analysis. Based on this result, oblique factor analysis (Promax rotation) with the factor number of three was carried out. From the results of factor analysis, three dietary patterns were extracted, and the background data for each dietary pattern were described. Also, Cox regression analysis including several adjustment factors was carried out.

All analysis was carried out using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

The detailed report on nutrition as a whole is reported in the present issue of the journal by Yoshimura *et al.* and Kamada *et al.*[13,14] In these reports, using the data of food intake that classified food into 16 classes, multivariable analysis was carried out, and from the dietary pattern obtained, the relationship to mortality was studied. Although the study design for the J-EDIT was a randomized control study by two groups, in which elderly diabetes patients were randomly allocated to standard therapy or intensive therapy,[12] there was no significant difference in the distribution of dietary patterns in the two groups (data not shown); therefore, we combined the two groups and analyzed them as a single cohort in the present.

Dietary patterns

First, the principal component analysis was carried out (data not shown). The cumulative contribution ratio was approximately 33% up to the third eigenvector, and 54% up to the sixth eigenvector. For the first eigenvector, there was a great contribution from green and yellow vegetables, other vegetables and mushrooms, seaweeds, fish, and beans. For the second eigenvector, the contribution from sugars, fats and meats was great. The third eigenvector was fruits, nuts, sweets (confectionaries), seasonings and articles for tastes. It was difficult to extract clear characteristics for the fourth eigenvector or greater.

From these results, we classified the dietary patterns into three groups, and carried out the factor analysis of three factors. Table 1 shows the results of the Promax rotation.

We interpreted these results suggest that group one is subjects who consume a large amount of green and yellow vegetables, other vegetables and mushrooms, seaweeds, fish, and beans; thus we determined the group as the fish and vegetable type. The third group was interpreted as the meat-diet type, consuming a large amount of meats and fats. The second group was notable for the intake of sweets, potatoes and fruits, with a large amount of fish and meat consumption and a low amount of grain; thus we determined that group as the snack and side-order type. We called the first group the "healthy type," the second group "snack type" and the third group "greasy type" based on their characteristics. The numbers of subjects in each group were: 328 in healthy type, 268 in snack type and 316 in greasy type.

Background data of each dietary pattern group

The backgrounds of the subjects by the dietary pattern are shown in Table 2. The age distribution was very similar in all dietary patterns. Bodyweight and body mass index (BMI) were slightly higher in the snack group; however, the difference was not clinically meaningful. No major difference was observed in glycated hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) levels among the three groups; however, the rate of receiving insulin therapy and no medication was low in the snack group, and a large percentage of patients reported taking oral antihyperglycemic drugs. No significant difference in other items was found in the three groups.

The frequencies of the history of ischemic heart disease were all within 15–17% and there was no difference in the three groups. The history of cerebrovascular disease in the greasy type group was 15%, and compared with that of 10% in the healthy group and 12% in the snack group, it was high a value; however, there was no significant difference between the groups.

Table 2 Baseline characteristics for the three dietary groups

	Healthy ($n = 328$)	Snack ($n = 268$)	Greasy ($n = 316$)	P-value*1
Male/female	144/184	112/156	160/156	
Age (SD)	71.7 (468)	71.8 (4.72)	71.9 (4.66)	
	Mean (SD)	Mean (SD)	Mean (SD)	
Height	155.1 (8.0)	155.2 (8.5)	156.4 (9.0)	0.09
Weight	56.8 (9.6)	58.9 (10.1)	58.4 (10.3)	0.027*2
BMI	23.6 (3.2)	24.4 (3.5)	23.6 (3.4)	0.02*3
Waist	82.7 (10.2)	84.6 (9.8)	84.3 (10.3)	0.06
Hip	93.6 (8.1)	94.1 (7.8)	93.9 (7.9)	0.69
HbA1c	8.0 (0.8)	8.1 (0.9)	8.1 (1.0)	0.66
FPG	166.3 (48.5)	166.4 (50.4)	169.4 (51.9)	0.71
T-chol	202.5 (34.3)	202.1 (35.7)	203.4 (36.0)	0.90
TG	124.3 (70.8)	137.0 (75.0)	140.1 (114.5)	0.06
HDL-chol	57.1 (18.9)	56.0 (19.2)	55.9 (16.6)	0.67
LDL-chol	121.8 (29.1)	118.6 (32.8)	120.5 (31.5)	0.47
SBP	137.8 (15.7)	135.2 (16.0)	136.2 (15.9)	0.14
DBP	74.8 (9.7)	74.6 (10.0)	75.2 (10.0)	0.78
Alb	4.2 (0.4)	4.2 (0.3)	4.2 (0.3)	0.08
Serum Cr	0.8 (0.2)	0.9 (0.6)	0.8 (0.3)	0.06
Urine A/C	198.2 (586.1)	215.1 (558.7)	209.3 (581.7)	0.94
eGFR	66.3 (17.0)	65.4 (21.7)	66.2 (18.9)	0.82
Past history, *n* (%)				
Ischemic heart disease	51 (15.6)	41 (15.3)	55 (17.4)	0.74
Cerebrovascular disease	34 (10.4)	33 (12.3)	49 (15.5)	0.14
Mode of therapy for diabetes mellitus, *n* (%)				
No medication	39 (11.9)	21 (7.8)	30 (9.5)	0.027*4
Oral antihyperglycemic drug	189 (57.6)	185 (69.0)	184 (58.2)	
Insulin	100 (30.5)	62 (23.1)	102 (32.3)	
Medication for dyslipidemia	117 (36.1)	119 (44.6)	124 (39.4)	0.11
Medication for hypertension	189 (58.3)	152 (57.4)	175 (55.7)	0.79
Smoking, *n* (%)				
Current	48 (15.5)	36 (14.3)	49 (16.4)	0.50
Former	85 (27.4)	75 (29.9)	99 (33.1)	
Never	177 (57.1)	140 (55.8)	151 (50.5)	

*1*P*-value for general association between the row and column variables. *2*P*-value of *t*-test 0.101 (healthy *vs* snack), 0.051 (healthy *vs* greasy). *3*P*-value of *t*-test 0.016 (healthy *vs* snack), 0.966 (healthy *vs* greasy). *4*P*-value of χ^2-test 0.015 (healthy *vs* snack), 0.595 (healthy *vs* greasy). Alb, albumin; BMI, body mass index; Cr, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T-chol, total cholesterol; TG, triglyceride.

Table 3 Diet pattern and all death events

Group	MI	Sudden death	CVD	Renal failure	Hyper-, hypo-glycemia	Accident	Malignant neoplasm	Pneumonia	Others	Total
Healthy	3	4	1	0	0	0	9	3	3	**23**
Snack	4	1	1	1	1	0	5	0	3	**16**
Greasy	3	5	3	0	0	0	11	1	5	**28**
Total	10	10	5	1	1	0	25	4	11	**67**

CI, coronary intervention; CVD, cerebrovascular disease; HF, heart failure; MI, myocardial infarction.

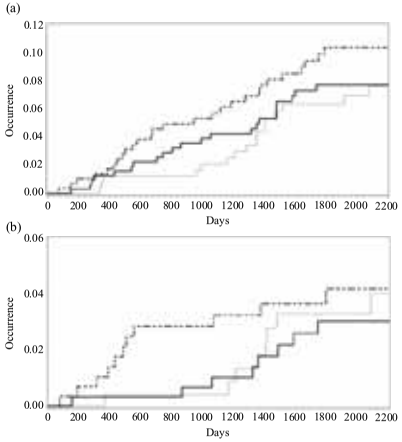

Figure 1 Kaplan–Meier curves for dietary pattern and the events that occurred. a) Overall mortality. b) Diabetes-related deaths.

Dietary patterns and events

The numbers of fatal events for each dietary pattern are shown in Table 3. No clear difference was observed in types of fatal events and the number occurred.

Survival analysis

Figure 1 shows the Kaplan–Meier curve of overall mortality and diabetes-related deaths. Both overall mortality and diabetes-related deaths were not significantly different between the groups ($P = 0.35$ for overall mortality and $P = 0.35$ for diabetes-related deaths, log–rank test for three groups), although the results show that there was a tendency of more deaths reported in the greasy type group, and less in the healthy or snack type groups.

Cox regression analysis of overall mortality and diabetes-related deaths, adjusted for several factors, were carried out. The only factors that showed significance were age and sex for overall mortality and age for diabetes-related deaths, and despite the large hazard ratio in dietary pattern and death between the greasy type and healthy type, there was no significant relationship (Table 4).

Young-old versus old-old

As suggested from the results of Cox regression analyses, age is a significant factor for both overall mortality and diabetes-related deaths. In order to lessen the effect of age, we investigated the relationship between diet and overall mortality or diabetes-related deaths by dividing the subjects into younger than 75 years-of-age (young-old) or 75 years-of-age or older (old-old) at the time of registration.

Figure 2 shows the relationship between overall mortality and dietary pattern by Kaplan–Meier curve. Among the young-old, the mortality rate for greasy type and healthy type were nearly equal, and higher than snack type; however, among the old-old, higher numbers of all cause deaths occurred in greasy type, and healthy types showed notable tendencies of a lower mortality rate. The results of the log–rank test did not identify the significant difference between the mortality rates of young-old in the three groups ($P = 0.62$); however, the mortality was lower compared with other types in the healthy type of old-old, and the difference was significant ($P = 0.05$). According to the Cox regression analyses of old-old, the hazard ratio of greasy type to healthy was 3.03 ($P = 0.04$, CI 1.07–8.57). Although there is no statistical difference, diabetes-related deaths also showed similar results that the healthy type had lower mortality (data not shown).

Vegetable, fish intake and events

The characteristic of healthy type is the high intake of vegetables and relatively high intake of fish. Therefore, we classified these two items (with adjustment for

Table 4 Cox regression

Variables	Hazard ratio	All death CI	*P*-value	Hazard ratio	DM-related death CI	*P*-value
Age (for 1 age)	1.10	(1.04–1.15)	<0.001	1.13	(1.04–1.22)	<0.001
Sex (female/male)	0.50	(0.30–0.83)	<0.001	0.49	(0.22–1.08)	0.08
HbA1c (for 1%)	1.04	(0.80–1.35)	0.79	1.21	(0.88–1.68)	0.24
SBP (1 mmHg)	1.01	(0.99–1.02)	0.50	1.00	(0.98–1.02)	0.93
Past History (Ischemic Heart Disease) with/without	0.94	(0.49–1.80)	0.84	1.25	(0.50–3.12)	0.63
Past History (Cerebrovascular Disease) with/without	1.25	(0.65–2.39)	0.51	2.04	(0.85–4.87)	0.11
Snack group / Healthy group	0.95	(0.50–1.81)	0.88	1.26	(0.47–3.38)	0.64
Greasy group / Healthy group	1.31	(0.75–2.31)	0.35	1.40	(0.56–3.51)	0.47

HbA1c, glycated hemoglobin A1c; SBP, systolic blood pressure

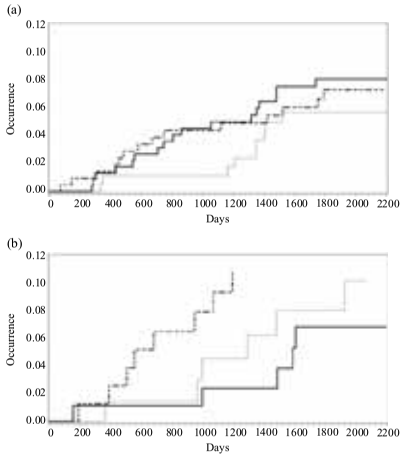

Figure 2 Kaplan–Meier curve for dietary pattern and overall mortality. a) Young-old (65 years-of-age or older to less than 75 years-of-age) b) Old-old (75 years-of-age or older, $n = 258$). The mortality rate for the healthy type dietary pattern in old-old was significantly low ($P = 0.05$) compared with other groups.

energy) into tertile, and investigated the relationship to overall mortality separately for young-old and old-old. In the tertiles for vegetable intake, no clear tendency was observed in young-old; however, in the old-old, we observed the tendency of lower mortality rate in the group with the larger amount of vegetable intake ($P = 0.24$, log–rank test for three groups. Fig. 3a,b, Table 5).

Also for the tertiles for fish intake, we did not observe a notable tendency, but there was a significant difference between the groups in old-old ($P = 0.020$, log–rank test), showing that higher intake reduced mortality. By Cox regression analysis using the same adjustment factors as the previous section, the hazard rate of the medium intake group to low intake group was 0.35 ($P = 0.035$), and 0.43 for the high intake group ($P = 0.12$, Fig. 3c,d, Table 5).

Discussion

The relationship between diet and disease has been discussed since ancient times, but the relationship between particular dietary patterns, such as the Mediterranean diet or DASH diet, and various diseases, such as arteriosclerosis and cancers, and the relationship to life prognosis have become the focus of active discussion from the beginning of the year 2000. These dietary patterns that have been said to be "good for health" have much in common with the diet of the healthy type we observed from the present diet survey.

The characteristics of the Mediterranean diet is a high intake of vegetables, beans, fruits, nuts, grains and olive oil, and a relatively high intake of fish, low to medium intake of dairy products, and low intake of meats.[7] The foods that compose the DASH diet are also similar in general, and in brief, the program encourages adequate intake of vegetable, fruits and low-fat dairy products, and reduced intake of meats and sugars.[15,16] The diet of the healthy type observed as the results of this analysis was characterized by the high intake of vegetables and seaweeds, and the relatively high intake of fish and beans, but the intake of meats, fats and sugars remained low. In contrast, the greasy type was characterized by the high intake of meats and fats. Despite the large difference in ethnicities and the geographies where the Mediterranean diet and DASH diet were born, it is of particular interest that very similar dietary patterns were observed.

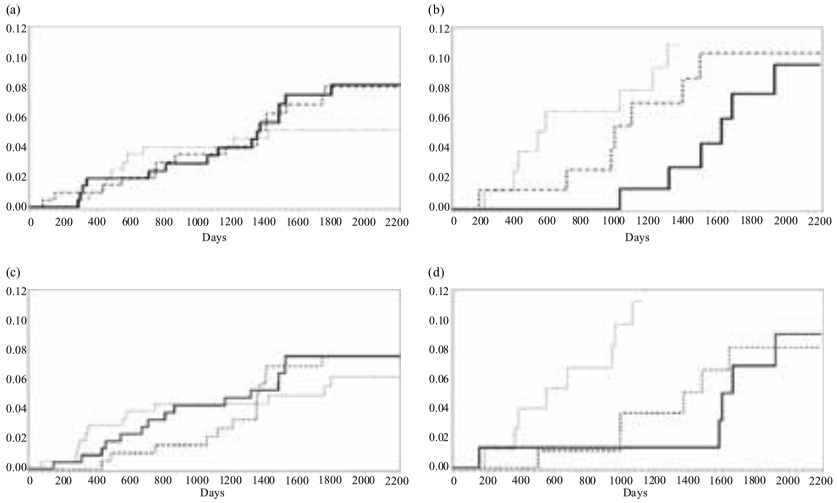

Figure 3 Kaplan–Meier curve for vegetable intake, fish intake and overall mortality. (a) Vegetable intake, young-old. b) Vegetable intake, old-old. (c) Fish intake, young-old. (d) Fish intake, old-old. Lower mortality rate was observed in old-old if vegetable intake was high. Also, when the fish intake was high, mortality rate was significantly low ($P = 0.0195$). Hazard rates for old-old to the amount of fish intake were 0.34 ($P = 0.0352$) for the group of medium amount intake, and 0.429 ($P = 0.117$) for high intake.

Table 5 Food Intake and all death

	Intake					
	Vegetable			Fish		
	P-value	Hazard ratio	CI	*P*-value	Hazard ratio	CI
All						
Log–rank	0.97	–	–	0.48	–	–
Middle intake (*vs* low intake)	0.86	1.06	(0.58–1.91)	0.29	0.72	(0.40–1.31)
High intake (*vs* low intake)	0.89	1.05	(0.57–1.91)	0.50	0.82	(0.46–1.47)
Young-old						
Log–rank	0.55	–	–	0.87		–
Middle intake (*vs* low intake)	0.34	1.49	(0.66–3.34)	0.70	1.17	(0.53–2.58)
High intake (*vs* low intake)	0.24	1.62	(0.73–3.63)	0.50	1.30	(0.61–2.77)
Old-old						
Log–rank	0.24	–	–	**0.0195***	–	–
Middle intake (*vs* low intake)	0.25	0.58	(0.22–1.48)	**0.0352***	**0.35**	**(0.13–0.93)**
High intake (*vs* low intake)	0.24	0.55	(0.20–1.49)	0.12	0.43	(0.15–1.24)

*P-value < 0.05.

We compared the background data for each dietary pattern, but there was no clear difference in the factors that possibly influence when comparing the pathogenesis of events.

As for the events that occurred in each dietary pattern, when all including young-old and old-old were subjected, statistically significant results were not obtained; however, we observed the tendency for more

deaths to occur in the greasy type and less in the healthy type in both analyses for overall mortality and diabetes-related deaths (Fig. 1).

From the Cox regression analyses adjusted by several factors, age was the highly significant factor. Considering the fact that the participants of the present study were a group of "elderly diabetes patients," we divided the subjects into young-old and old-old, and a Kaplan–Meier curve was drawn for overall mortality. As a result, the mortality rate for the greasy type and healthy type were almost equivalent, and higher in the snack type in young-old; however, in old-old, a higher mortality rate was reported in the greasy type, but a lower tendency was notable in the healthy type.

These findings suggested that the greasy type diet that includes a large amount of sugars, fats and meats is a factor for poor life prognosis, and the healthy type diet for elderly, especially for old-old, might reduce the occurrence of all deaths and diabetes-related deaths.

As the mechanism for these phenomena, we consider that with the greasy type dietary pattern, the risk of causing poor lipid metabolism, glucose metabolism and increased obesity, and aggravating arteriosclerosis are increased. In contrast, with the healthy type dietary pattern these would be improved or decreased.[17–19] However, J-EDIT subjects are Japanese and their BMI were not inherently very high. As shown in Table 2, the BMI are close to 24 in all dietary patterns. Therefore, we consider BMI was not the major contributor for the improved prognosis. Being diabetes patients of advanced age originally meant they were, in a way, long-term survivors. In particular, the old-old are long-term survivors and likely to be long-term patients of diabetes. However, taking these facts into account, the dietary patterns and mortality rates still showed a certain amount of tendencies. Therefore, we think dietary habit is of importance as one of the factors that determine life prognosis.

The characteristics of the healthy type dietary pattern are high intake of vegetables and seaweeds, and relatively high intake of fish. The analyses of vegetable and fish intake by tertiles (Fig. 3, Table 5) suggests that elderly, especially old-old, showed an inverse relationship of increased vegetables and fish consumption, and mortality pattern. This result is in agreement with previously reported studies.[20–22] This finding also strongly agrees with the report by Takahashi *et al.* published in the present issue of the journal, that concluded that an adequate amount of vegetable intake might lead to favorable control of blood glucose or triglyceride values.[23]

The reason for the relationship between the healthy type dietary pattern and better prognosis observed in old-old is not clear at this moment. Being able to eat an adequate amount of vegetables means the person retains healthy mastication ability. Such reversal of cause and effect might be considered as well. Also, the association of activated immune functions by vegetables,[24] an idea that is the current subject of active discussion, might be a possibility.

We have extracted three dietary patterns (healthy type, snack type and greasy type) from the diet survey of J-EDIT and life prognosis for the greasy dietary pattern with high intake of sugars, fats and meats is poor. In contrast, the patients in the healthy type dietary pattern group with a high intake of vegetables and fish will likely become the long-term survivors. The healthy type dietary pattern, with a high intake of vegetables and fish, has many similarities with the Mediterranean diet and DASH diet, and tends to have a lower number of death events occur compared with other types. Thus, the present results show the influence of dietary pattern on life prognosis cannot be neglected in elderly Japanese patients with type 2 diabetes.

The major limitation of the present study was the small number of subjects. Previous studies showing the importance of dietary patterns scaled the numbers of subjects in the tens of thousands to hundreds of thousands. The reasons we consider for not being able to obtain significance in the results of the present study are that this was a group of elderly patients, and the small size of the study; with fewer than 1000 patients, when limited to the old-old, the numbers of cases was 258. Estimation for the number of subjects to detect a statistically significant relationship between diabetes-related deaths and dietary pattern based on the data from the present study is as follows: assuming that diabetes-related death occurs in 1% in 1 year in the healthy type dietary pattern, the clinically significant hazard ratio of the greasy type dietary pattern is 1.25, and 6-year follow up is expected as in the present study, therefore a minimum of 15 000 cases is necessary. We hope that such a study will be carried out.

Acknowledgments

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Conflict of interest

The J-EDIT Study Group has not cleared any potential conflicts.

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ORIGINAL ARTICLE

Risk factors associated with cognitive decline in the elderly with type 2 diabetes: Baseline data analysis of the Japanese elderly diabetes intervention trial

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Aim: Recent evidence has shown that type 2 diabetes mellitus (T2DM) in the elderly is a risk factor for cognitive dysfunction or dementia. However, the precise mechanisms have not yet been elucidated. In the current study, we attempted to elucidate the association of clinical indices and diabetic complications at baseline with cognitive declines after 6-year follow up in type 2 diabetic elderly.

Methods: The subjects were 261 participants who were administered the Mini-Mental State Examination (MMSE) at baseline and after 6 years, at the end of the observation period. The cognitive decline was determined as a 5-point or greater decline in MMSE scores during the observation period. Logistic regression analysis to find the factors associated with cognitive decline, adjusted for age and sex, were carried out, and factors with *P*-values of less than 0.2 were included in four models of multiple logistic regression analysis.

Results: We found that the existence of diabetic nephropathy, higher systolic blood pressure and higher serum triglycerides (or lower high-density lipoprotein cholesterol) at baseline were significantly associated with cognitive declines after 6 years in Japanese elderly diabetics in all four models.

Conclusion: The comorbidity of diabetic nephropathy, hypertension and hypertriglyceridemia at baseline were associated with more than 5-point declines in MMSE. Elucidation of the underlying mechanisms of this association is warranted. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 103–109.**

Keywords: diabetic nephropathy, high-density lipoprotein cholesterol, Mini-Mental State Examination, systolic blood pressure, triglycerides.

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Introduction

Recent evidence has shown that type 2 diabetes mellitus (T2DM) in the elderly is a risk factor for cognitive dysfunction or dementia.[1] However, the precise mechanisms underlying T2DM-related cognitive dysfunction or the development of dementia have not yet been elucidated.

Higher blood glucose itself is a risk for cognitive impairment. A large-scale follow-up study in type 1 DM, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, showed that higher glycated hemoglobin A1c (HbA1c) levels are associated with cognitive decline.[2] Data from a relatively short-term intervention study also suggest that the status of glycemic control might ameliorate cognitive performance.[3,4]

DM is a disease involving the impairment of glycemic metabolism, but it is also a complex metabolic disorder and is often comorbid with several other metabolic disturbances, including hypertension and dyslipidemia,[5] which themselves are vascular risk factors. These disturbances have been reported to be associated with cognitive dysfunction in diabetics.[6] Some studies have shown an association between blood pressure and the prevalence of dementia.[7,8] Dyslipidemia has also been reported to be associated with cognitive dysfunction.[9,10]

Furthermore, diabetes is associated with microvascular complications (retinopathy, nephropathy, neuropathy), and these are also reportedly associated with cognitive dysfunction.[11–14]

Although, as aforementioned, several factors have been hypothesized to contribute to diabetes-related cognitive dysfunction, to our knowledge there have been few studies in which the cognitive declines in elderly diabetics were prospectively observed.

In the current study, we attempted to elucidate the association of vascular risk factors and complications at baseline with cognitive declines after a 5-year follow up in diabetic elderly.

Methods

Participants

The subjects were 261 Japanese Elderly Interventional Trial (J-EDIT)[15] participants who were administered the Mini-Mental State Examination (MMSE) at baseline and at the end of the 6-year observation period. The study protocol was approved by the ethical committees at all of the enrolled institutions, and written informed consent was obtained from each patient.

Functional assessment

The MMSE was administered to most patients on registration.[16] The second assessment was carried out at the end of the 6-year observation period. The MMSE is a global test of orientation, attention, calculation, language and recall with a score of 0–30.

Depressive mood was assessed by a short version of the Geriatric Depression Scale (GDS-15).[17]

Assessment of diabetes mellitus, complications and comorbidities

The diagnosis and patient data regarding DM, blood examinations and complications were obtained from the clinical charts.[18] After overnight fasting, blood samples were taken by venipuncture to assess serum levels of glucose, HbA1c, total cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL-C). The value for HbA1c (%) is estimated as a National Glycohemoglobin Standardization Program equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society) (%) + 0.4%.[19] Diabetic nephropathy was assessed according to the mean urinary albumin-to-creatinine ratio (ACR) and was classified as no nephropathy (ACR < 30 μg/mg) or the existence of nephropathy (microalbuminemia: 30 ACR < 300 μg/mg or more advanced). Diabetic retinopathy was assessed by fundoscopic examination carried out through dilated pupils by experienced ophthalmologists, and was classified into two categories: mild (no retinopathy or intraretinal hemorrhages and hard exudates), or serious (soft exudates, intraretinal microvascular abnormalities, venous calibre abnormalities, venous beading, neovascularization of the disc or other areas in the retina, preretinal fibrous tissue proliferation, preretinal or vitreous hemorrhage and/or retinal detachment). Diabetic neuropathy was defined as either the loss of the Achilles tendon reflex without neuropathic symptoms including paresthesia, or the presence of neuropathic symptoms.

Statistical analysis

A 5-point or greater decline in MMSE during the 6 years was defined as a significant cognitive decline.[20] Descriptive statistics for baseline-characteristics in patients with and without cognitive decline were compared by χ^2-tests or *t*-tests. Logistic regression analyses were carried out to find the factors associated with cognitive decline over the 6-year period. For the first of the analyses, logistic regression models for baseline variables were separately fitted, all of which included age at baseline, sex and GDS-15 scores, and items with the *P*-value of <20% were used for the next analyses. We then specified several combinations of the items used and fitted multiple logistic regression models corresponding to them, in which a *P*-value of <5% was considered to be statistically significant. All analyses were carried out with SAS software (version 9.1.3; SAS Institute, Cary, NC, USA).

Results

Table 1 summarizes the baseline characteristics of the patients with or without declines of 5 points or greater MMSE scores. There were no significant differences in terms of the medication profile. Previous clinical incidence of stroke was recorded in three patients out of 23 in the cognitive decline group and 19 patients out of 238 in the cognitively preserved group. MMSE at baseline also showed no difference between the groups. Patients with cognitive decline were significantly older, and had higher systolic blood pressure (SBP), triglycerides (TG), lower HDL-C and serum albumin, and more nephropathy, retinopathy and neuropathy.

A total of 20 patients had stroke during the observation in the group without cognitive decline (238 in total), whereas three out of 23 patients with cognitive decline did so ($P = 0.453$ by χ^2-test).

To find the factors associated with more than 5-point declines in MMSE over the 6-year period, logistic regression models adjusted by age, sex and GDS-15 scores were fitted separately for baseline variables listed in Table 1.

The factors associated with MMSE declines ($P < 0.02$) were SBP, TG, HDL-C and the existence of diabetic nephropathy, retinopathy and neuropathy (Table 2).

We constructed four multiple logistic regression models to determine the predictors of cognitive decline,

Table 1 Baseline characteristics by Mini-Mental State Examination decline status (subjects without information on diabetes complications were excluded)

	All subjects ($n = 261$)	5-point decline in MMSE		P-value‡
		Yes ($n = 23$)	No ($n = 238$)	
Sex (male)*	111 (42.5)	10 (43.5)	101 (42.4)	0.923
Age at baseline† (years)	70.6 (4.3)	72.8 (5.4)	70.4 (4.1)	0.010
MMSE	28.6 (2.1)	28.0 (2.0)	28.6 (2.1)	0.218
HbA1c (%)†	8.0 (0.8)	8.0 (0.7)	8.1 (0.8)	0.734
TC (mg/dL)†	202.4 (32.1)	207.8 (44.7)	201.9 (30.7)	0.402
TG (mg/dL)†	127.4 (70.0)	161.3 (84.2)	124.1 (67.7)	0.015
HDL (mg/dL)†	57.1 (17.1)	50 (11.9)	57.7 (17.4)	0.039
LDL (mg/dL)†	120.7 (29.3)	125.5 (37.3)	120.3 (28.5)	0.415
Albumin (mg/dL)†	4.2 (0.3)	4.1 (0.4)	4.3 (0.3)	0.032
Hypertension (presence)*	179 (68.6)	19 (82.6)	160 (67.2)	0.129
SBP (mmHg)†	134.9 (14.9)	144 (21.4)	134 (13.9)	0.002
DBP (mmHg)†	74.5 (9.3)	75.0 (9.5)	74.5 (9.3)	0.826
Weight circumference (cm)†	82.7 (10.0)	85.7 (10.5)	82.5 (9.9)	0.157
BMI (kg/m^2)†	23.6 (3.5)	23.7 (3.0)	23.6 (3.5)	0.839
Nephropathy (presence)*	33 (12.6)	8 (34.8)	25 (10.5)	<.001
Retinopathy (presence)*	110 (42.1)	15 (65.2)	95 (39.9)	0.019
Neuropathy (presence)*	170 (65.1)	20 (87.0)	150 (63.0)	0.021
Stroke history (presence)*	22 (8.4)	3 (13.0)	19 (8.0)	0.404
IHD history (presence)*	33 (12.6)	3 (13.0)	30 (12.6)	0.952
Smoking at baseline*	42 (16.9)	5 (23.8)	37 (16.3)	0.380
Current drinker at baseline*	148 (56.7)	13 (56.5)	135 (56.7)	0.985
Ex-drinker at baseline*	80 (30.7)	6 (26.1)	74 (31.1)	0.619
Insulin use (presence)*	78 (29.9)	11 (47.8)	67 (28.2)	0.049
Hypoglycemia (presence)*	75 (28.7)	10 (43.5)	65 (27.3)	0.102
Received antihypertensive drug at baseline*	139 (53.3)	13 (56.5)	126 (52.9)	0.742
Received antihyperlipidemic drug at baseline*	108 (41.4)	9 (39.1)	99 (41.6)	0.819
Received ACE inhibitor at baseline*	49 (18.8)	6 (26.1)	43 (18.1)	0.347
Received statin drug at baseline*	13 (5.0)	2 (8.7)	11 (4.6)	0.391
Received fibrate drug at baseline*	7 (2.7)	1 (4.3)	6 (2.5)	0.605
Received ACE inhibitor or ARB at any timing*	157 (60.2)	18 (78.3)	139 (58.4)	0.063
Received statin drug at any timing*	154 (59)	13 (56.5)	141 (59.2)	0.800

n (%). †Mean (SD). ‡P-values are based on χ^2-test for binary data (symbol) and t-test for continuous data (symbol†). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL, high density lipoprotein cholesterol; IHD, ischemic heart disease; LDL, low density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 2 Results of logistic regression analysis adjusted by age and sex

	Odds ratio (95% CI)	P-value
BMI (kg/m2)	0.96 (0.82–1.13)	0.638
Waist circumference (cm)	1.03 (0.97,1.08)	0.338
SBP (per 10 mmHg)	1.43 (1.06,1.92)	0.019
DBP (per 10 mmHg)	1.11 (0.67,1.81)	0.691
Hypertension	1.92 (0.62,5.95)	0.260
Insulin use	1.25 (0.49,3.19)	0.634
FBS (mg/dL)	1.00 (0.99,1.01)	0.704
HbA1c (%)	1.03 (0.62,1.72)	0.901
TC (per 10 mg/dL)	1.07 (0.95,1.22)	0.267
TG (per 10 mg/dL)	1.07 (1.01,1.12)	0.013
HDL-C (per 10 mg/dL)	0.66 (0.47,0.93)	0.018
Albumin (g/dL)	0.61 (0.2,1.88)	0.391
Retinopathy	2.02 (0.81,5.07)	0.133
Nephropathy	2.37 (0.82,6.91)	0.113
Neuropathy	4.38 (0.98,19.58)	0.053
Stroke	1.10 (0.29,4.18)	0.889
IHD	0.53 (0.11,2.46)	0.418
Hypoglycemia	1.79 (0.71,4.49)	0.217
Smoker	1.87 (0.56,6.24)	0.310
Current Drinker	1.03 (0.32,3.31)	0.965
Ex-Drinker	2.14 (0.52,8.77)	0.290

BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IHD, ischemic heart disease; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

adjusting MMSE decline-associated factors simultaneously (Table 3). As a result of the possible colinearity between TG and HDL-C, either of these two factors was used in the model. All four models were adjusted for age, sex and GDS-15. Model 1 included SBP, TG and the existence of nephropathy. Model 2 included the existence of retinopathy instead of nephropathy. Model 3 included the existence of neuropathy instead of nephropathy or retinopathy. Model 4 included SBP, TG and the existence of nephropathy, retinopathy and neuropathy. Table 3 shows the results of multiple logistic regression analyses. In each model, SBP, TG and the existence of diabetic nephropathy were significantly associated with more than 5-point declines in MMSE during the 6-year period. The adoption of HDL-C instead of TG into the multiple logistic regression analyses showed similar results.

Discussion

In the current study, we found that the existence of diabetic nephropathy, higher systolic blood pressure and higher serum TG or HDL-C at baseline are significantly associated with cognitive decline over a 6-year period in Japanese elderly diabetics.

The mechanism of the association between diabetic nephropathy and cognitive decline remains to be elucidated. Several observational studies reported that nephropathy or microalbuminuria was a risk factor for cognitive decline.[21,22] Microalbuminuria has been reported to be a risk factor for cerebral small vessel disease (lacunae and white matter lesions),[23] and cerebral small vessel disease is one of the major causes of cognitive impairment.[24,25] In diabetic patients, diabetic nephropathy, endothelial dysfunction and inflammation are reportedly mutually interrelated;[26] and these factors might affect cognition. Inflammation[27,28] and endothelial dysfunction[29,30] are both reportedly associated with cognitive dysfunction. Our previous study, which analyzed the association between clinical indices and baseline MMSE scores, showed that the existence of diabetic nephropathy was associated with lower baseline MMSE scores in this same cohort.[31]

Hypertension was also associated with cognitive declines in the current study. Several studies have shown that the combination of hypertension and diabetes exacerbates the cognitive function.[32,33] The underlying mechanism of the association between hypertension and cognitive impairment in diabetics might include cerebrovascular diseases and vascular dysfunction. It has been known that hypertension facilitates vascular occlusion and compromises cerebral infarction,[34–37] including small silent ones. Cerebrovascular alterations precede the cognitive declines.[38]

Table 3 Results of multiple logistic regression analysis

	Model 1		Model 2		Model 3		Model 4	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
TG (per 10 mg increase) or HDL-C (per 10 mg increase)	1.07 (1.01–1.14) 0.67 (0.45–0.98)	0.018 0.038	1.06 (1.00–1.13) 0.68 (0.47–1.00)	0.045 0.052	1.07 (1.00–1.13) 0.70 (0.48–1.01)	0.036 0.055	1.07 (1.01–1.14) 0.71 (0.49–1.03)	0.029 0.072
(TG) SBP (per 10 mmHg increase)	1.46 (1.04–2.05)	0.030	1.47 (1.05–2.06)	0.024	1.52 (1.08–2.13)	0.016	1.44 (1.02–2.04)	0.037
(HDL)	1.42 (1.0–2.0)	0.048	0.70 (0.48–1.01)	0.055	1.47 (1.04–2.08)	0.031	1.41 (1.00–1.99)	0.053
(TG) Existence of nephropathy	4.48 (1.28–15.67)	0.019	–	–	–	–	3.72 (1.02–13.65)	0.047
(HDL-C) (TG) Existence of retinopathy	4.06 (1.17–14.05) –	0.027 –	2.76 (0.95–8.01)	0.063	– –	– –	3.22 (0.89–11.59) 2.09 (0.68–6.38)	0.074 0.196
(HDL-C) (TG) Existence of neuropathy	– –	– –	2.78 (0.96–8.08) –	0.060 –	– 4.42 (0.95–20.62)	– 0.058	2.08 (0.68–6.33) 4.09 (0.86–19.45)	0.198 0.077
(HDL-C)					4.24 (0.92–19.68)	0.065	3.68 (0.79–17.19)	0.098

All four models were adjusted with age, sex and Geriatric Depression Scale-15. Model 1 included systolic blood pressure (SBP), triglyceride (TG) or high-density lipoprotein (HDL), and the existence of nephropathy. Model 2 included the existence of retinopathy instead of nephropathy. Model 3 included the existence of neuropathy instead of nephropathy or retinopathy. Model 4 included SBP, TG, and the existence of nephropathy, retinopathy and neuropathy. Upper lines in each column show the results of the models including TG, and lower lines show the results of the models including HDL.

Hypertension also alters the structure of cerebral blood vessels and disrupts intricate vasoregulatory mechanisms that assure blood supply to the brain,[39] and the dysfunction of the blood vessels might fail to supply adequate blood supply to the working neurons.

We found that hypertriglycemia at baseline is associated with cognitive decline. Several studies have focused on hypertriglyceridemia and its relationship to dementia.[40–42] Whether moderate hypertriglyceridemia is an independent risk factor for cardiovascular disease remains a source of debate, but a meta-analysis of thousands of patients followed up for >10 years has shown that a triglyceride elevation of 1 mmol/L increases the risk of cardiovascular disease independently of HDL-C.[43]

Lower HDL-C was also associated with cognitive decline in the current study, although it seemed slightly weaker than that of TG. Several studies reported the association of low HDL-C and cognitive impairment or dementia.[44–46]

Micro or small vessel impairments not necessarily accompanied with neurological symptoms might underlie the association between higher TG or lower HDL-C levels and the cognitive declines found in the current study, although the precise mechanism should be elucidated.

Neither fasting blood glucose nor HbA1c were associated with cognitive declines in the current study. Factors other than blood glucose control, including factors found in the current study, might have a larger impact on cognitive function in diabetics. The participants involved in the J-EDIT had relatively worse control of blood glucose, though this control improved significantly during the follow-up period. The changes in glucose control might have affected the results.

Several medications, including statins[47] and renin-angiotensin inhibitors,[48] are reportedly associated with cognitive protection. No significant difference, however, was found in terms of the medication at baseline between the groups with or without cognitive decline.

In summary, we have analyzed the factors associated with greater declines in cognitive function, based on MMSE scores, over a 6-year period. The comorbidity of diabetic nephropathy, hypertension and hypertriglyceridemia at baseline were associated with more than 5-point declines in MMSE. Elucidation of the underlying mechanisms of this association is warranted.

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Conflict of interest

There is no conflict of interest. The J-EDIT Study Group has not cleared any potential conflicts.

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ORIGINAL ARTICLE

Risk factors associated with cognitive decline in the elderly with type 2 diabetes: Pooled logistic analysis of a 6-year observation in the Japanese elderly diabetes intervention trial

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Aim: Considerable attention has been paid to the association between type 2 diabetes mellitus (T2DM) and cognitive dysfunction in the elderly. T2DM is often comorbid with several other metabolic disturbances, including hypertension and dyslipidemia. These comorbid diseases might be associated with cognitive impairment. Many clinical indices should be included as variables for the association with cognitive decline. In the current study, we tried to identify the associated factors with cognitive decline during a 6-year period in elderly T2DM considering the changes in the clinical indices during the follow-up period.

Methods: The subjects in the present study were 63 Japanese Elderly Interventional Trial participants who were administered the Mini-Mental State Examination at baseline, at the third year, and at the end of the 6-year follow-up period. We applied the pooled logistic analysis method to consider the changes in clinical indices during the observation period and tried to identify the factors associated with cognitive decline during the 6 years in elderly type 2 diabetics using repeated measured data for glycated hemoglobin A1c, blood pressure and serum lipids.

Results: In the current study, low high-density lipoprotein-cholesterol and higher diastolic blood pressure were significantly associated with cognitive decline by pooled logistic analysis in the 6-year observation of older diabetic subjects. Higher glycated hemoglobin A1c had a tendency toward association with cognitive decline.

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Conclusion: The results suggest that comprehensive management of diabetes, including dyslipidemia and hypertension, might contribute to the prevention of declines in cognitive function in older diabetic patients. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 110–116.**

Keywords: diastolic blood pressure, glycated hemoglobin A1c, high-density lipoprotein cholesterol, Mini-Mental State Examination.

Introduction

Considerable attention has been paid to the association between type 2 diabetes mellitus (T2DM) and cognitive dysfunction in the elderly. Numerous cross-sectional studies have investigated neuropsychological functioning in non-demented patients with T2DM.[1,2] Systematic reviews of the literature show a cognitive profile of mild to moderate decrements in cognitive functioning in patients with T2DM.[3,4]

Higher glycemic levels measured by glycated hemoglobin A1c (HbA1c) were associated with lower scores in a wide range of cognitive assessments in the The Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) study.[5] That study, however, only analyzed the data cross-sectionally. Several longitudinal studies have examined the risk of cognitive decline associated with type 2 diabetes.[6–8] However, these studies have not examined the effects of the status of blood glucose, blood pressure and serum lipid profiles. T2DM is often complicated with several other metabolic disturbances, including hypertension and dyslipidemia.[9] These comorbid diseases might be associated with cognitive impairment. Indeed, a longitudinal study has shown that the comorbidity of hypertension with T2DM exacerbates cognitive decline.[10] Many clinical indices should therefore be included as variables for the association with cognitive decline.

In the current study, we applied the pooled logistic analysis method to consider changes in the clinical indices during the follow-up period and to identify the associated factors with cognitive decline during a 6-year period in elderly T2DM.

Methods

Participants

The subjects were 63 Japanese Elderly Interventional Trial (J-EDIT)[11] participants who were administered the Mini-Mental State Examination (MMSE) at baseline, at the third year, and at the end of the 6-year follow-up period. The study protocol was approved by the ethical committees at all of the enrolled institutions, and written informed consent was obtained from each patient.

Functional assessment

The MMSE was administered to most patients on registration.[12] The second and third assessments were carried out at the third year and the end of the 6-year observation period. The MMSE is a global test of orientation, attention, calculation, language and recall with a score of 0–30.

Depressive mood was assessed by a short version of the Geriatric Depression Scale (GDS-15).[13]

Assessment of diabetes mellitus, complications and comorbidities

The diagnosis and patient data regarding DM, blood examinations and complications were obtained from the clinical charts.[14] After overnight fasting, blood samples were taken by venipuncture to assess serum levels of glucose, HbA1c, total cholesterol, triglycerides and high-density lipoprotein cholesterol (HDL-C). The value for HbA1c (%) is estimated as an National Glycohemoglobin Standardization Program equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society)(%) + 0.4%.[15] Diabetic nephropathy was assessed according to the mean urinary albumin-to-urinary creatinine ratio (ACR) and was classified as no nephropathy (ACR < 30 μg/mg creatinine) or the existence of nephropathy (ACR30 μg/mg creatinine). Diabetic retinopathy was assessed by a fundoscopic examination carried out through dilated pupils by experienced ophthalmologists, and was classified into two categories: mild (no retinopathy or intraretinal hemorrhages and hard exudates), or serious (soft exudates, intraretinalmicrovascular abnormalities, venous calibre abnormalities, venous beading, neovascularization of the disc or other areas in the retina, preretinal fibrous tissue proliferation, preretinal or vitreous hemorrhage and/or retinal detachment). Diabetic neuropathy was defined as either a loss of the Achilles tendon reflex without neuropathic symptoms including paresthesia, or the presence of neuropathic symptoms.

Statistical analysis

A 5-point or greater decline in MMSE compared with baseline was defined as a significant cognitive decline at

the 3- and 6-year examinations.[16] Descriptive statistics for baseline characteristics in patients with and without cognitive decline were compared by χ^2-tests or *t*-tests. Profiles of HbA1c, blood pressure and serum lipid, which were measured at baseline, 3 years and 6 years after follow up, were summarized for the with and without cognitive decline groups.

We used pooled logistic regression models[17,18] to identify the factors associated with cognitive decline within a relatively short period, using repeated measured data for HbA1c, blood pressure and serum lipids. Briefly, we first divided each individual's observation into two separate 3-year long intervals according to the MMSE examination schedule: from baseline to the end of the second year, and from the start of the third to the end of the sixth year. We treated each interval as a short-term follow-up study, where only cognitive decline-free individuals could enter the subsequent "study" and then pooled the repeated observations to model the probability of developing cognitive decline in each 3-year interval. This pooling repeated-observation method is the extension of person-time analyses in epidemiology, which allows information from individuals who remain at risk during the first interval to be updated by measurements at the 3rd-year examination in the second interval. Two observations per individuals contributed to the analyses if they were free of cognitive decline in the first interval, otherwise one observation contributed. Although our companion study[19] found that the existence of diabetic nephropathy at baseline predicted cognitive decline during the 6 years, we didn't include it in this pooled logistic analysis as a result of the small sample, so that we could focus on the predictive power of following repeated measured covariates: HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), HDL-C and triglycerides (TG). These covariate values included in the analyses were averaged over the baseline, first and second years in the first interval, and averaged over the fourth to sixth years in the second. Three models were made, and all models were adjusted for age, sex and GDS-15. Because the association of a depressive mood with cognitive dysfunction has been reported,[20,21] the GDS-15 score was included in the adjusting values. Because the underlying risk of developing cognitive decline might be different in the first and second intervals, the interval effect was included in all models. Confidence intervals (CI) for odds ratios (OR) were calculated for generalized estimating equation (GEE) type robust standard errors. All analyses were carried out with SAS software (version 9.1.3; SAS Institute, Cary, NC, USA).

Results

Nine subjects had cognitive decline during the observational period. Table 1 summarizes the baseline characteristics of the patients with or without declines of 5 points or greater for the MMSE scores. Patients with cognitive decline were older and had higher SBP and TG, lower HDL-C, and more nephropathy and neuropathy.

The values at baseline, the third year and the sixth year are shown in Table 2. HbA1c and TG were continuously higher, and HDL-C was lower in the group of

Table 1 Baseline characteristics

	All ($n = 63$)	Cognitive decline ($n = 9$)	Non-cognitive decline ($n = 54$)	*P*-value
Sex (male)*	28 (44.4)	3 (33.3)	25 (46.3)	0.469
Age at baseline†	72.4 (5.1)	76.6 (5.1)	71.7 (4.8)	0.007
HbA1c (%)†	7.8 (0.5)	7.8 (0.4)	7.9 (0.5)	0.674
TC (mg/dL)†	213.1 (33.9)	228.2 (53.5)	210.6 (29.5)	0.151
TG (mg/dL)†	131.2 (80.0)	187.3 (90.3)	121.9 (75.0)	0.022
HDL-C (mg/dL)†	60.8 (17.0)	48.6 (13.3)	62.9 (16.8)	0.018
LDL-C (mg/dL)†	126.6 (29.0)	142.2 (38.9)	124 (26.6)	0.082
SBP (mmHg)†	138.7 (13.7)	142.9 (13.2)	138 (13.7)	0.328
DBP (mmHg)†	74.6 (8.6)	75.8 (4.3)	74.4 (9.1)	0.669
BMI (kg/m^2)†	22.9 (2.8)	23.7 (3.5)	22.8 (2.7)	0.415
Nephropathy (presence)*	12 (19.4)	3 (33.3)	9 (17.0)	0.251
Retinopathy (presence)*	28 (57.1)	4 (50.0)	24 (58.5)	0.655
Neuropathy (presence)*	49 (83.1)	6 (100.0)	43 (81.1)	0.243
Smoking at baseline*	5 (9.1)	1 (12.5)	4 (8.5)	0.717

*n (%). †Mean (SD). *P*-values were calculated by χ^2-test for dichotomous variables and by *t*-test for continuous variables. BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 2 Changes of clinical indices

	Cognitive decline ($n = 9$)	Non-cognitive decline ($n = 54$)	All ($n = 63$)
HbA1c			
Baseline	7.8 (0.4)	7.9 (0.5)	7.8 (0.5)
3 years	7.9 (0.9)	7.7 (0.8)	7.7 (0.8)
6 years	7.6 (1.1)	7.4 (0.9)	7.4 (1.0)
TC			
Baseline	228.2 (53.5)	210.6 (29.5)	213.1 (33.9)
3 years	190.9 (24.2)	200.1 (30.2)	198.8 (29.4)
6 years	183.6 (24.2)	179.2 (32.6)	179.7 (31.7)
HDL-C			
Baseline	48.6 (13.3)	62.9 (16.8)	60.8 (17.0)
3 years	45.1 (10.6)	56.8 (14.1)	55.1 (14.2)
6 years	51.8 (4.6)	56.6 (13.6)	56.1 (13.0)
LDL-C			
Baseline	142.2 (38.9)	124 (26.6)	126.6 (29.0)
3 years	114.3 (23.7)	119.7 (26.9)	118.9 (26.3)
6 years	106.6 (19.0)	103.8 (26.2)	104.1 (25.3)
TG			
Baseline	187.3 (90.3)	121.9 (75.0)	131.2 (80.0)
3 years	155.7 (58.9)	120.3 (62.4)	125.5 (62.7)
6 years	123.5 (36.3)	94.7 (43.3)	97.9 (43.2)
SBP			
Baseline	142.9 (13.2)	138 (13.7)	138.7 (13.7)
3 years	136.5 (7.7)	133 (16.9)	133.5 (16.0)
6 years	128 (14.8)	131.8 (14.2)	131.3 (14.2)
DBP			
Baseline	75.8 (4.3)	74.4 (9.1)	74.6 (8.6)
3 years	73.6 (12.6)	69.9 (8.5)	70.4 (9.1)
6 years	67.7 (6.1)	68.5 (10.5)	68.4 (10.1)

DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 3 Results of multiple pooled logistic regression analysis

	Model 1			Model 2			Model 3		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
HbA1c	2.14	0.91–5.02	0.08	1.96	0.74–5.17	0.18	1.85	0.70–4.88	0.22
HDL-C	0.32	0.13–0.79	0.01	0.31	0.11–0.90	0.03	0.29	0.12–0.73	<0.01
SBP	1.55	0.84–2.87	0.16				1.16	0.40–3.41	0.78
DBP				5.28	1.79–15.62	<0.01	4.64	1.17–18.35	0.03
TC							1.13	0.69–1.84	0.63
TG							1.00	0.88–1.14	0.96

DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

cognitive decline. The TC and both SBP and DBP decreased in both groups during the observational period.

We presented the results of three pooled logistic regression models to determine the predictors of cognitive decline (Table 3). All three models were adjusted for age, sex and GDS-15. Model 1 included HbA1c, HDL-C and SBP. Model 2 included HbA1c, HDL-C and DBP. Model 3 included HbA1c, HDL-C, SBP, DBP, TC and TG. In each model, lower HDL-C (per

10 mg/dL increase for HDL-C: OR = 0.32 [95% CI = 0.13–0.79] in Model 1 to 0.29 [95% CI = 0.12–0.73] in Model 3) and higher DBP (per 10 mmHg increase for DBP: R = 5.28 [95% CI = 1.79–15.62] in Model 2 and 4.64 [95% CI = 1.17–18.35] in Model 3) were significantly associated with more than 5-point declines in MMSE during the 3-year period in each interval. The results in Model 1 through Model 3 suggest that higher HbA1c also tends to be associated with cognitive decline (per 1% increase for HbA1c: OR = 2.14, [95% CI = 0.91–5.01] in Model 1; OR = 1.85, [95% CI = 0.70–4.88] in Model 3).

Discussion

In the current study, lower HDL-C and higher DBP were significantly associated with cognitive decline by pooled logistic analysis during the 3 to 6-year follow-up period in older type 2 diabetic patients. Higher HbA1c had a tendency toward an association with cognitive decline.

Our previous study that analyzed the association between the clinical indices collected at baseline in the J-EDIT study and cognitive decline[19] showed that baseline HDL-C was a significant predictor of cognitive decline during the 6-year period, and systolic, but not diastolic BP, was associated with cognitive decline. The factors associated with cognitive decline were similar to the present study. We found no association of TG, HDL-C, BP or HbA1c with lower MMSE score in the cross-sectional analysis in the baseline data of the J-EDIT.[21] Comprehensive treatment in metabolic disturbance in T2DM might have impacts over a longer time frame.

Several observational studies have found that low HDL-C is significantly associated with greater cognitive decline.[22–24] HDL-C contains apolipoprotein E (APOE). One of the four isoforms, the APOE-ε4, is a well-known risk factor for Alzheimer's disease,[25] and multiple findings show that the association between APOE-ε4 and decreased levels of HDL-C increase the susceptibility to Alzheimer's disease.[26,27] Furthermore, low HDL-C and the APOE-ε4 genotype are both associated with an increased incidence of atherosclerosis, a significant contributor to cerebral hypoperfusion,[28] and stroke.[29,30] In the current study, the APOE genotypes were not determined. The relationship among APOE genotypes, low HDL-C and cognitive decline should be further investigated. Ward *et al.* have reported that decreased levels of HDL-C are associated with cognitive declines and gray matter reductions.[31] Quantitative brain imaging analysis might be warranted to elucidate the underlying mechanism of decreased levels of HDL-C in patients with cognitive decline.

The mechanism of the association between higher diastolic hypertension and cognitive decline remains unclear. Impaired cognitive function in T2DM patients is associated with small vessel disease in the brain.[32] DBP levels accelerate white matter lesions[33] and hippocampal atrophy.[34] It can be hypothesized that higher DBP affects cognitive functions by the accelerations in small arterioles in the brain. Indeed, higher DBP has been found to be associated with cognitive impairment in two cross-sectional studies. However, the DBP in the current study was lower than in these two studies,[35,36] at baseline lower than 80 mmHg and at follow up lower than 70 mmHg. These values were lower than the recommended BP in clinical guidelines for diabetics.[37] Several studies have shown that lower diastolic blood pressure (lower than 70 mmHg) might be associated with a risk for dementia[38,39] or white matter lesions and brain atrophy.[40,41] The target blood pressure for antihypertensive therapy in older diabetics should therefore be set very carefully.

As shown in Table 2, HbA1c was continuously higher during the 6 years in the group with cognitive decline. In Model 1 in Table 3, a statistical model including HbA1c, HDL-C, SBP is presented, with higher HbA1c being statistically associated with cognitive decline. In the analysis of the association between the clinical indices and cognitive decline in the same cohort, we did not find that HbA1c at baseline was a significant factor.[19] A recent report from the Atherosclerosis Risk in Communities Study also did not find a significant association between HbA1c at baseline and cognitive decline after a 6-year observation.[42] In the current analysis, however, HbA1c during the 6 years was significantly associated with cognitive decline. The finding in the current study further implies the importance of glycemic control for the preservation of cognitive function in older diabetes patients. In our own analysis that analyzed the indices at baseline, we did not find the association between HbA1c at baseline and cognitive decline.[19] A single HbA1c value might not be indicative of long-term glycemic control. Therefore, it would not necessarily be linked to changes in the central nervous system and secondary effects on cognitive performance. Repeated assessments of HbA1c are needed to increase the precision of the measurement and to thereby elucidate the effects of glycemic control on cognitive performance.

The limitations of the current study are as follows. First, the study was observational. The cause and effect was not clear in the nature of the research design. Second, the number of subjects with cognitive decline was small. A future study carried out at a larger scale would be warranted.

In conclusion, the results of the current study suggested that comprehensive management of diabetes, including dyslipidemia and hypertension, might contribute to the prevention of declines in cognitive function in older diabetic patients.

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Conflict of interest

There is no conflict of interest. The J-EDIT Study Group has not cleared any potential conflicts.

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浸軟に伴う皮膚の器質的変化・バリア機能低下のメカニズム
-「超予防」的観点からの老年看護学アドバンスト・スキンケア研究の展開 -

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１．はじめに・・・老年看護学における「超予防」と「アドバンスト・スキンケア」研究の実践課題としての皮膚浸軟

私どもの老年看護学分野は従来、褥瘡などの高齢者に好発する皮膚疾患、皮膚損傷に対する看護研究を展開してきた。また近年私どもの研究室では、看護学研究者だけではなく、医師・分子生物学研究者・工学研究者などを参集して multidisciplinary なチーム研究を展開できる体制を構築してきた。この体制により、臨床現場の課題から抽出したテーマに関して、生物学的なメカニズムの解明を行い、その知見を工学的な新しい看護ケア用プロダクトの開発に結び付け、もって再び臨床現場での患者のケア・QOL 向上に裨益せしめたいと考えている。このように、臨床現場に端を発し、生物学・工学的吟味を経て再び臨床現場へと回帰する看護研究のフローを、私どもは「バイオエンジニアリング・ナーシング」と名付け、21 世紀型の新しい看護研究のコンセプトとして世に問うているところである。

但しこうした射程を持つ看護研究は、ともすれば従来の医学研究で生物学的・工学的アプローチが成功している方向性の亜流にとどまり、現場密着型の看護研究としてのオリジナリティの深みに欠くものとなりかねない危険性がある。その限界を乗り越え、真に看護研究としてのあり方を貫徹するためには、取り上げる研究テーマが真の意味で看護臨床に根ざしたものである必要がある。すなわち、疾病を対象とした従来の医学一般がともすれば見落としがちな、一見地味かもしれないが患者の QOL に極めて重要な事象を研究題材としてとらえる、一種のフィールドワーク的センスが要求されてくる。

今回の報告書において取り上げる「皮膚浸軟 (Skin maceration)」というテーマは、その意味で極めて看護学的な研究対象である。浸軟（口語でいう「ふやけ」）とは、「組織、特に角質が水分を大量に吸収して白色に膨潤した状態」[1]をいう。これは正常な皮膚でも見られる一過性の現象であることから、従来皮膚科学を中心とする臨床医学の範疇では、疾病とはみなされてはこず、従ってその実態やメカニズムに関する先行研究は極めて乏しい。しかしながら、創傷看護やスキンケア看護の現場においては、過剰な滲出液を有する褥瘡や慢性潰瘍の周囲皮膚の浸軟が、創傷の治癒を阻害する例をしばしば経験する。また高齢者においては、失禁によって皮膚浸軟ひいてはオムツ皮膚炎を惹起するケースにしばしば遭遇する。失禁はナーシングホーム入居高齢者の半数以上[2]、在宅高齢者の 3 割近くに認められる[3]。私どもの先行研究でも、失禁を有する入所高齢者の 36%が皮膚損傷を有することが判明しており[4]、皮膚浸軟は特に高齢患者の QOL にとっては極めて重要な課題である。皮膚科的臨床医学的「疾患」に対して「予防」という言葉を使用するならば、こうした浸軟のような「疾患以前の状態」でありながら現場的に重要な病的現象については、単に予防というよりも「超予防」という言葉がよりふさわしい。そして皮膚浸軟を含め、高齢者の皮膚の「超予防」にフォーカスした老年看護学研究を、私どもは自負をこめて特に「アドバンスト・スキンケア」研究と呼んでいる。

私どもが特にアドバンスト・スキンケア研究の題材として皮膚浸軟に着眼したことには、次のような問題意識がある。従来皮膚浸軟は一過性可逆性の現象とみなされ、従来の看護ケアにおいても、滲出液の多い創傷周囲や高齢者オムツ皮膚炎の部位には、撥水剤を塗布して自然回復を待てば良い、と安易に考えられてきた。しかし、本当にそれで良いのだろうか？浸軟皮膚が回復するまでのタイムラグは、実は皮膚に器質的な変化が生じ、バリア機能（保湿・外界からの異物侵入阻止などの皮膚の保護機能）が低下して、細菌やアレルゲンなどが経皮的に侵入しうる極めてクリティカルな時期なのではないか？さらに、尿便失禁による失禁の場合は、単なる水分のみならず尿便の pH や消化酵素の影響も受け、皮膚のダメージはより著しく、細菌などの経皮的侵入もより重篤なのではないか？実際、失禁からオムツ皮膚炎で苦しんでいる高齢者がたくさんおられることは、従来のケア法が不十分なことを現に示しているのではないか？。こうした臨床現場に端を発する疑問に対して、経験論的なノウハウの蓄積である従来の看護ケアの限界を超えて、根本的に新しいケア介入法を開発するには、私どもの「バイオエンジニアリング・ナーシング」の立場から言えば、生物学的な方法論によって「皮膚浸軟のメカニズム」を解明することが不可欠であると考える。

この報告書においては、私どものこうした看護学理念に基づき、主にラットモデルを用いたメカニズム解明研究の成果として、水分による皮膚浸軟の病態に関する研究、さらに尿便失禁を想定したタンパク分解酵素溶液による皮膚浸軟での細菌の経皮的侵入に関する研究について、その概略をご紹介する。

２．水分による皮膚浸軟のラットモデルの確立ー浸軟した皮膚の表皮の構造変化・バリア機能の破綻と、加齢によるその亢進

はじめに、水分で生じる皮膚の「ふやけ」のみで、皮膚の器質的変化、バリア機能の低下が起こるか否かを調べる目的で、ラットにおける水分による皮膚浸軟モデルの確立を行った。

ラットとヒトでは皮膚構造が異なるので、ヒト皮膚の浸軟状態と同一現象と見なしうるラットモデルを作らねばならない。そのためにはヒトの浸軟皮膚で生じている現象を知る必要がある。そこでまず私どもは、健常人ボランティア 6 名を募り、十分なインフォームドコンセントのもと、足底土踏まず部分（角層が厚いため浸軟を起しやすく、かつ分層皮膚の採取に当たって歩行などの障害を起こしにくい部位）の片側に生理食塩水で作成した１％アガロースゲルを 6 時間貼付し、足底皮膚の浸軟を生ぜしめた。この状態で、皮膚のバリア機能の無侵襲的評価指標である transepidermal water loss(TEWL) を測定した。さらに局所麻酔下で浸軟皮膚組織と反対側健常皮膚組織を分層にてメスで採取し、電気顕微鏡での観察を行った。その結果、ヒト浸軟皮膚では健常側より TEWL が上昇していることが判明した[5]。透過型電子顕微鏡での観察では、健常皮膚と比較し、ヒトの浸軟皮膚では、従来の報告のような角質層で細胞間隙の拡大、細胞間脂質層の損傷に加え、興味深いことに表皮細胞基

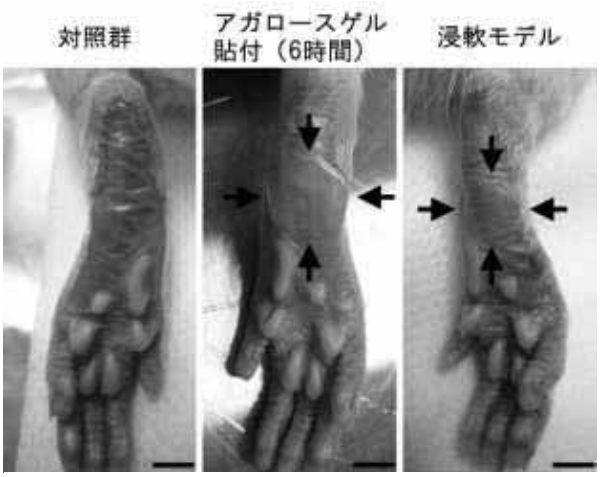

図 1 : ラット足底にアガロースゲルを貼付して作成した皮膚浸軟モデル。（文献 5）より。Bar: 5mm）

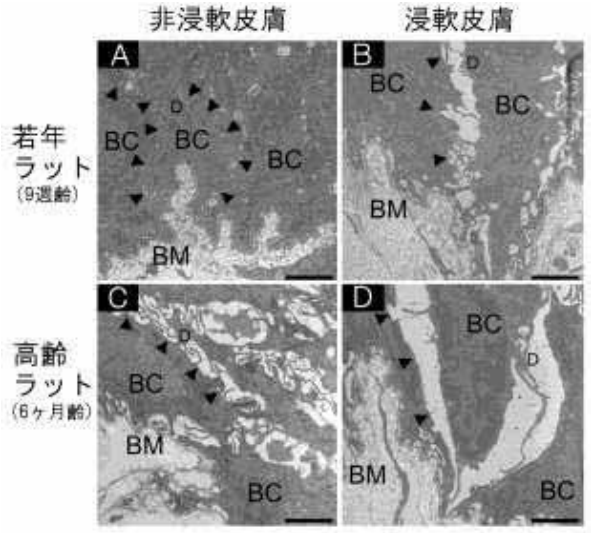

図 2 : ラット浸軟モデルにおける皮膚基底層の器質的変化（透過型電子顕微鏡像。文献 5）より。Bar:1.7μm）
BC：皮膚基底細胞　BM：基底膜　D:デスモソーム。
矢頭：細胞間隙。浸軟若年ラットの細胞間隙拡大が、高齢ラットの非浸軟状態に類似している。

底層・有棘層における細胞間隙の拡大、細胞突起の減少が認められた[5]。

この知見をもとに、ラット皮膚の浸軟モデルを確立することとした。オス Sprague–Dawley (SD)ラット足底にヒトと同様アガロースゲルを 6 時間貼付して皮膚浸軟を生ぜしめ（図１）、透過型電子顕微鏡にて観察すると、ヒトにおける浸軟と同様の所見、特に表皮基底細胞間の間隙の拡大、細胞突起の減少を認めた（図２）。このことより本モデルがヒト皮膚浸軟のモデルと見なせることが確認された。特に興味深いことに、９週齢の若年ラットの浸軟皮膚で見られた基底細胞間隙の拡大の程度は、６ヶ月齢の高齢ラットの非浸軟状態と同様であり（図２のＢ．Ｃを比較）、浸軟に伴う皮膚の器質的変化が加齢変化と類似している可能性が示唆された[5]。

さらに、実際に浸軟皮膚でバリア機能が低下していることを実験的に示すため、上記ラット浸軟モデルにおいて、蛍光高分子（CFDA）をアガロースゲルに加えたもので浸軟を作成し、表皮から毛包、真皮にかけての蛍光の浸透状態を蛍光顕微鏡で

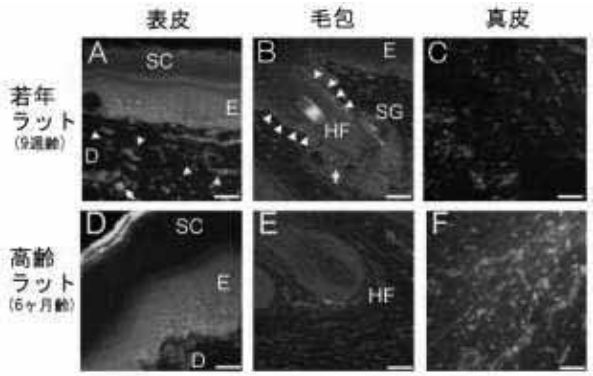

図 3 : ラット浸軟モデルにおける蛍光高分子(CFDA)の経皮的侵入。緑色が蛍光高分子、青は細胞核染色(DAPI)。
SC：角層　E：表皮　D：真皮　HF：毛包　SG：脂腺。
浸軟時の表皮→毛包→真皮への蛍光高分子の侵入が、高齢ラットほど著しい。（文献 5）より。Bar: 50μm）

観察した。その結果、若年ラットの浸軟皮膚より高齢ラットの浸軟皮膚において、蛍光の浸透がより著しいことが判明した[5]（図 3）。

以上の結果は、ラットを用いてヒトと同様の皮膚浸軟状態を再現した世界初の動物モデルである。また同時に、浸軟状態では表皮基底細胞の間隙が拡大するという器質的変化が生じており、異物が侵入しやすいクリティカルな状態であることを、蛍光高分子を用いて初めて明瞭に示した研究である。また浸軟皮膚の病態が皮膚の加齢性変化と類似しており、加齢皮膚での浸軟は若年皮膚での浸軟よりもバリア機能の低下が著しいという、皮膚のアンチエイジングの観点からもきわめて興味深い知見も得ることが出来た。臨床的には、高齢者の皮膚は若年者に比べて、水分による浸軟でバリア機能の障害を来しやすいことが示唆され、高齢者における失禁・オムツ皮膚炎を惹起しやすいメカニズムの一端が明らかになったものと思われる。同時に、浸軟による器質的変化を示すことにより、単に撥水剤の塗布による自然回復に依存してきた従来の浸軟ケアの妥当性についても、一石を投じるものと言えよう。

本研究はその新規性が認められ、皮膚科の英文雑誌に掲載された[5]。但し、本研究における大きな limitation は、生理食塩水を含有するゲルを用いて浸軟状態を作成したため、老年看護の臨床現場でしばしば問題になる尿便失禁を伴う浸軟における、尿便中の pH やタンパク分解酵素の影響を一切考慮に入れていないモデルであるということである。そこで私どもは、引き続いて、アガロースゲルに pH 緩衝剤およびタンパク分解酵素を添加したさらに臨床の尿便失禁に近いラット浸軟モデルを開発した。以下その概要を示す。

３．タンパク質分解性浸軟ラットモデルにおける組織障害と細菌の侵入

「はじめに」で述べられたナーシングホームにおける先行研究において、Bliss ら[2] は失禁と会陰部皮膚炎の関連を調べたところ、尿失禁のみでは皮膚炎との関連は見いだされなかったが、便失禁、あるいは尿と便の両者の失禁の場合には有意な関連が見られるとしている。また、Driver[6] は、ICU における便失禁患者では、従来の洗浄と撥水剤による看護ケアを 4 週間励行しても、19%のケースにおいて会陰部皮膚炎の発生を予防できなかったと述べている。これらの報告は、臨床における尿便失禁に伴う皮膚損傷において、単に水分だけではなく、尿便中に含

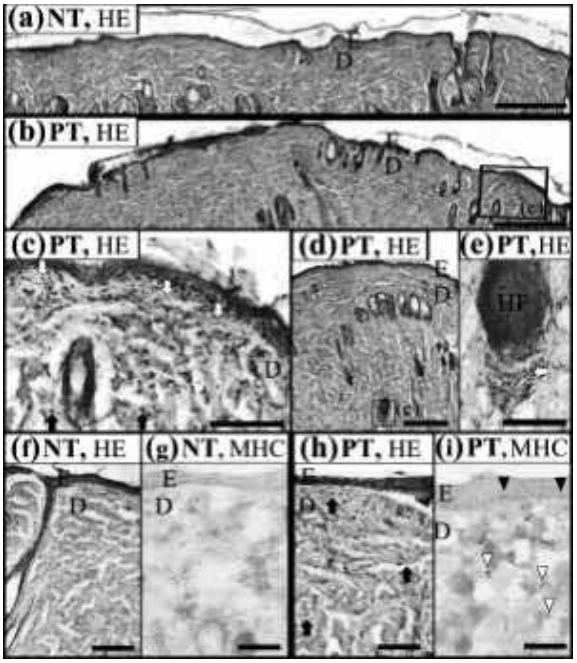

図 4 : タンパク質分解性浸軟ラットモデルにおける皮膚の炎症の惹起。NT : 無処理群 (a, f, g)　PT : タンパク分解酵素処理群 (b-e, h, i)。図 b, d 中の枠は、図 c, e の範囲を示す。E : 表皮　D : 真皮　HF : 毛包　HE : ヘマトキシリン・エオジン染色　MHC : 抗 MHC-II 免疫染色（ランゲルハンス細胞やマクロファージ等の抗原提示細胞のマーカー）。c, h の黒矢印は真皮内の炎症細胞浸潤、c. e は赤血球の漏出を示す。また無処理群(g)と比較し、タンパク室分解性浸軟群(i)では表皮内（黒矢頭）および真皮内（白矢頭）に MHC-II 陽性細胞が浸潤している。

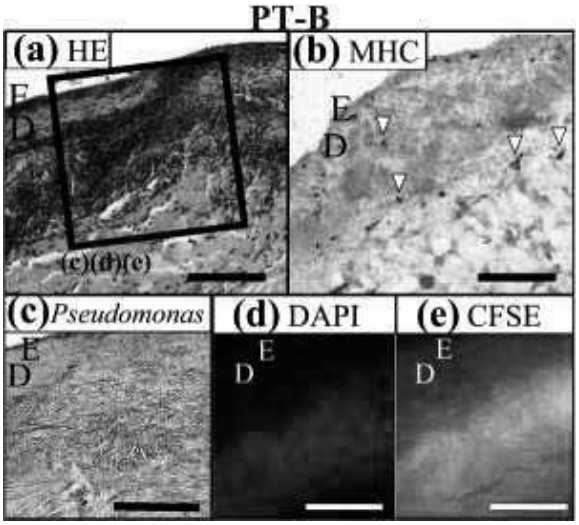

図 5 : タンパク質分解性浸軟皮膚における緑膿菌の真皮内への侵入。HE 染色像(a)における枠は c, e の範囲を示す。E : 表皮　D : 真皮。b 白矢頭は免疫染色での MHC-II 陽性細胞、c の茶色は抗緑膿菌免疫染色で描出された緑膿菌の局在を示す。DAPI（核染色 d）および CFSE シグナル（緑膿菌のラベルに用いた蛍光色素 e）の局在と一致し、緑膿菌が表皮から真皮に大量にクラスター状に侵入し炎症を惹起していることがわかる。

まれる成分が重要な要因となっていることを示唆するものである。便にはリパーゼなどの脂肪分解酵素のほか、タンパク分解酵素が含まれることが知られており[7, 8]、このタンパク分解酵素が皮膚を直接刺激・分解し、炎症を惹起したり、異物や細菌の侵入を起している可能性が考えられる。

そこで、本研究においては、6 ヶ月齢のオス SD ラットの背部皮膚を剃毛し、タンパク分解酵素であるトリプシン (0.25%wt/vol) およびα－キモトリプシン (0.4%wt/vol) の溶液（pH7.4 のトリスバッファーに溶解）を含んだ 1%アガロースゲルを 4 時間貼付した群を「タンパク質分解性浸軟群 」（以下 proteplytic treatment: PT 群）と名付けた。PT 群の皮膚を 24 時間後に採取し、無処理群（以下 no treatment: NT 群）の皮膚と組織学的に比較を行った。その結果、PT 群の皮膚では NT 群と比較し、HE 染色像で明らかな炎症細胞浸潤の増強を認め（図 4 c, h 黒矢印）、一部真皮浅層および毛包周囲では赤血球の血管外漏出が観察された（図 4 c, e 白矢印）。また、抗原提示細胞（皮膚においてはランゲルハンス細胞やマクロファージ等）のマーカーである MHC-II 免疫染色を行ったところ、PT 群（図 4 i）では NT 群（図 4 g）と比較し、MHC-II 陽性細胞の浸潤が、表皮および真皮（図 4 i のそれぞれ黒矢頭と白矢頭）に明瞭に認められた。これらのことから、「タンパク質分解性浸軟」の状態では、表皮・真皮に炎症が生じることが明らかとなった[9]。

さらに、「タンパク質分解性浸軟」の状態でさらに、蛍光色素 CSFE で緑色にラベルした緑膿菌を接種する実験を行った。具体的には 6.3×10^7 CFU/mL の濃度の緑膿菌培養液をしみこませた径 8mm の濾紙を、PT 処理後の皮膚に 30 分間置いた（以下 proteplytic treatment- bacteria: PT-B 群と呼ぶ）。処理・細菌接種後 24 時間で皮膚を採取した。そして PT 処理を行わずに細菌を接種した群との組織学的比較を行った。その結果、PT 処理を行わなかった群においては接種した細菌は表皮角層および顆粒層よりも深い層への侵入は認められなかった。それに対して、PT-B 群の HE 染色では炎症性細胞と細菌のコロニーが一塊となったものと考えられるクラスター像が、表皮を超えて真皮に至る層で認められた（図 5 a）。これらの細胞塊の少なくとも一部は MHC-II 陽性の炎症性細胞であったが（図 5 b）、抗緑膿菌抗体での免疫染色のシグナル（図 5 c）および CSFE 蛍光（図 5 e）の局在が、上記のクラスターの部位と一致していることから、PT-B 群においては細菌が表皮から真皮に侵入し、皮膚内部で増殖して炎症および組織創傷を惹起しているものと考えられた[9]。

上記実験におけるタンパク分解酵素の負荷量は、ヒトの便の生理的状態に類似している[8]。細菌接種実験には、便に多く含まれる大腸菌やクロストリジウムではなく緑膿菌を用いたが、緑膿菌は細菌の運動性という点で大腸菌などと似通っており[9]、実際に臨床において尿便失禁由来の会陰部皮膚炎から緑膿菌が検出される場合も多い。これらのことから、この実験系における皮膚組織損傷の状態は、臨床における尿便失禁による浸軟を模したモデルということが出来ると考えられる。

この研究での最も重要で、新規性の高い発見は、「タンパク質分解性浸軟」においては、炎症や組織損傷が皮膚の表層よりもむしろ深層から進行し、細菌のクラスター形成も真皮において著しい、ということである。先の章で述べた水分のみの浸軟においてすら、異物の侵入は真皮層まで到達することを考えると、タンパク質分解性浸軟においてはよりバリア機能の損傷は深刻で破壊的であると言える。臨床的には、尿便失禁による皮膚炎の形成機序として、皮下膿瘍を形成しそれが破裂する、と

いうメカニズムも考えられるかもしれない。

いずれにせよ、こうした「タンパク質分解性浸軟」の病態はもはや撥水剤による保護で自然回復を待つ、という従来の看護ケアでは対応できないものと考えられる。老年看護の臨床現場では、肛門バルーンの挿入や吸収型オムツの使用などを含め、皮膚がなるべく尿便にさらされないようにする方策がとられる。しかし本研究で明らかになったメカニズムをふまえると、より病態メカニズムに踏み込んだ根本的かつ徹底的なケア方法、例えばタンパク分解酵素阻害剤を含んだケア用品を、下痢が予想される状態（例えば経腸栄養の変更時など）から予防的に使うなどの、新たなストラテジーが提案されるべきであると考える。なお、これらの結果は修士課程大学院生の論文として英語で発表され[9]、現在英文雑誌投稿中である。

４．終わりに

以上、「皮膚浸軟」という疾患以前の病態に対し、私どもが行っている動物実験をふくめた看護研究の一端を御紹介した。皮膚の「ふやけ」というきわめて日常的なありふれた現象を対象として、このように緻密に実験と解析を積み上げ、新たな高齢者看護ケアへの洞察に結びつけていくプロセスは、看護研究ならではの着眼点と醍醐味であり、まさに「超予防的アドバンスト・スキンケア」という言葉にふさわしいものと自負している。同様に、疾患以前の日常的な現象で、かつ高齢者の QOL に著しく影響する「超予防的アドバンスト・スキンケア」のテーマとして、私どもは現在「かゆみ」の分子生物学的メカニズムの解明にも取り組んでいるところである。

また、冒頭に述べたように、現場的科学としての看護学としては、臨床現場での問題把握から、その生物学的メカニズムの解明を経て、工学的に新たな看護ケア用品を開発して、最終的に臨床に裨益するという「バイオエンジニアリング・ナーシング」の円環構造を貫徹することが非常に重要である。本稿で述べたテーマに関しては、高齢者における失禁と皮膚炎の実態把握研究[4]に端を発し、上述のような生物学的検討を踏まえ、現在男性高齢者をターゲットとした尿とりパウチつきの画期的なハイ・スペック失禁ケア用具の開発に着手・進行している[10]。こうした研究の一連のフローが、失禁・浸軟という看護研究ならではの課題を軸に展開しえていることを、私どもは自らの研究者としてのオリジナリティーの最たる表れと自負している。

今後も来るべき超高齢化社会に備え、当教室から独自の老年・創傷看護学研究を世界に向けて発信してまいる所存である。

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都市部団地及びその周辺地域住民の介護保険サービスの利用傾向に関する研究
ーUR 豊四季台団地内外の居住実態に関する調査研究（その４）ー

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１．研究の背景

既に超高齢社会となっている日本は、世帯構成においても都市部を中心に、急激な単身高齢者及び高齢者夫婦のみの世帯の増加が見込まれている。介護施設や病院の設置に対して抑制的な政策が進められている状況を考慮すると、要介護度の重度化が進んだ場合でも世帯構成によらず在宅生活が続けられる仕組みの構築が必要である。

在宅生活を社会的に支える仕組みとして構築されている介護保険制度は、平成 24 年度の改正において、介護サービスに対して次に示すような地域包括ケアという考え方が踏襲されている。

・医療との連携強化
・介護サービスの充実強化
・予防の推進
・見守り、配食、買い物など、多様な生活支援サービスの確保や権利擁護等
・高齢期になっても住み続けることができる高齢者の住まいの整備（国土交通省と連携）

これらを踏まえ、地域密着型サービスとして複合型サービスと定期巡回・随時対応型訪問介護看護サービスという 2 つのサービスが加わった。また、地域包括ケアの前提である住まいに関しては、見守りや生活相談等のサービスを提供するサービス付き高齢者向け住宅が高齢者住まい法の中で制度化されている。

このように要介護期の在宅生活を取り巻く制度は地域包括ケアの構築という観点から充実される方向にある。

他方、居住者側からみると、医療・介護サービスを使いこなすことは、住み慣れた場所で多少衰えながらも自立し、尊厳を持って継続居住できる「Aging in Place」を実現させていく上では重要なことである、といえる。

２．研究の目的と意義

既報[※1]から、超高齢社会において在宅生活の継続を実現し得る住まいのあり方を模索する一環で、千葉県柏市の UR 豊四季台団地内外に居住する方に対して、主に住まいに対する不安要素、生活を営む上での工夫等を明らかにしてきた。本研究は、背景や在宅生活を継続していく上で訪問系サービスの供給充実化と使いこなしが重要である、という既往研究の示唆 1)を踏まえて、要介護高齢者の居住形態や介護保険制度に基づくサービスの利用実態に着目した。

要介護認定を受けている者を対象とし、介護 3 サービス（訪問介護、通所サービス、短期入所サービス）利用傾向をみることで、当該地域における要介護者の利用形態の特徴を見出そうとするものである。

対象地域である柏市の UR 豊四季台団地及びその周辺地域は既に高齢化率が 35%を超えているところもあり、当該地域が抱える課題は、20 年後の日本を先取りしていると考えられている。将来の超高齢社会における課題解決を図る上での基礎資料とされたい。

３．研究方法

本調査において利用するデータは、行政が保有している柏市全域における介護保険給付データと住民基本台帳データ等を突合させたものを個人情報となる部分は削除した上で入手したものである。本稿で表示するデータは、表 1 の項目が中心になっている。なお、分析対象とする UR 豊四季台団地内外のエリアは、柏市における日常生活圏域でいうと、豊四季台という地域となる。

表１．取得データの利用項目

基本属性	生年月、性別、住所（日常生活圏域）、世帯構成、住居形態
給付実績情報	利用サービス種、回数、利用サービス提供事業者情報

４．調査結果と考察

４－１．高齢者及び要介護認定者の属性

取得データから、豊四季台地域に居住されている高齢者及び要介護認定者の世帯の構成、要介護認定率、住居形態等の構成を柏市全域と比較することで、当該地域の要介護高齢者の相対的な位置づけを確認する。

表２．高齢化率

	高齢者人口（人）			高齢化率		
	65～74歳	75～歳	65～歳	65～74歳	75～歳	65～歳
柏市	47,591	30,796	78,387	11.8%	7.7%	19.5%
豊四季台	3,686	2,895	6,581	12.5%	9.8%	22.3%

表３．高齢者世帯の構成比[※2]

	高齢者世帯（世帯）				構成比			
	高齢者独居	夫婦のみ	夫婦以外の高齢者のみ世帯	その他の高齢者のいる世帯	高齢者独居	夫婦のみ	夫婦以外の高齢者のみ世帯	その他の高齢者のいる世帯
柏市	15,351	14,493	454	24,619	28.0%	26.4%	0.8%	44.8%
豊四季台	1,777	1,209	50	1,709	37.4%	25.5%	1.1%	36.0%

表４．要介護認定率の構成比

	要介護認定者数（人）					要介護認定率			
	65歳～	65～74	75歳	40～64	合計	65歳～	65～74	75歳～	40～64歳
柏市	10,067	歳692	8,375	歳423	10,480	12.8%	歳6.6%	27.2%	0.3%
豊四季台	864	145	719	28	892	13.1%	3.9%	24.8%	0.3%

表５．在宅生活者の住居形態の構成比（施設系利用者以外）[※3]

		要介護度								
		支1	支2	介1	介2	介3	介4	介5	総計	割合
豊四季台	戸建	61	48	84	64	51	20	30	358	49.7%
	集合	14	14	29	26	5	6	3	97	13.5%
	公的賃貸	44	49	66	43	30	20	14	266	36.9%
	高専賃	0	0	0	0	0	0	0	0	0.0%
	合計	119	111	179	133	86	46	47	721	100.0%
	割合	16.5%	15.4%	24.8%	18.4%	11.9%	6.4%	6.5%	100.0%	
柏市	合計	1,281	1,173	2,090	1,807	1,168	695	694	8,908	-
	割合	14.4%	13.2%	23.5%	20.3%	13.1%	7.8%	7.8%	100.0%	

世帯構成、要介護認定率等の各種構成に関して豊四季台と柏市を比較した。表 3 から高齢者世帯において、独居の割合が豊四季台で顕著に高い。表 4 から要介護認定率を年齢別でみると、

前期高齢者で豊四季台の割合が高く、表5から要介護1までの軽度者が豊四季台で多いのが特徴となっている。在宅生活者の住居形態を比較すると、母数も多いが戸建と公的賃貸に要介護3～5（以下、中重度者）が集まっている傾向がある。他方で、中重度者の割合が少ないことは、当該地域に継続居住しきれていないとも見ることができ、今後精査が必要である。

４－２．介護３サービスの利用傾向

表６．要介護度３～５の介護３サービスの利用傾向

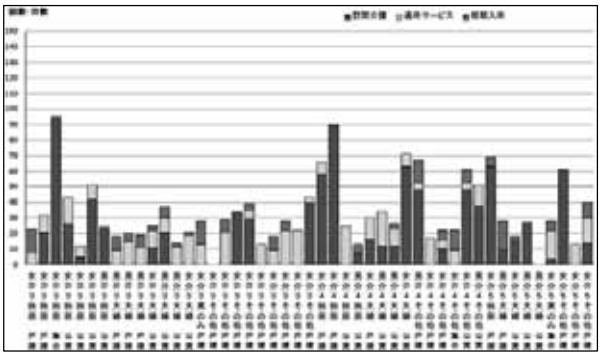

表6は、豊四季台地域在住の中重度者で各要介護度における利用限度額に対して6割以上利用している者の介護3サービスの利用回数であるが、訪問介護の回数が多い者と通所、短期入所の組合せ利用の者と二つのパターンが見られる。訪問介護の利用回数が一日複数回（30回超）と多い者は、全体で47人中11人（23.4%）であった。内訳は、独居では、戸建で3人、集合で1人、公的賃貸で1人であった。夫婦では、公的賃貸で1人であった。その他では、戸建で3人、公的賃貸で2人であった。夫婦世帯で利用が少ないということはあるものの、戸建居住者で比較的多く訪問介護サービスが利用されている傾向がみられた。

表７．住居形態別要介護度毎の訪問介護サービスの利用傾向

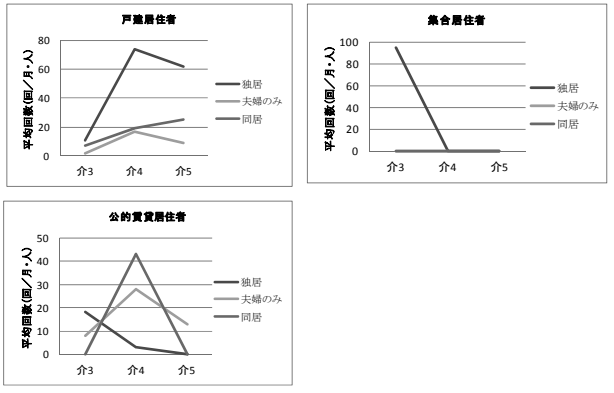

表7は、豊四季台地域在住の中重度者における住居形態別に見た訪問介護サービスの利用傾向である。要介護度毎に平均回数を見ることで利用傾向と捉えているが、要介護3から5へ重度化に伴って利用回数が増加傾向にあるのは戸建居住者におけるその他世帯のみで、他の属性は増加を示すものはあるものの、要介護5では顕著に少なくなっている。要介護度の重度化に伴って訪問介護サービスの需要は高まることになろうが、その観点からはうまくサービスを使いきれていないのが実態である。

５．まとめと今後の課題

本研究においては、豊四季台地域における要介護認定者の度合いとその居住形態及び、介護3サービスの利用傾向を整理した上で、訪問介護サービスの使いこなしについて触れた。その中では月当たりの平均回数で、訪問介護サービスの利用回数が要介護度の重度化に比例して増えない傾向が見られた。とはいえ、ケース毎にみると、要介護5でも訪問介護を多く利用しながら在宅生活を継続されるケースも散見された。住居形態に起因する居住環境や世帯構成等複数要因が想定されるが、引き続き在宅居住者の住まい方からアプローチを続けて要介護者がうまく訪問系サービスを利用しながら要介護度が重度化しても継続居住できる住環境を深掘りする。

注釈

※1. 団地建替えに伴う高齢者世帯の生活実態からみる住環境要求-UR豊四季台団地内外の居住実態に関する調査研究（その1）／西野，廣瀬，西出，大月
都市部団地及びその周辺地域住民の住まいへの不安要素に関する研究-UR豊四季台団地内外の居住実態に関する研究（その2）／廣瀬，西野，大月，西出
（日本建築学会大会学術講演梗概集（北陸）2011年8月）

※2. 世帯構成において、「高齢者独居」は、単身高齢者のみの世帯、「夫婦のみ」は、どちらか一方が高齢者である夫婦の世帯、「夫婦以外の高齢者のみ世帯」は、親子、兄弟等の配偶者を除く同居家族が含まれた世帯（全員高齢者）、「その他の高齢者のいる世帯」は、親子、兄弟等の配偶者を除く同居家族が含まれた世帯（若年者も含む）とする。

※3. 支は要支援を、介は要介護を示す。住戸形態では集合、戸建に持ち家、借家の区別はなく、公的賃貸には県営・市営・UR賃貸住宅が含まれる。

参考文献

1）東京大学: 平成23年度厚生労働省老人保健事業推進費等補助金「介護等を受けながら住み続けられる高齢者の住まいのあり方に関する調査研究」

謝辞

本調査は、厚生労働省の平成23年度老人保健健康増進等事業「介護等を受けながら住み続けられる高齢者の住まいのあり方に関する調査研究事業」（事業No. 66 東京大学）の一環で行ったものである。

団地に居住している高齢者世帯の入浴の実態について

UR 豊四季台団地内外の居住実態に関する調査研究

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1はじめに

高齢期になっても住み慣れた家で在宅生活を継続可能な住環境への提言に向け、昨年に引き続き住まい方の調査を行っている。本稿では「浴室」に着目し、在宅高齢者の入浴に関する実態を捉える事を目的とする。

2 調査概要

調査対象地である豊四季台団地は、昭和39 年に入居を開始したU R 団地である。

調査方法は、2010年6月に全戸配布により行ったアンケート調査、2010年10月～2011年7月に行った訪問ヒアリング調査、2011年11月に行ったワークショップ（以下WS）で得られたデータを基に分析を行った。

調査対象者は、被介護保険者であっても、在宅で一人または夫婦で生活しており、日常生活動作に介助を要しない者であるため、本稿では、「元気高齢者」とする。

3 入浴頻度

入浴頻度は様々であり、一日2回（朝・晩）や毎日入る場合もあれば、「入浴が面倒」や浴槽を跨ぐのが「大変」という理由で、三日に1回もある。また、入浴習慣については、「夜だと具合が悪くなる」という理由から、朝入浴する事例もある（表1）。

4転倒への不安

入浴への不安の要因として多く挙げられているものに、「転倒への不安」がある。これは、危険性を感じているだけではなく、実際浴室内で転倒により骨折などを経験している。浴室内での行為に安心感を得る方法として、「手すりの設置」、滑り止めの設置などによる「床材の工夫」などによる物的環境改善と、「シャワー浴」のみなど入浴方法の変更が挙げられる。また、建替団地であることから、和洋折衷浴槽である新団地への転居を希望する事例がある。(表2)

5 浴槽高さ・大きさと浴室広さ

5.1 浴槽高さ

浴槽高さについては、和式浴槽では、跨ぎ越しが高く入浴が困難であると感じている。

一方、入浴を可能とする方法として、「手すりの設置」、「段差解消」などによる物的環境改善と「シャワー浴」による入浴方法の変更が挙げられる（表3）。

5.2浴槽の大きさ

浴槽の大きさへの認識としては、和式浴槽を利用している旧団地居住者が「浴槽が小さい」と感じている。その一方、和洋折衷式浴槽である新団地居住者と推測されるWS参加者の5名は、「湯船に浸かって足を伸ばすと立てなくなる」と感じている（表4）。

5.3利用機器からみた浴室広さ

浴室洗い場の狭さを指摘する事例がある。また、洗い場で利用する機器として「イス」が挙げられている。これらの状況から、洗い場に必要な空間の目安として、イスを利用しながら洗い場で「体を洗う」などの行為が行える空間が必要となる事が見込まれる（表5）。

6浴室掃除

浴室掃除そのものが「大変」になる場合、「高さ」の問題で掃除が行き届かないなどの問題がある。これらの解決方法として、「掃除道具」や「頻度」の工夫が挙げられる。その他、ヘルパーに掃除を依頼するなど、人的サポートを利用している（表6）。

7入浴の外部化

介護保険のデイサービスで入浴を済ませる他、「元気高齢者」であっても、スポーツジム併設の浴室、銭湯などを利用し、入浴を済ませており、入浴の外部化が行われている（表7）。

8考察と今後の課題

8.1 考察 –元気高齢者に浸透する入浴の外部化–

元気高齢者の場合、スポーツジムなどの浴室施設や銭湯などの利用による入浴の外部化が行われている実態を捉える事ができた。これは、浴槽高さ、浴室広さ、掃除が要因として考えられる。そのため、入浴の外部化は、被介護保険者だけではなく、元気高齢者の中でも今後浸透していく可能性が高いと推測する。

8.2課題 –脱衣行為を含めた入浴行為全体の実態把握-

今回は、浴室環境のみに焦点を当てたが、在宅生活の継続可能な環境を捉えるためには、入浴に伴う動作としての脱衣行為なども含めた入浴実態から、住環境を検討する事が必要である。

表1 入浴頻度と習慣

分類		具体的内容
入浴頻度	*2回/1日*	・朝、夜入る。(2名)
入浴頻度	*1回/1日*	・毎日家のお風呂に入る。健康のための心がけ。
入浴頻度	*1回/1日*	・毎日必ず入る 2名
入浴頻度	*1回/1日*	・お風呂は毎日入る。入らない時は朝シャワー→病院へ行く時。
入浴頻度	*1回/2日*	・1日おき 1名(夏はシャワー)
入浴頻度	*1回/3日*	・3～5日に1回 1名(お風呂面倒)
入浴頻度	*1回/3日*	・入浴は3日に1回。
入浴頻度	*1回/3日*	・3日に1回。面倒。
入浴頻度	1回/3日	股関節(左足)が悪く、入浴時は大変で縦手すりを使いながらやっと入れるが、入浴は3日に1回程度。
入浴頻度	**1回/3日**	最近は入浴は3日に1回程度
入浴頻度	**1回/3日**	・入浴は3日に1回で浴槽に入るのが一番気持ちいい
習慣	*朝風呂*	・夜だと具合が悪くなると困るので朝入る。

表2 転倒への不安と解決方法

問題点		
分類		具体的内容
転倒	*不安感*	・お風呂は転倒などこわいとは思う。
転倒	*不安感*	・滑ったら大変。
転倒	*不安感*	・転倒の恐れ。
転倒	*不安感*	・転倒の心配
転倒	*経験*	・転倒してからずっとシャワーのみにしている。
転倒	*経験*	・滑って胸を打ったことがある。
転倒	*経験*	・滑って骨折したことがある。ゴムの敷物を敷きなさいと言われたが滑る。
転倒	*経験*	・湯船の床が滑りやすい(一度転倒)
転倒	*経験*	・風呂場で転倒して腕を骨折した。
転倒	*経験*	・転倒して骨折した。
解決方法		
分類		具体的内容
安心感	*手ずり*	・手すりが付いているので安心。
安心感	*手ずり*	・手すりを付けたりしている。一応安心。
安心感	*手すり*	・手すりをつけたので不安に感じない。
安心感	*材質*	・床は滑りにくいので安心。
安心感	*材質*	・滑り止めを付けているので不安なし(1名)
入浴法	*シャワー浴*	・転倒してからずっとシャワーのみにしている。
転居希望		・お風呂のことを考えると早く建て替え先に移動したい(旧団地居住者)。

表4 浴槽の大きさ

分類		具体的内容
検討事項	**認識**	・浴槽が小さく、浴槽の上がりが高い
	動作	・湯船につかって足を伸ばすと立てなくなる(5名)

表5 浴室広さ

分類		具体的内容
問題点	狭さ	お風呂を広くしたいけど、しょうがないから我慢している。
	狭さ	・洗い場も狭く、シャワーを浴びる際にこちょっと不便
要因	*イス*	・マットとイスを利用。
	イス	・高めのイスに座る。

表7 入浴の外部化

分類		具体的内容
代替	*施設*	・健康センターで入る。
代替	*施設*	・スイミング行くとプールに併設のお風呂に入れて便利。
代替	*施設*	・スポーツクラブでお風呂に入っている。
代替	*施設*	・スポーツクラブで入る。
代替	*施設*	・スポーツクラブのお風呂に入りに行く。近くに銭湯が無いので。
代替	*施設*	・プールに行ったときに入る。
代替	*施設*	・毎日プールでサウナ。
代替	*温泉/銭湯*	・温泉に週2回行く。
代替	*温泉/銭湯*	・家で入られない。他県の銭湯(週1回)。
代替	*温泉/銭湯*	・他県に家族がいるので、そこの温泉に入りに行っている。
代替	*デイ*	・デイサービスで入る。
代替	*デイ*	・週3回のデイサービスで入浴するので家では入らない。

表3 浴槽高さの問題と解決方法

問題点		
分類		具体的内容
浴槽	*浴槽高さ*	・1日2回・湯船日高さに困っている
	浴槽高さ	バスタブのふちが高すぎて危ない.
	浴槽高さ	・旧棟では、湯船の高さが高すぎる(床にバスタブを直置き)
	浴槽高さ	・お風呂が深い。
	浴槽高さ	・昔は、浴槽が深くて入るのが大変。
	浴槽高さ	・バスタブが深くてまたぐのが大変。
	浴槽高さ	・浴槽の高さが高い。
	浴槽高さ	・浴槽が高い。
	浴槽高さ	・お風呂が高い。
	浴槽高さ	フロが高く年を重ねるにつれて入れなくなった。
	浴槽高さ	・浴槽が小さく、浴槽の上がりが高い
	浴槽高さ	自分で足を持ち上げて何とか入浴する
解決方法		
分類		具体的内容
手すり設置	手すり	股関節(左足)が悪く、入浴時は大変で縦手すりを使いながらやっと入れるが、入浴は3日に1回程度。
	手すり	・またぐ時、足が引っ掛かって大変。手すりにしっかりつかまって気を付けて入っている。
	手すり	・手すりをつかんで入る。
	手すり	・股関節(左足)が悪く、入浴時は大変で、縦手すりを使いながらやっと入れる状況
段差解消	式台	風呂場への段差があり、踏台がないと中に入れない。
	すのこ	・浴室にすのこを敷き、浴槽との段差を少なくしている(1名)。
方法	**シャワー**	浴槽に入るのは面倒なので、年中シャワーで済ます

表6 浴室掃除の問題と工夫

問題点		
分類		具体的内容
掃除	*大変*	・カビが生えるので壁を拭くのが大変
掃除	*大変*	・掃除が大変。
掃除	*大変*	・お風呂掃除が面倒だがする。
掃除	**大変**	・掃除はきれいにしようとすると本当に大変なので、入浴後は必ず水で一通り流すようにルール化している
掃除	**大変**	・浴室掃除は妻が行うが、滑り止めに敷いているマットの細かい目の部分が大変
掃除	*高さ*	・手が届かない。
掃除	*高さ*	・危ないので天井の掃除はやらない。
掃除	*頻度*	・掃除は毎日しない。
掃除	**頻度**	・掃除は3日に1回
掃除	*道具*	・上の方は手が届かない(柄の付いたモップを使うとよいとの意見あり)
掃除	**シャワー**	・下を向いて洗うのが、苦手であるため、浴室掃除はあまりせず、夏はシャワーを利用。
掃除	**時期**	・風呂掃除は入浴後に汚れていたら洗う
工夫		
分類		具体的内容
掃除	**道具**	・風呂掃除は柄がついたブラシで行っている
掃除	**道具/頻度**	床のタイルが汚れないように、スノコを敷いてシャワーを浴び、掃除はシャワーを浴びたその後に週1回程度の頻度
掃除	**ヘルパー**	・掃除はヘルパーがたまにしてくれるが、それ以外は入浴後に自分でする

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商店街における着座空間に関する研究
- UR 柏豊四季台団地内の商店街を対象に -

李潤貞（建築）・西出和彦（建築）

Yunjeong LEE(Arch)・Kazuhiko NISHIDE (Arch)

1. 研究の背景

買い物は人の生活を維持するための基本的な行動であり、レジャーとしての余暇を楽しむ発展的行動でもある。それらの行動が見られる商店街は人の日常生活に欠かせない重要な場であるといえるだろう。

また、都市空間の中で都市の生活様式や歴史を保ちながら、その都市ならではの街並みを形成し、生活に必要な商品のみならずサービスや娯楽・情報などを提供し、店主にとっては生活の場でもある。さらに、地域コミュニティの核として多様な祭りやイベントなどに利用され、人々に楽しみを提供する「娯楽の場」であり、誰でも気軽に利用でき自然に交流を生み出す「公共の場」でもある。

一方、マイカーの普及に伴うモータリゼーションの進行や少子高齢化などの人口構成の変化によるライフスタイルの変化などで消費者の購買行動が変化し、大型店が消費者の支持を集め、中心市街地は衰退し、中心市街地を構成している商店街に空き店舗の増加が著しくなった。また、後継者の問題や設備の老朽化など商店街内部の問題も商店街が低迷しシャッター通りになる要因となっている。

近年、衰退しつつある商店街に活気を取り戻すための施策、あるいは広く街づくり活動の一環として街路の拡張や舗装、街路灯の設置、また、休憩空間の設置などの環境整備やイベントなどが進められている。また、高齢化率 22.5%という 5 人に 1 人が 65 歳以上の高齢者である高齢化社会に突入した今、商店街利用者の高齢化も進んでいることから歩行行動を常とする商店街で身体が衰えた高齢者への配慮として休憩空間の重要性が増すものと考えられている。

本研究では、商店街において休憩を含む宣伝や店のしつらえとしてなど、設置側の多様な意図によって設けられた着座空間に着目した。

2. 研究の目的

近年、少子高齢化に伴う人口構成の変化などにより人と人の関係や地域とのつながりが希薄になりつつあるなかで、交流の場が求められている。特に、同じ地域に居住して共通の関心を持っている人々の集団であるコミュニティへの関心が高まっている。

本研究では、商店街が地域の公共空間の一つでありながら地域の伝統や文化およびコミュニティの中心であったことに注目する。特に、高齢者への配慮および商店街の環境整備の一環として設置されている商店街の着座空間に焦点を当て、その設置状況および設置環境の特徴を把握する。また、着座空間を利用する利用者の行動や評価を分析することで、人々に対する着座空間の働きおよびその意義を明らかにすることを目的とする。さらに、着座空間がコミュニティを形成に寄与する可能性を探る。

3. 調査の概要

商店街における着座空間の利用状況を調べるために選定した調査対象地は、千葉県柏市にある豊四季台団地内の商店街である。豊四季台団地内商店街を調査対象地に選定した理由は、少子高齢化が商店街の衰退の要因として挙げられている中で、現在65歳以上の高齢者が団地内人口の37%を占めており高齢化が著しく進んでいるからである。

また、2004 年から都市再生機構による建て替え事業の対象となっており、商店街を含むエリアが第 2 期の事業対象地として 3〜4 年後位に建て替えが予定されており、建築的な知見が求められているからである。さらに、団地の中心に立地している商店街には、商店街の中央のパブリックスペースに着座空間が多数設置され、多くの人に利用されているからである。

3-1 豊四季台団地内商店街における着座空間の設置状況

豊四季台団地内商店街には、計 14 ヶ所に着座空間が設けられている。店が店舗の前に設置したものが 4 ヶ所で、パブリックスペースに設置されているのが 10 ヶ所である。その配置場所を図面上にプロットし設置状況を写真で表した。(図 1)

図 1 でわかるように、豊四季台団地内商店街における着座空間は、店頭や通路、広場に設置されており、段階構成を持っている。また、木の下やピロティ部分およびトイレの傍らなど異なる特性の空間に設置されており、設置場所に多様性がある。また、ベンチや椅子などの身体支持具の形状や素材および大きさなどのデザイン面も多様性を持っている。

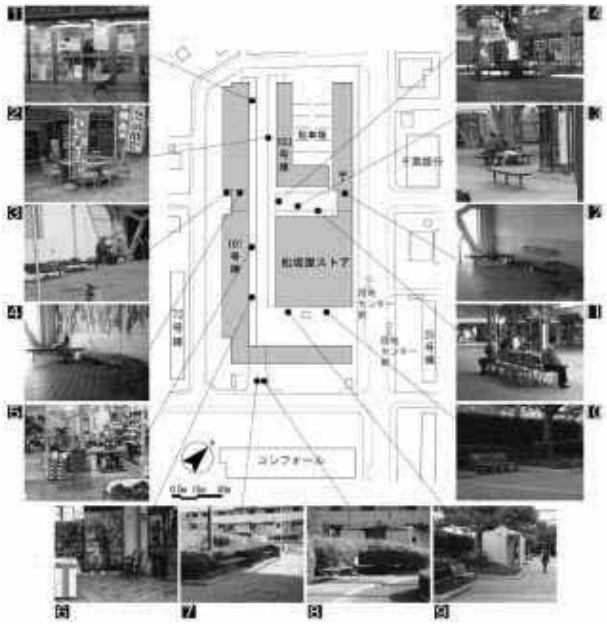

図 1　豊四季台団地内商店街における着座空間の設置状況

3-2 観察調査

豊四季台団地内商店街を対象に商店街のパブリックスペースにおける着座空間の利用実態を把握するために、2009 年 11 月 3 日(火、祝日)から 5 日(木、平日)までの 3 日間、午前 9 時から午後 5 時まで行動観察調査を行った。

商店街全体に設置されている 14 カ所の着座空間のなかで商

店街のほぼ中央にある広場に位置しており、人の利用が多くみられ､観察調査が容易である 6 カ所を対象に行動観察を行った。調査手法としては着座空間を利用する人の性別・年齢を推測し、5 分毎にその利用行動を記録した。観察調査の対象である 6 カ所の着座空間を地図上に示した。(図 2)

図 2　調査対象の配置図

4.　調査の結果

4-1　着座空間の利用状況

観察調査を行った 3 日間に 6 ヵ所の調査対象の場所ことに観察された利用行動を写真と共にまとめて考察を行った。

■調査対象①での利用状況

調査対象所①は午前中の利用はあまり見られない。(図 3)

次の写真でわかるように、建物の下に設置されているため薄暗い。日が当たらない午前中はなおさらのことである。日当たりが良くなく薄暗い感じが、午前中の他の場所に比べ利用が少ない理由の一つとしてうかがえる。日が当たる午後になると人の利用が多くなり､集まりが形成される｡図 4 の写真のように、同じ場所に居ても座って話す人や少し離れて座って聴いている人、座らないでトラスに寄りかかって他のところを眺めている人など、利用行動は多様である。集まってくる人が増え、午後 3 時頃に利用が一番多く見られる。ベンチの前を通る人が座っている人たちに軽く挨拶して通り、場合によっては立ち止って話しをすることがあった。ベンチに座っている人がベンチの前を通る人を呼び止めることも見られた。

図 3　場所①の利用状況

図 4　場所①の利用状況

■調査対象②での利用状況

背もたれがある直線型の 4 つのベンチが、背もたれを合わせて置かれているため知らない人たちが背を向けて座ることで視線を交わすことなく利用することができる。(図 5) しかし、背もたれを合わせて置かれていることが、大人数のグループが話しを交わすには、不利に働くことがわかる。(図 6)

図 5　場所②の利用状況

図 6　場所②の利用状況

■調査対象③での利用状況

直線型の 3 人掛けのベンチが、広場のほぼ中央の周りが開かれたところに置かれている。人や自転車の通行があるところで、個人の利用が多く見られる。

空間にゆとりを持っており、自転車やベビーカーを止めて利用する場合がある。(図 7) また、スーパーの入口に近いため、荷物整理をする時によく使われている。(図 8)

図 7　場所③の利用状況

図 8　場所③の利用状況

■調査対象④での利用状況

ベンチが木を囲んだ丸型の 10 人位座れる大きさで、老若男女を問わず複数の人が同時に使うことができる。丸い型で視線が合わないため、知らない人同士でも自然に隣に座ることができる。(図 9) スーパーの入口の近くにあるため、買い物後に休憩および荷物置きとしてよく使われている。ベンチの近くに飲み物やタバコ自販機があって、飲食および喫煙でよく使われている。

広場に位置していて空間的にゆとりがあり、ベンチを利用する際ベンチの前に自転車やショッピングカートを置く人がいる。ベンチが丸型であるため、グループの場合は座っている人の前に人が立って話しをする光景が見られる。(図 10)

図 9　場所④の利用状況

図 10　場所④の利用状況

■調査対象⑤での利用状況

場所①とほぼ同じ空間特性を持っているが、グループの利用が見られた①と比べて一人が二人の少人数で使われることが多い。(図 11)

空き缶やゴミ箱用の空き箱が置かれていることから、ここで飲食する人やタバコを吸う人がいることが推測できる。

誰かが持ち込んだと思われる違うデザインの椅子 2 脚が、壁際に置かれている。(図 12)

図 11　場所⑤の利用状況

図 12　場所⑤の利用状況

■調査対象⑥での利用状況

団地内商店街の出入口前の広場の着座空間で、3 つのカーブ型の背もたれのないベンチが一列に並んでいる。また、誰かが持ち込んだと思われる違うデザインの椅子 3 脚が壁際に置かれている。

一日中日がよく当たる所で、朝から男性の利用がよく見られる。3 脚のベンチが 1 列に並んでいて、各々のベンチにグループや個人、男性と女性が共用している。(図 13)背もたれのない長いカーブ型のベンチに、酔った人が寝ていることがあった。商店街から少し離れたところであり、日当たりがよく長いベンチの形状が影響していると考えられる。(図 14)

図 13　場所⑥の利用状況

図 14　場所⑥の利用状況

固定のベンチに座っている人と対面会話する時やベンチを使っている人たちと関わらないで一人になる時に、持ち込みの椅子が良く使われている。(図 15)

同じ場所で午前中には男性グループの利用が午後には犬連れの女性グループの利用が見られる。(図 16)

図 15　場所⑥の利用状況

図 16　場所⑥の利用状況

4-2　着座空間の利用実態

以下の図 17 は、観察調査を基に 6 ヶ所での 3 日間の全体の利用状況をまとめたグラフである。グラフの縦軸は時間帯、横軸は着座空間の各設置場所を示している。利用者を性別によって色分けし、円の大きさや数字で人数を表した。

グラフから着座空間の全体の利用特徴をみると、着座空間を利用する時間は男女を問わず、10 時から 12 時、14 時から 16 時で午前と午後の 2 時間が多いことがわかる。また、午前中は男性の利用が多く、午後は女性の利用が多い。男性は利用場所が 6 ヶ所の中で④と⑤に集中している反面、女性は利用場所の範囲が広い。

また、建物の下の囲まれた場所である①と、商店街と少し離れた広場に置かれている⑥は同性グループが利用することが多く、広場の中心部に設置されている③と⑤は、1 人か 2〜3 人で利用することが多い。ベンチが背もたれ同士合わさっている②は男女が共用していることが多く見られ、視線が重ならないベンチの向きが影響していると考えられる。大きい木を囲んだ形の④も老若男女が共用している場合が多く見られ、利用者の視線が重ならない丸い形であることが影響していると考えられる。

5.　まとめ

商店街に着座空間が多数設置されており、人の利用が多く見られた豊四季台団地内商店街を対象に観察調査を行い、設置現況および利用実態を調べ、利用状況を把握した。

その結果、豊四季台団地内商店街のパブリックスペースに置かれている着座空間は、設置場所によって、開放的か閉鎖的かであり、着座空間の基本的な構成要素であるベンチ・椅子の形状および向きなどの相違があるなど、多様な空間特性を持っていることがわかった。また、設置場所によって利用される時間や利用者の性別が異なり、広場に設置されている所は個人の利用が多く広場から離れた所に設置されている着座空間にはグループの利用が見られるなど、個人や集団によって利用される場所が異なることがわかった。さらに、着座空間の利用行動は多様であるが、注目すべき点としてほぼ同じ時間に決まった場所に同じ顔ぶれのグループが集まりコミュニティの形成があることから、商店街のおける着座空間がコミュニティ形成に寄与する可能性があることを示唆していることである。

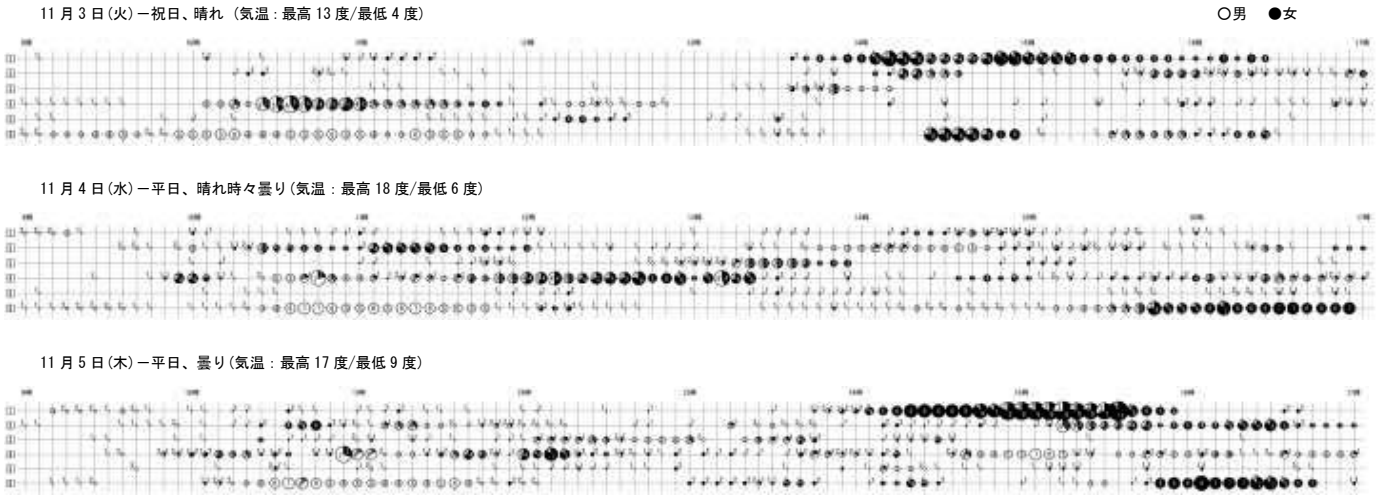

図 17　6 ヶ所の調査対象着座空間の利用状況

高齢運転者の運転継続と断念に関する研究

Survey on attitude about a car driving and a stop driving in a satellite cities

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1. はじめに

高齢化の進展により、高齢運転者の事故の問題がますます顕在化していく。事故を抑制するには、高齢者の運転を控えさせる方向にすればよいが、一方で、特に公共交通の貧弱な地方地域においては、運転断念が自立した生活の断念につながることにもなる。

加齢による身体特性の変化は、視力や聴力等の感覚器の問題、脳内の情報処理の速度の問題、適正な操作ができるかどうかの手足の特性の問題などがあげられるが、最近特に認知判断の部分において、認知症による特性低下も考慮する必要があると言われている[1]~[3]。

高齢運転者の再教育については、警察庁が 70 歳以上の高齢者の運転免許更新時に 3 時間の高齢者講習を義務付けている。また、最近の道路交通法の改正により、認知症が疑われる高齢者に医者の診断を受けさせるために、高齢者講習時に認知機能検査を付加することが決まり、平成 21 年 6 月から講習予備検査が導入された。しかしながら、そこで抽出される高齢者はごく僅かのかなり重度の認知症患者のみで、かなりの数にのぼるといわれている軽度認知障害（MCI)の疑いを持つ人への対応はなされていない。

そこで、本研究プロジェクトでは、自動車利用者の生活や地域に影響を与える断念後の生活のあり方について、次に示す自治体・地域と共同でケーススタディを行っている。

Ⅰ．運転断念に関する調査研究
- 運転必要地域における免許返納の意識調査
- 免許返納後の代替手段に関する調査
- 返納要因に関する調査

Ⅱ．高齢運転者の運転教育と評価
- 高齢者講習における実車講習時の走行データとプロセス分析
- 軽度認知障害が疑われる運転データの分析
- 運転教育プログラムの開発

Ⅲ．軽度認知障害のあるドライバの運転可能判断
- 運転可能評価システムの開発と評価

また、これらのケーススタディを通して、今後の日本各地で想定されることへのモデルケースを構築することを目標とする。本報告では、柏市における高齢ドライバの運転断念に関する意識調査[4]について述べる。

2. 調査概要

2.1 調査方法

調査は、千葉県柏市内の 23 地区ある社会福祉協議会の活動地区から、地域特性を踏まえて選定された 10 地区に在住する 65 歳以上の男女を対象とし、2010 年 6 月、2500 票（各地区 250 票）配布した。調査方法は無記名によるアンケート調査で、両市役所を通して住民基本台帳を用いたランダムサンプリングを行い各地域に配布した。同 7 月下旬において回収数は 1312 票（回収率 52.5%）であった。

2.2 調査項目

アンケートの調査項目は、基本的には 2008 年に福井県で実施した項目と同様としたが、地域特性を踏まえ、公共交通機関の利用や自転車の利用などの項目を変更・追加した。設問は合計 59 項目あり，免許所有者・免許非所有者・免許返納者に対して、共通の設問とそれぞれの設問を作成した。

(1) 共通項目

基本属性、健康状態、生活環境や活動生活の状況、外出の状況（頻度や目的）、公共交通の利用

(2) 免許所有者のみ

免許の種類、運転状況（運転頻度や目的）、同乗者の有無、事故や違反歴、運転の継続や中止に対する意識、運転中止に対する意識と自覚、運転に関する差別や不満、免許返納に対する考え

(3) 免許返納者

免許の返納状況（取得・返納年齢）、免許返納の理由、返納の経緯、運転断念に対する不安や不満、減らした外出機会

2.3 調査の内訳

回答の内訳は、免許保有者 900 人（68.6%)、非保有者 302 人（23.0%)、免許返納者 110 人（8.4%)であった。また、最も利用頻度の高い免許の種類は、自動車 798 人（88.7%)、原付 26 人（2.9%)、バイク 8 人（0.8%)、自動車・バイク両方 4 人（0.4%)、その他 11 人（1.2%)、無回答 53 人（5.8%）であった。表 1 に運転免許の有無とその内訳を示す。

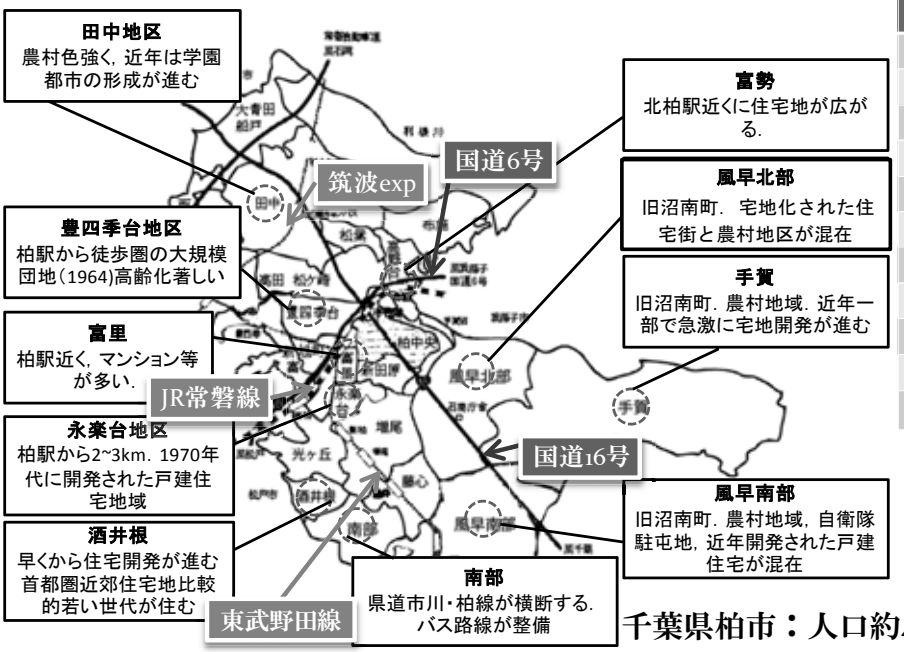
表 1　運転免許の有無とその内訳

免許保有状況	免許保有者	990 人(68.6%)
	非保有者	302 人(23.0%)
	免許返納者	110 人(8.4%)
免許の種類の内訳	普通自動車	755 人(57.5%)
	(AT限定)	39 人(3.0%)
	普通二輪	78 人(5.9%)
	大型二輪	219 人(16.7%)
	原付	66 人(5.0%)
	中型･大型･大型特殊	135 人(10.3%)
利用頻度が高い免許種類	自動車	807 人(61.5%)
	バイク	8 人(0.6%)
	(自動車･バイク	5 人(0.4%))
	原付	27 人(2.1%)

2.4 調査対象地域

千葉県柏市は、千葉県の北西部に位置する首都近郊地域であり、人口約 40 万人（人口密度 3,463 人/km^2）、高齢化率は 19.20%である[6]。公共交通機関は、中央部は JR 常磐線、東武野田線、県北部は首都圏都市鉄道つくばエクスプレスがある。鉄道の駅が少ない地域では路線バスが運行し、また、公共交通空白地域ではコミュニティバス、ジャンボタクシーが導入されている。

3.2 外出状況



地区	人口	高齢化率
田中	31,189	13.9%
富勢	24,843	19.0%
豊四季台	6,663	36.0%
富里	18,735	15.5%
永楽台	11,609	21.3%
南部	22,540	18.7%
酒井根	12,050	21.0%
手賀	6,038	19.4%
風早北部	8,237	18.0%
風早南部	21,083	15.2%

平成20年4月1日現在[5]

千葉県柏市：人口約40万人，高齢化率19.2%

図 1 柏市における対象 10 地区の特徴と人口・高齢化率

本調査では、公共交通機関の利便性や高齢化率によって自車運転に依存する傾向が大きいと考え、10 地区（田中、富勢、豊四季台、富里、永楽台、南部、酒井根、手賀、風早北部、風早南部）を選択した。各地区の特徴、人口および高齢化率を図 1 に示す。

3. 単純集計

3.1 属性

(1) 年齢・性別

回答者の平均年齢は 73.07±6.27 歳、性別は男性 1015 人（77.4%）、女性 280 人（21.3%）であり、男性の回答者は女性の約 3.6 倍であった。性別・年齢構成を図 2 に示す。

(2) 世帯人数

回答者の 1 世帯当たりの人数は、平均 2.64±1.34 人であり、地方都市（福井県）で実施した平均世帯数 3.8±1.89 と比較すると夫婦を中心とした核家族が多いことが分かる。なお、柏市の平均世帯人数は 2.5 人（平成 21 年調べ[6]）である。

(3) 職業

回答者の職業は、無職 903 人（68.8%）が最も多く、次いで自営業 110 人（8.4%）、臨時的雇用 94 人（7.2%）であった。また、地方都市と比較し農業従事者 52 人（4.0%）は少ない。総合的にみると、何らかの仕事をしている者より無職の割合が 70%と高かった。

(4) 健康状態・介護支援

健康状態の主観については、良い・とても良いと回答した者が 602 人（45.8%）、普通が 587 人（44.7%）、悪い・とても悪いが 81 人（6.2%）であり、主観的健康感は高いと言える。また、回答者のうち 71 人（5.4%）が介護認定（要介護・要支援）を受けていた。

(5) 居住地域

回答者の居住地区および各地区における回収率（各地域に 250 票配布）を図 4 に示す．酒井根，南部，富勢は 40%以上であったが，最も高齢化率の高い豊四季台は 25%を下回っており，地区によって回収率が異なる結果となった．

(1) 外出頻度

外出頻度は毎日 529 人（40.3%）が最も多く、週 3 回～6 回 481 人（36.7%）、週 1 回～2 回 210 人（16.0%）であり、週 3 回以上外出する人の割合は 77%であった。

(2)公共交通機関の利用

月に 3 回以上利用する公共交通機関は、電車 541 人（41.2%）、バス 400 人（30.5%）、使用していない人 507 名（38.6%）であった。何らかの公共交通機関を利用している割合は 71.7%であり、地方都市と比較すると利用率が非常に高いことが分かった。

(3) 外出の目的

1 ヶ月間の主な外出の目的は買物 750 人（57.2%）、運動・ウォーキング 463 人（35.3%）、趣味や遊び 426 人（32.5%）、通院は 351 人（26.8%）、旅行 249 人（19.0%）であった。対象地域の傾向としては、日常生活に必要不可欠な買物や通院の他に、運動やウォーキングなどの健康維持、趣味や遊び、旅行などの余暇活動を目的とした外出が多い

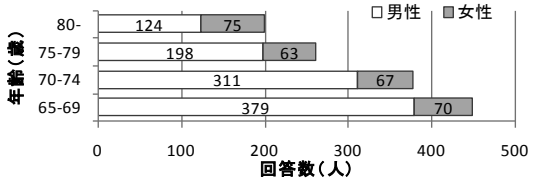


図 2 性別・男女構成(5 歳年齢階級別)

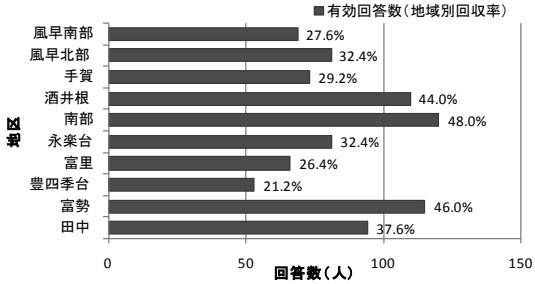


図 3 各地区の回収率

特徴がある。
(4) 外出の方法
1 ヵ月に 3 回以上ある外出方法は、徒歩 820 人（62.5%)，自家用車（自分の運転）724 人（55.2%)、自転車 423 人(32.2%)、鉄道 306 人(23.3%)、路線バス 275 人(21.0%)、自家用車(家族や知り合いの人の運転する車)166(12.7%)であった。徒歩や自家用車、鉄道や路線バスによる外出が主だが自転車による移動方法も 3 割程度採用していることが分かった。
(5) 外出に対する満足度
現在の外出の方法や頻度などについての満足度は、満足・まずまず満足 1136 人（86.6%)、満足していない・非常に満足していない・満足していない 134 人（10.2%）と対象地域における外出状況の満足度は高いことが分かった。

3.3 運転状況

(1) 運転頻度
免許所有者の運転頻度は、週に 3 回～6 回 336 人（25.6%）が最も多く、毎日 313 人（23.9%)，週に 1～2 回 133 人（10.1%)であった。過去の研究と同様，高齢の免許所有者の半数（49.5%)は週に 3 回以上、約 6 割（59.5%)と高い傾向にあることが分かった。
(2) 運転の目的
運転して外出する目的は、買物 600 人（45.7%)、趣味や遊び 332 人（25.3%)、通院 209 人（15.9%)、仕事 188 人(14.3%）、送迎 152 人（11.6%)であった。生活に必要不可欠な買物や通院の他に、趣味や遊びなどにも自動車を使用していることが分かった。
(3) 同乗者
自動車を運転する際の同乗者は配偶者 612 人（46.6%)が最も多く、息子・娘 199 人（15.2%)、同乗者はなく一人で運転する者は 193 人（14.7%)であり、一人で運転する場合より同乗者がいるケースが多いことが分かった。
(4) 事故歴・違反歴
過去 5 年間に事故歴があると回答した者が 72 人（5.5%)、違反歴があると回答した者が 155 人（11.8%)であった。
(5) 運転中止の意思
これまでに運転をやめようと思ったことがあると回答した者は 128 人（9.8%)、運転をやめようと思った理由としては、高齢になったため 82 人(64.1%)、自信がなくなった、疲れやすくなった 17 人（13.3%)、人にやめることを進められた 13 人（10.2%)であった。これは、運転断念を検討したことのある人は、高齢になると運転をやめたほうがよいという意識を持っていることを示唆している。
(6) 運転継続の意思
あと何年運転を続けたいかという運転継続の意思については、5～9 年 337 人（25.7%)、10 年以上（22.9%)、2～4 年（15.2%)であった。この結果は、地方都市の高齢者の結果とほぼ同等であった。

3.4 運転断念後の希望

(1) 外出意欲
運転断念を想定した場合、現在と比較して外出意欲がどのように変化すると思うかについては、意欲が変わらない・増えると回答した者は 267 人（20.3%）、減る・かなり減ると回答した者は 612 人（46.6%)と半数近くが減少してしまうであろうと考えていた。
(2) 外出手段
運転断念後に想定している外出手段は、徒歩 543 人（41.4%)、自転車 500 人（38.1%)、路線バス 476（36.3%)、鉄道 360 人（27.4%)であり、自力による移動の他に、公共交通機関への期待があることが分かった。

3.5 免許返納者

(1) 免許返納理由
免許を返納した理由を、単純に高齢になったためと回答した者は 66 人（返納者のうち 60%)、人から勧められた 34 人（30.9%)、見えにくくなった 22 人(20%）、疲れやすくなった 10 人（9.0%)であり、運転断念を検討したことがある人とほぼ同様の結果となった。
(2) 免許返納を勧めた人
免許を返納することを誰から勧められたかという回答については、配偶者 17 名（返納者のうち 50.0%)が半数を占め、息子 41.2（41.2%)、娘 9 人（26.5%）と近しい親族である場合が多いことが分かった。
(3) 運転断念による心理状況
自動車の運転ができなくなったことに対してどう感じるかについては、日常生活に不便を感じる 48 人（返納者のうち 43.6%)、特にない 46 人(41.8%)，納得できないなど、不満を感じる 8 人（7.2%)であり、不便や不満を感じる人が半数存在することが分かった。
(4) 運転断念による外出回数の変化
自動車の運転ができなくなったことで、外出回数を減らしたものは、特にない 39 人（返納者のうち 35.5%)、買物 28 人（25.5%)、趣味や遊び 22 人（20%)であった。
(5) 外出意欲
運転断念後の外出意欲の変化については、変わらない・増えた 59 人（返納者のうち 53.6%)、減った・かなり減った 42 人（38.1%)であり、現在運転している人が予想しているほど外出意欲が低下していないが、約 40%の返納者が、運転断念によって外出意欲が低下していることが分かった。
(6) 外出手段
運転断念後の外出手段は，徒歩 58 人（返納者のうち 52.7%)、自転車 47 人（42.5%)、路線バス 45 人（40.9%)、知り合いの車 36 人（32.7%)と上位 3 項目は現在自動車を運転しているドライバが予想している外出手段とほぼ同じ順位となった。また、免許を返納した後に自転車を外出手段として選択する者が多いことが分かった。

4. 性別・年齢・地区に関する分析結果

4.1 免許保有率

(1) 性別による比較
性別と免許保有状況の割合を図 4 に示す。免許保有と非保有の割合は男女で大きく異なり、女性が非保有者の割合が高い。返納者の割合は男女ともに 8%であった。国内における高齢免許保有率の男女比は 5:1 程度であることから、割合比は同程度あるいは女性の免許保有割合が高いと言える。
(2) 年齢による比較
5 歳年齢階級別の免許保有状況の割合を図 5 に示す。免許保有の割合は、年齢が高くなるにつれて低くなり、年齢が低いほど非保有者も少ないことが分かる。この結果は性別による結果同様全国的な傾向と同様と捉えることができる。
(3) 地区による比較
各地区における免許保有状況を図 6 に示す。柏駅から徒歩圏の豊四季台地区の免許保有率が低く、また同じく柏駅から近い富里地区における保有率が低い。一方で、鉄道駅から比較的距離のある手賀、南部、駅のない風早北部では免許保有率が高い。

したがって、柏市の対象地域における免許保有状況は、(a)男性が女性より高く、(b)高齢になるほど低くなり、(c)鉄道駅までの距離が大きいほど保有率が高い特徴を持つ。

4.2 移動の状況

(1) 性別による比較

自車による運転頻度を図 7 に示す。性別よる大きな違いは認められなかった。

(2) 年齢による比較

年齢別自車運転頻度を図 8 に示す。一般的に運転頻度は高齢になるほど減少していく傾向があるが、今回の調査ではそのような傾向は認められなかった。

(3) 地区による比較

地域ごとの運転頻度を図 9 に示す。運転頻度が高い（週に 3 回以上）のは、駅から比較的距離のある手賀、田中、風早南部、駅のない風早北部で、駅近隣の富里、富勢、永楽台の運転頻度はそれほど高くはなかった。

以上より、柏市の対象地域における移動状況は、自動車の運転頻度については(a)年齢・性別との関連性が低く、(b)地区の特性である鉄道の駅までの距離に依存することが分かった。

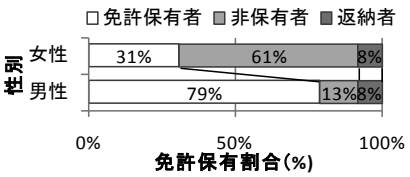


図 4 男女別免許保有状況

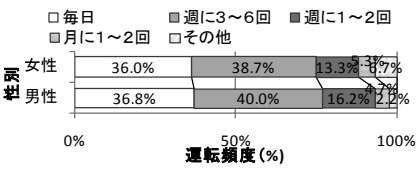


図 7 男女別自動車運転頻度

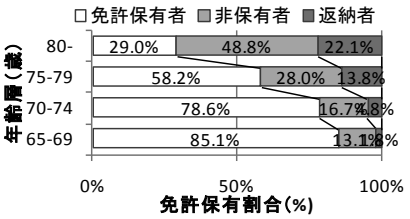


図 5 年齢別免許保有状況

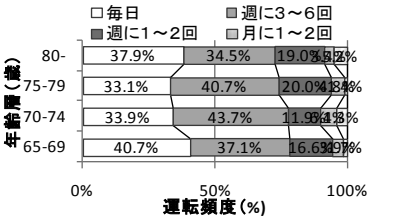


図 8 年齢別自動車運転頻度

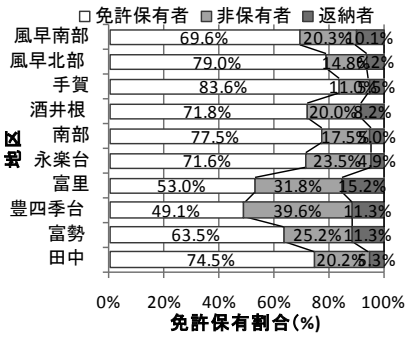


図 6 地区別免許保有状況

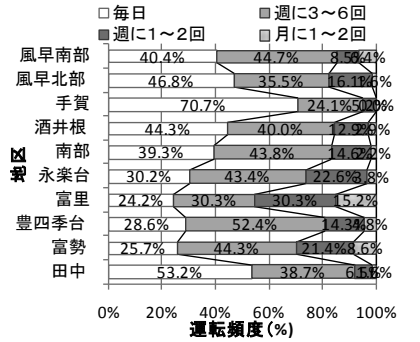


図 9 地域別自動車運転頻度

5. まとめ

本研究では、高齢ドライバの自動車依存や運転断念による高齢者への影響や要因を明らかにするために、千葉県柏市在住の 65 歳以上の高齢者を対象とした自動車の運転と運転継続に関する意識調査の単純集計と、運転状況・移動状況の分析を行った。その結果、次のことが分かった。

- 回答者の属性は、地方都市と比較すると核家族が多い地域であり、65 歳以上の高齢者の 7 割が無職である。健康状態の主観は評価が高い。
- 週 3 回以上外出する高齢者は 80%近く、また、鉄道、バスなどの公共交通機関の利用率が高い。外出は日常生活や生命維持を目的とした買物や通院だけではなく、健康維持や余暇活動を楽しむ割合も高い。外出は自家用車や公共交通機関を用いることが主だが、自転車の利用もある．外出に対する満足度は高い。
- 免許保有者の運転頻度は高く、同乗者がいるケースが多い。運転の継続意思については、地方都市の高齢者の意識と同様 5～9 年の割合が高い。運転断念後は外出意欲が低下すると予測しており、徒歩や公共交通機関の利用を希望している。
- 免許返納者は配偶者などの近しい親族から運転中止を勧められており、半数以上が不便や不満を抱いている。返納後の外出回数や意識は大きく変化しておらず、代替手段として徒歩や自転車、公共交通機関を利用している。
- 対象地域における免許保有率は男性が女性より高く、高齢になるほど低くなり、鉄道駅までの距離が大きいほど高い特徴を持つ。
- 自動車の運転頻度は地方都市の結果とは異なり、年齢や性別との関連性が低いことが分かった。また、地区の特性である公共交通機関や周辺環境に依存する傾向があることが示唆された。

今後は、運転断念が高齢ドライバの日常生活へ与える影響を明確にし、高齢ドライバ特有の自動車依存の要因と日常生活に必要な移動活動の維持などを評価する方法へと展開したい。また、地区や地方都市との比較分析を行い、高齢ドライバの心身特性や環境・地域特性に合わせた移動手段の選択や提案を目指す。

謝辞

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身体の協調に基づいた起立動作解析

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1. 研究背景

現在我が国の 65 歳以上の高齢者が占める割合は 23%を超え，世界で最も高齢化が進んだ社会であるといえる．また日本は最長寿国家であり，社会保障費の増大や介護士への精神的・肉体的負担が顕著であり，高齢化社会への対策は喫緊の課題であるといえる．特に加齢による身体機能の衰えは，平成 19 年度国民生活基礎調査において，脳卒中，認知症に次いで要介護の第 3 位を占めており，身体機能が衰えることで，日常動作が阻害され，高齢者の生活の質（QoL）が低下してしまうため，超高齢化した我が国において，高齢者の身体機能の低下を予防すること（介護予防）は喫緊の課題であるといえる．

介護予防の実現のために，我々はこれまでに様々な動作の起点であり，正常な日常動作の遂行に重要である起立動作に着目した研究を行ってきた．起立動作は複数の筋肉を同時に活動させる複雑な動作であり，未だに有効な訓練方法は確立していない．特にトレーニングに関しては，単純な筋力増強は必ずしも運動機能の改善につながるわけではなく，複数の筋肉の協調のさせ方を学習することが重要となる．そのため本研究の目的は，若年者と高齢者の起立時の生体データ（身体軌道・床反力・筋肉活動位）を取得し，起立の達成に重要な筋協調を抽出し，身体軌道に及ぼす影響をもとに分類することで，若年者と高齢者の違いを明らかにし，特に高齢者が弱った運動機能を解明することとする．

2. 研究手法

2. 1. シナジー解析

本研究では，シナジー仮説と呼ばれる筋協調に基づいた解析を行った．シナジー仮説は Bernstein によって提唱され [1]，人間の複雑な動きは複数の筋協調を調節することで達成されるとしている．本稿では，d'Avella によって提案された数理モデル (eq. (1))とい Decomposition Algorithm [2]を用いて，実際に観測された筋活動位からシナジーをそれぞれ抽出した．用いられたモデルでは，シナジーの波形を決めると，あとは時間遅れ(TD_x)と発火強度(c_x)を指定することで，実際の筋活動位を表現する．抽出すべきシナジーの個数は，異なるシナジーの数に対して交差検証法によってモデルの精度計算を行うことで，十分な精度が得られる個数とした．

$$\mathbf{M}(t) \cong \sum_{x=1}^{n} c_x \mathbf{W}_x (t - TD_x) \quad (1)$$

2. 2. 筋骨格系

シナジーが実際の身体動作に与える影響を調べるために，筋肉を入力として身体軌道を出力に取る筋骨格系を作成した (図 1 参照)．3 層のニューラルネットを 2 つ使用して，活動筋電位から関節トルク，ある時点での関節トルクと身体姿勢から次の時点の身体姿勢を推定することができる [3]．ニューラルネットの学習に関しては誤差逆伝播法を用いて，実際に取得したデータを使用した．推定誤差の評価については決定係数を用いて算出した．

2. 3. シナジーの分類

本研究では，シナジーが身体軌道に与える影響に基づいて，若年者と高齢者から抽出したシナジーを K 平均法により分類した．特にシナジーが与える起立動作に影響を調べるために，本稿では起立動作を 4 つのフェーズに分けた．それぞれ，上体の前屈(Phase I)，腰の持ち上げによる重心の前方移動(Phase II)，上体の持ち上げ (Phase III)，起立後の姿勢安定化制御(Phase IV)に分けられる []．

シナジーの影響を調べるために，抽出されたシナジーの発火強度をそれぞれ弱めた筋活動位を 2. 2 で実際に作成された筋骨格系に入力した．そこでは学習された身体軌道とは異なった軌道が得られ，その両方の軌道を比較することで，弱めたシナジーの影響を調べた (図 2 参照)．

2. 4. 実験

図 2 に示される実験環境を用いて起立動作時の生体データ(身体軌道・床反力・筋活動位)を取得した．身体軌道はモーションキャプチャシステム[HMK-200RT; Motion Analysis]を用いて，64 Hz で肩・腰・膝・足首の 3 次元座標を取得した．床反力は Nitta 社製の 6 軸力覚センサを 3 つ用いて作成した床反力系

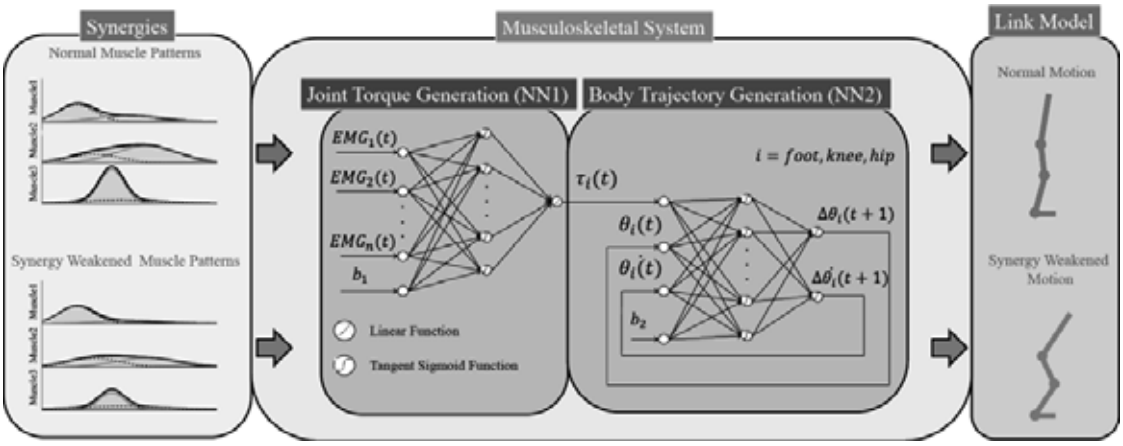

Figure 1. シナジーの影響を調べる手法概要

を2枚使用して, 臀部と足部からの床反力を64 Hzで計測した. 筋活動位は図2-(b)に表示されている8種類の筋肉からそれぞれ計測した. 全てのデータは 0.2 s の平滑化フィルターをかけ, 筋電データは10 Hzのハイパスフィルターと50-60 Hzのハムノイズフィルターをかけて, さらに左右の筋肉の平均を使用した.

本実験には 10 名の被験者に参加してもらった. それぞれの被験者は 3 名の若年者グループ (P1-P3; MEAN=24.0 yrs, STD=3.5 yrs)と 7 名の高齢者グループ (P4-P10; MEAN=67.1 yrs, STD=7.3 yrs)に分類した. 手の影響を取り除くために両腕は胸の前で交差してもらい, 12-20 回の起立動作を行ってもらった. また実験を始める前に全ての被験者に実験に関する説明を行い, 同意を得た.

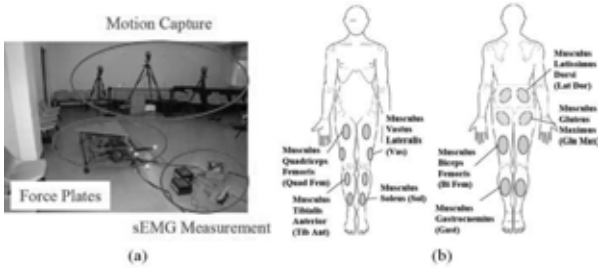

Figure 2. (a) 実験環境 (b) 計測した筋肉部位

3. 結果

3. 1. 抽出されたシナジー

図3に実際に抽出されたシナジーの波形とそれぞれの時間遅れを示す. 各四角形は筋肉の発揮度合を示しており, それぞれの行は異なる筋肉の発火を表している. 色は白くなればなるほど, 強く発火していることを示す. 赤い点線はそれぞれの Phase の開始点を表しており, Phase I の赤線からの差によって, 各シナジーの時間遅れを示している.

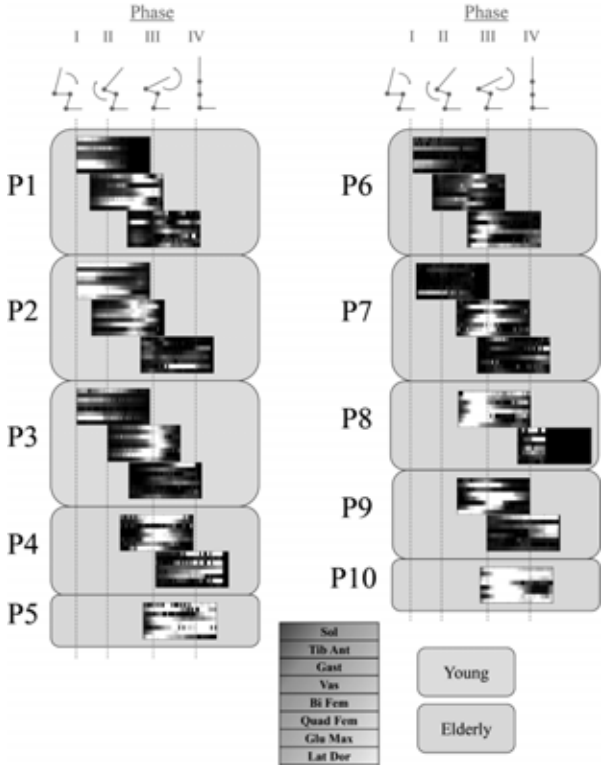

Figure 3. 抽出されたシナジー

3. 2. 筋骨格系の検証

表1にニューラルネットによる推定結果の精度を表す. それぞれの関節トルクと関節角度は十分に精度よく推定されており, 2 つのニューラルネットを用いて活動筋電位から身体軌道を推定出来ていることが分かる.

Table I. ニューラルネットによる推定結果

	MEAN	STD
足首トルク	0.75	0.29
膝トルク	0.91	0.16
腰トルク	0.81	0.16
足首角度	0.77	0.21
膝角度	0.95	0.09
腰角度	0.72	0.16

3. 3. シナジーが軌道に与える影響と分類

若年者と高齢者から抽出されたシナジーは各 Phase の足首・膝・腰関節に与える影響に基づいて K 平均法により 4 つのクラスター(Cluster I-IV)に分類された. 本稿では i 番目の被験者より抽出されたシナジーを Pi-j と表す. この時各クラスターに所属するシナジーは以下の通りである.

・Cluster I : P1-1, P1-2, P2-2, P3-1
・Cluster II : P6-1, P6-2, P7-3
・Cluster III : P1-3, P2-1, P2-3, P3-2, P3-3, P4-1, P7-2, P8-1, P9-2, P10-1
・Cluster IV : P4-2, P6-3, P5-1, P7-1, P8-2, P9-1

図4は各クラスターに所属するシナジーが各関節に与えた影響の平均を示す. 青いバーは足首関節, 赤いバーが膝関節, 緑は腰関節をそれぞれ表しており, エラーバーは標準偏差を表している. これにより, Cluster I と Cluster II のシナジーは前屈と重心の前方方向移動を示し, Cluster III に所属するシナジーは上体の持ち上げ動作を担っている. Cluster IV のシナジーは起立後の姿勢安定化制御を担当している.

図5に各 Cluster に所属するシナジーの平均波形を示す. 図

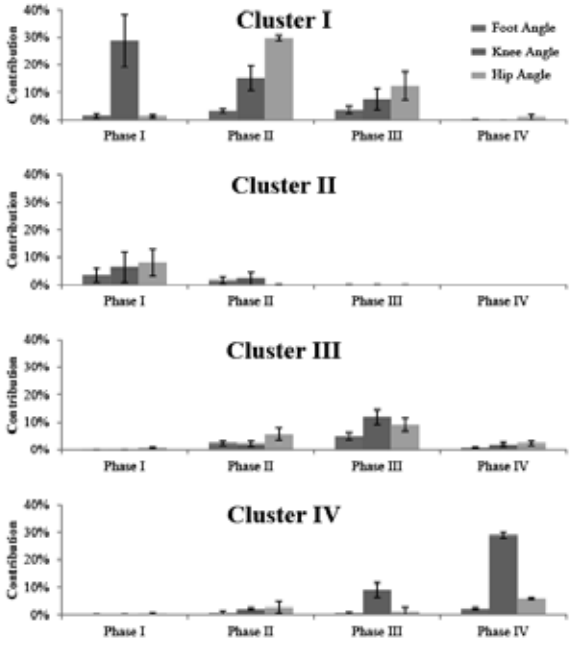

Figure 4. シナジーが各 Phase の関節角度に与える影響

3 と同様に白ければ白いほどより筋肉が発揮していることを示しており，各行は異なる筋肉の発火を示している．本図により，Cluster I と Cluster II は同様の役割（前屈と重心の前方移動）を果たしており，同じ筋肉の発揮が見られるが，Cluster II の方が発揮度が弱くなっていることが分かる．また Cluster III に所属するシナジーはほぼ全ての筋肉が発揮しており，Cluster IV のシナジーでは，主に膝関節の制御を担う筋肉が発揮している．

4. 結論

本解析により，若年者と高齢者から起立を達成すべきシナジーが抽出された．各人の筋骨格系は実験によって得られたデータによって学習され，各シナジーの発火強度を弱めた筋肉波形を入力することで，身体軌道に与える影響を調べ，影響に基づいてグループ分けを行った．その結果，人のシナジーは 4 つのクラスターに分類され，それぞれ以下のような役割を担っていることが明らかとなった．

Cluster I : 若年者からのみ抽出され，前屈動作と重心の前方移動を担当している．
Cluster II : Cluster I と同様の役割を果たすが，一部の高齢者からのみ抽出された．
Cluster III：若年者と高齢者の両グループから抽出され，上体の持ち上げ動作を担っている．
Cluster IV：一部の高齢者からのみ抽出され，起立後の姿勢安定化制御を担っている．

以上のことから若年者と高齢者のシナジーを比較した時に，一部の高齢者は前屈動作と重心の前方移動を苦手としており，さらに起立後の姿勢安定化制御について特別な努力を要することが解明された．

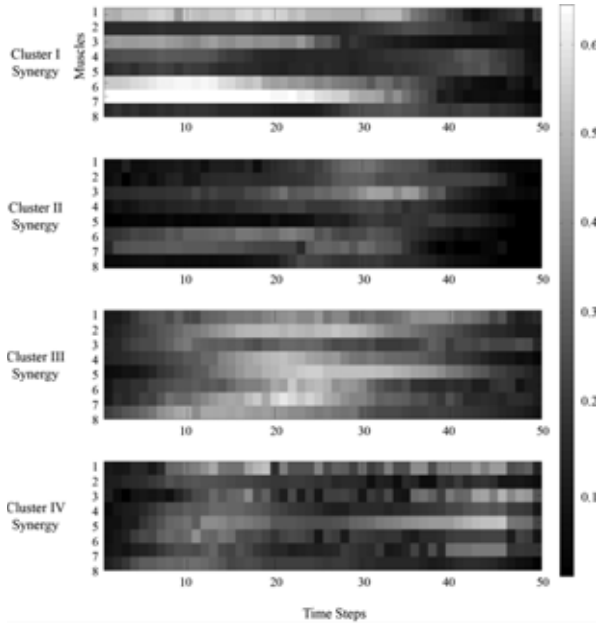

Figure 5. 各 Cluster の平均シナジー波形

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レセプトデータを用いた医療費・介護費の分布特性に関する分析

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2000 年に介護保険が創設された政策目的の一つに、本来、介護サービスとして対処されるべき需要が、医療分野の資源を消費しているという状況を改善し、非効率な医療費を削減したいということがあった。その典型例が社会的入院であるが、措置によって規制されている介護サービスの供給が急増する需要に追いつけず、その出口として医療機関を使うことから、非効率な医療費増が発生していた。これを、介護保険によって、本来の需要に即した安価な介護サービスの供給を増やしてゆくことにより、医療に置き換わっていた需要を減らし、全体として医療・介護費の効率化につなげようと言うのである。

しかしながら、介護保険開始後、そのような政策目的が達せられたのかどうかを検証した研究は極めて少なく(畑農 2004、花岡・鈴木 2007、印南 2009、菊池 2010)、その数少ない先行研究も、介護保険導入によってどれだけ医療費が減少したのか否か、畑農(2004)を除いて、明確な定量的結論が出ているわけではない 。また、そもそも医療費と介護費の間にどのような関係があるかについてさえも、それほど多くの研究が行なわれているわけでは無く(池田 2004a,b、河口ほか 2005a,b、菅原ほか 2005、橘口ほか 2004a,b、前田 2002)、正の相関関係か、負の相関関係か意見が分かれている 。その原因の一つは、この分野におけるデータの整備状況の不備にある。医療分野においては、レセプトデータを用いた研究は数多くなりつつあるが、医療と介護のレセプトデータを個人単位でつなぎ合わせるデータセットを作成できている例はまだまだ少なく、また、その数少ない例外も、非常に限られた市町村レベルの研究に止まっている 。

そこで本稿は、福井県全体の医療費、介護費のレセプトデータを個人単位でつなぎ、より代表性の高いデータセットを用いて、医療費、介護費の関係性や分布特性について、分析を試みる。両者の関係のみならず、介護費については、基本的な分布特性もあまり明確に分かっているとは言いがたい。医療費については、一部の人々が医療費の大半を使うという資源配分が行われている状況が以前から知られているが(小椋・鈴木 1998)、介護の場合はどうなのか。また、医療費については、その集中の持続性は低いことが知られているが（菅・鈴木 2005)、介護費の場合にはどうなのであろうか。こうした基礎的な知見を得ることが本稿の目的である。

本稿で用いるデータは、2009 年度から、福井県と東京大学高齢社会総合研究機構が実施している共同研究によって収集された医療・介護保険のレセプトデータ（業務支払データ）である。福井県及び福井県の各市町の協力の下に、各市町の個人情報保護審査会、東京大学倫理審査委員会で承認を受け、福井県国保連合会から提供を受けた。

それぞれのデータの収集期間は、介護保険レセプトデータが 2003 年 4 月～2008 年 10 月、医療保険レセプトデータが 2003 年 10 月～2008 年 9 月である。両者に共通する期間は 2003 年 10 月～2008 年 9 月であるが、これを個人 id 、性別を用いてマッチングし、65 歳以上の高齢者に限定した。また、2008 年 4 月以降は、75 歳以上の高齢者が後期高齢者医療制度に移行して医療保険レセプトデータから脱落しているため 、分析の連続性、代表性を鑑み、2003 年 10 月～2008 年 3 月までのマッチングサンプルを分析対象とした。医療保険、介護保険ともに無受診月や無受診者を含むベースである。医療保険脱退月以降のデータ、介護保険脱退月以降のデータは他人のデータが入っている場合があるため、脱退月以降のデータを削除した。こうして得られたマッチングサンプルは 1,085,116 であり、医療保険レセプトデータ全体の 9.88%がマッチングされたことになる。医療保険のみのレセプトデータは、9,828,045（同 89.48%)、介護保険のみのデータは 70,677(0.64%)である。本稿の分析で主に用いられているデータは、医療保険、介護保険がマッチングできたものであり、これを「要介護認定者サンプル」と呼ぶことにする。この「要介護認定者サンプル」による分析は、要介護認定を受けた 65 歳以上の高齢者に対する限定的な分析であることに留意する必要がある。一方、より広い観点から、要介護認定者サンプルに、医療保険のみの要介護認定を受けていないサンプルを加えたものを「全サンプル」と呼んで必要に応じて用いている 。

また、分析に当たっては、分析が容易なように、月次データを年次データへと集計して分析を行っている。具体的には、2003 年度～2007 年度までの 5 年のデータを作成している。2003 年度は、2003 年 10 月から 2004 年 3 月までの半年分のデータしか存在しないが、年換算をしている。また、死亡者、脱退者については、当該年度途中までを年換算して年次データとしている。

分析の結果、様々なことがわかった。一部の上位分位の人々の医療費が、全体の大半を使うということは良く知られた事実であるが、本データにおいても、それが確認されることとなった。一方、介護費については、医療よりも集中度はやや低いこともわかった。

次に、医療費と介護費の相関関係を調べたところ、全体としては弱いながらも正の相関関係があるが、それは介護施設入所者や入院患者が大きく影響していることがわかった。施設入所者や入院患者を除いた在宅高齢者についてみると、医療費と介護費の関係は無相関か、若干ながら正の相関となっている。

最後に、5 年間の生存者サンプルを抽出し、医療費、介護費の集中度の持続性を分析した。9・10 分位の医療費のその前後の変化をみると、やや大きく減少してゆく傾向があるが、介護費については持続性が高く、なかなか平均へ回帰しない状況がわかった。

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介護予防給付の導入が要支援者の要介護状態の変化に与える影響

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介護保険制度が 2000 年 4 月に導入されて以来，要介護認定者はこの 10 年間で約 2.2 倍増加した。特に，制度開始直後の要介護 1 以下の軽度の要介護認定者は著しく，2005 年度の介護保険改革が行われる前までには，その増加率は対前年比 10%以上の伸びを見せていた。その一方で，そうした軽度の要介護者に対するサービスが，必ずしも彼らの要介護状態の改善につながっていないという指摘もあり，2005 年度の介護保険制度改革では，これまでの日常生活の支援という側面が強かった「介護」を重視するシステムから，要介護状態の重度化を防ぐ「予防」を重視するシステムへの転換が行われた。具体的には，特定高齢者を対象とした地域支援事業と，要支援者を対象とした介護予防給付が新設された。それらでは，生活機能を維持向上させるための既存サービスの内容・提供方法・提供期間の見直しや，効果が明確な運動器の機能向上や栄養改善などをプログラムの一環として取り入れることなどが組み込まれた。

しかし，こうした予防重視のシステムが導入されて，すでに 5 年以上が経過しているにもかかわらず，その効果に関する定量的な分析は，介護予防継続的評価分析等検討会（2008a, 2008b, 2009），辻他（2009），徐・近藤（2010）および伊藤・大渕・辻（2011）が行っているのみにとどまっている。そこで，本研究では，2005 年度の介護保険制度改革で導入された介護予防給付が，要支援者の要介護状態にどのような影響を与えたのかを検証する。特に本研究では，長期間にわたる個人レベルの月次パネルデータを用いた計量経済分析を行うことによって，介護予防給付が軽度要介護者の要介護度に与える影響をより詳細に検証している。

本研究で用いるデータは，福井県下全 17 市町の介護保険給付費レセプトデータである。このデータには，介護保険の要介護認定者 71,369 人（福井市のみ生活保護者世帯が除かれている）の個人番号（個人情報保護のため，福井県国民健康保険連合会で個人番号に代わるランダムな番号を割り当ててもらい，研究者側は，個人を特定化することができないような措置をとっている），保険者番号（市町村合併前時点），性別，資格取得年月，資格喪失年月，および 2003 年 4 月から 2009 年 10 月の各月における年齢，要介護度，サービスコード，利用実日数，保険請求額，利用者負担額などに関する情報が含まれている。本研究では，この個人レベルの月次パネルデータを用いて，介護予防給付の導入が，初回の要介護認定において旧要支援または要支援 1 のいずれかの判定を受けた認定者の要介護状態の経過的な変化にどのような影響を与えたのかを検証する。ただし，2003 年 3 月以前にすでに要介護認定を受けているものは，すでに介護サービスを利用している可能性があり，正確な比較が行えない可能性があるため，2003 年 3 月以前に要介護認定を受けた個人をサンプルから除外した。また，初回の要介護認定が，介護予防給付の対象とならない要介護 1 以上であった個人と，2003 年 4 月以降に要介護認定を受けた個人で，初回要介護認定時に 64 歳以下であった個人もサンプルから除外した。すなわち，分析に用いるサンプルは，2003 年 4 月以降に初めて要介護認定を受け，かつ初回の要介護認定「要支援」または「要支援 1」と判定された 1993 人（観測値数：27931）である。なお，介護予防給付は，要支援 2 と判定された者でも利用することができるため，初回の要介護認定で，要支援 2 以下の判定を受けた 3010 人（観測値数 45331）を対象とするサンプルでも同様の分析を行った。なお，このデータには，各個人の世帯属性や所得水準，保険料段階，および提供されている詳細な介護サービスの項目，サービス提供事業者に関する諸属性が含まれていない。また，一部の個人については医療費の使用状況も把握できるが，全員の医療費の使用状況は把握することができない。こうした諸変数は介護需要に大きな影響を与えうるので，本研究の分析結果解釈には一定の留意が必要である。

詳細な分析に先立って，まず，介護予防給付の導入前後における要支援者の要介護度の経時的な推移を比較した。特定の時点におけるそれぞれの要支援者割合をみてみると，初回認定の 12 か月後では，導入前グループが 77.6%，導入後グループが 59.8%（要支援 2 までとすると 77.5%）となっており，介護予防給付受給者の要介護度の悪化が顕著に表れている。しかしながら，15 か月後にはこれらの大小関係は入れ替わり，18 か月後には導入前グループが 49.4%で，導入後グループが 55.5%（要支援 2 までとすると 74.0%），24 か月後には導入前グループが 38.3%で，導入後グループが 43.2%（要支援 2 までとすると 64.2%）となっている。その後は，導入前グループでは 40%前後，導入後グループでは 45%前後を安定的に推移している様子が確認できる。すなわち，このグラフを見る限りでは，介護予防給付の導入は，要支援者の状態悪化を幾分か抑制する効果があるように思われる。また，性別や年齢階層によっては，こうした傾向が異なる様子も観察された。

加えて，Ordered Probit モデルによる計量経済分析を行った結果，介護予防給付の導入が軽度要介護者の要介護状態の悪化を抑制する効果があることを示唆する結果が得られた。具体的には，介護予防給付を受けている者は，そうでないものに比べて，要支援 1 にとどまる確率が 22.5-31.4%ポイント有意に高く，要支援 2 以上に悪化する確率が 3.1-14.4%ポイント有意に低いことが分かった。

ただし，本研究には以下のような限界や課題がある。本研究では，長期間にわたる個人レベルの月次パネルデータを用いているが，データの制約上，要介護認定者の世帯属性や所得の状況，および医療との関連性に関して詳細な分析を行うことができない。これらの要素も介護需要とは密接な関係にあると考えられるので，こうした変数を用いて詳細な分析を行うことは今後の重要な研究課題である。また，介護予防給付の効果を推定する際には，どのくらいの期間ならば要介護状態の維持・改善に効果があるのかという観点からの分析も非常に重要であると思われるので，例えば survival analysis（duration analysis）などを用いた検証なども，今後の重要な研究課題であるといえよう。さらに，本研究では，介護予防給付の導入に伴って，実際に費用がどの程度変化したのかを分析の対象としていないが，介護

予防給付のあり方を検討するうえでは，それに関する費用対効果についてもあわせて検証すべきであろう。

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国民健康保険の医療費と保険料の将来予測
- レセプトデータに基づく市町村別推計 -

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１．研究目的

本研究の目的は，レセプトデータを用いて，国民健康保険（国保）の医療費と保険料の将来推計をおこない，保険財政の安定的な運営を図る上で参考となる情報を提供することである。福井県の 17 市町の国保加入者のレセプトデータ（2007 年４月から 2009 年９月分）を集計して，2015，2020，2025 年度の医療費と１人当たり保険料を推計する。

将来の医療費を予測するには，高齢化の進展による人口構成の変化を考慮する必要がある。そのためには，現時点での年齢階層別１人当たり医療費のデータを整備し，将来の医療費の伸び率を設定し，将来の人口推計と合わせて，将来の医療費を推計する手法が広く使われている。市町村別の年齢階層別医療費のデータは通常は利用可能ではなく，特別の集計を必要とする。

また，本研究が着目する国保では，費用負担の異なる制度が含まれている点にも注意を要する。

国保では，高額医療費の再保険事業と全国的に財政調整がおこなわれる前期高齢者の医療費が大きな部分を占めている。レセプトデータを用いることで，費用負担方式が異なるこれらの医療費を制度に忠実な形で分類して集計できるのが，本研究の分析の大きな利点である。

また，市町単位で医療費と保険財政の予測をおこなうことも大きな特徴であり，重要な政策的含意をもつ。2010 年には，高齢者医療制度改革会議で，後期高齢者医療制度に代わる新しい制度の案が示された。そのなかでは，中長期的には国保は都道府県単位に再編成されていく構想が示されている。小規模の自治体では危険のプールが十分にはおこなえないという問題点があり，再編・統合には一定の意義があるといえる。その意義を把握するために，まずは市町村単位の財政運営がどの程度不安定なものかを把握する必要がある。本研究では，人口構成の変化によって自治体間にどの程度の財政状況の違いが生じるのかを検証することができる。

２．研究方法

福井県の 17 市町から提供を受けた国民健康保険加入者のレセプトデータ（2007 年４月から 2009 年９月分）を集計して，2009 年度の年齢別１人当たりの医療費の推計，2015，2020，2025 年度の医療費推計，保険財政予測をおこなった。

個人情報保護のため，福井県国民健康保険連合会（国保連）で個人番号に代わるランダムな番号を割り当ててもらい，研究者側は個人を特定化することができないような措置をとっている。また，レセプトデータを使用するにあたって，市町と国保連に分析目的とデータを匿名化して個人情報の保護を図る方法を説明し，使用の許可を受けた。また，データの個人情報保護方法については同時に，東京大学倫理委員会で倫理審査を受け，承認を得た。

2.1　医療費の推計

医療費は，市町別の被保険者（老人保健制度加入者を除く）の年齢階層別医療費のデータをもとに，被保険者人口の将来予測を利用して推計する。

人口の多い市ではさらに細かい年齢階層別でも安定した集計値が得られ，年齢が高まるとともに医療費が高まることが確認される。２次医療圏別の集計では，地域間で医療費の違いがあることも観察された。しかし，加入者の将来推計が５歳刻みしか得られないために，医療費を年齢階層別にまとめざるを得なかった。

保険財政予測での推計対象の医療費は療養諸費とする。われわれが提供を受けたレセプトデータの医療費は療養の給付（診療費・調剤）に対応するので，各市町で数値を比例的に拡大して，療養諸費の実績値に合致させるようにする。

医療費は，以下の４つの手順を経て推計される。

（手順１）基準時点の医療費の推計

基準となる 2009 年度の医療費は，2007 年度から 2009 年度の３か年の平均をとる。本研究分析時点では 2009 年度は前半のレセプトしか利用可能でなかったため，前半の集計値を２倍して年度の数値とした。物価の変動を調整するため，消費者物価指数（総合）を用いて 2009 年度価格に変換している。

費用負担方式の違いによって，医療費を４種類に分類し，集計する。

（※１）高額医療費共同事業対象分。１か月 80 万円超のレセプトの 80 万円を超える部分とする。
（※２）保険財政共同安定化事業対象分。１か月 30 万円超のレセプトの８～80 万円の部分とする。
（※３）前期高齢者分。前期高齢者（65～74 歳）のレセプトで，上の（※１），（※２）を除く部分。
（※４）その他。（※１）から（※３）以外の部分。

（手順２）将来の医療費増加率の設定

１人当たり医療費の伸び率は５歳刻みの年齢階層別（０～４歳から 70～74 歳まで）に，以下の２ケースを想定した。

（ケース１）

各市町の全年齢階層で同じ伸び率をとるものとし，「医療費等の将来見通し及び財政影響試算」（厚生労働省保険局，2010 年 10 月）にしたがい，各市町の伸び率を年率 1.5%とおく。市町の１人当たり医療費の伸び率の違いは，市町の人口構成の変化に違いによって生じることになる。

（ケース２）

レセプトデータから，各市町の 2007～09 年度の年齢階層別１人当たり医療費の伸び率の実績を計算する。2009 年度は，この実績値と 1.5%の中間値をとるものとする。2025 年度には全市町の伸び率が 1.5%となるように，実績値のウエイトが線形に減少するような加重平均で各年度の伸び率を設定する。これは，近い将来では直近の各市町の伸び率の違いが反映されるという考えに立ったものである。

（手順３）将来の被保険者数の推計

2009 年度の 5 歳階級別被保険者数に，人口比率を乗じて，将来の被保険者数を推計する。人口比率は，『日本の市区町村別

将来推計人口（平成20年12月推計)』(国立社会保障・人口問題研究所）での推計年度の市町人口を 2009 年度の人口で除したものである。ただし，この推計は簡便法であり，国保被保険者の年齢構成と市町全体の年齢構成が一致していないことから誤差が生じる可能性に注意する必要がある。

（手順４）将来の医療費の推計

将来の市町の医療費は，2009年度の１人当たり医療費に推計年度までの医療費伸び率と被保険者数を乗じて推計した。

3.2 医療保険財政の推計

将来の保険料は，基準時点の 2009 年度の保険料と基準時点から推計時点までの保険料の変化を推計して，その和として求めることにする。

2009年度の加入者１人当たり保険料は，医療費を制度上の費用負担方式でまかなうとしたときに必要な保険料として計算した。現実の保険料は，保険料軽減のための市町の一般会計からの繰り入れ（国民健康保険保険基盤安定事業）を始め，各種の調整により，これとは一致しない。とくに一時的な収支の変動や一般会計の繰入金は，現実の保険料とここで推計される保険料との大きな乖離につながるため，これを推計に取り入れることはここでの目的にはそぐわない。

将来の保険料変化は，４分類された医療費別に以下のような手順で推計した。

（※１）

高額医療費共同事業対象分の医療費は，59%が共同事業の交付金，34%が定率国庫負担，７%が都道府県の調整交付金で賄われる。59%の交付金の内訳は，公費負担が29.5%，保険料が20.5%，国の調整交付金が９%となる。以上の制度の規定により，医療費の変化分の20.5%が保険料の変化分になると推計した。

（※２）

保険財政共同安定化事業対象分の医療費は，59%が共同安定化事業の交付金で，34%が定率国庫負担，７%が都道府県の調整交付金で賄われる。59%の交付金の内訳は，保険料が 50%，国の調整交付金が９%となる。そこで，医療費の変化分の50%が保険料の変化分になると推計した。

（※３）

前期高齢者の医療費で（※１），（※２）以外の部分は，財政調整制度によって全国で保険料がプールされて平準化する形になる。このため他の項目とは違って，岩本・福井（2011）等で使用された医療・介護保険財政モデルの 2010 年９月暫定版に基づいて，全国レベルの保険料を推計する 。

今回の医療・介護保険財政モデルでは，「医療費等の将来見通し及び財政影響試算」(厚生労働省保険局，2010年10月）の想定に基づき，１人当たり医療費が年1.5%増加するとして，医療費の将来推計をおこなっている。推計された前期高齢者の医療給付費を，財政調整によって各制度で加入者１人当たり均等に負担するとの前提で，１人当たり負担を計算し，それが保険料に相当するものと考える。将来の加入者数は，「将来推計人口（2006 年 12 月推計)」(国立社会保障・人口問題研究所）の出生中位・死亡中位の０～74歳人口を用いている。

（※４）

その他の医療費分については，医療費推計値に 2009 年度の『国民健康保険事業状況』から得られた給付費の医療費に占める割合の実績値（81.42%）を乗じることによって，基準時点と将来の給付費を求めた。この給付費と後期高齢者拠出金と介護納付金について，50%が保険料，９%が国による調整交付金，７%が都道府県による調整交付金，34%が定率国庫負担で賄われる。そこで，給付費，後期高齢者拠出金，介護納付金の変化分の50%が保険料の変化分になると推計した。

医療・介護保険財政モデルによって推計された後期高齢者の医療給付費を，「新たな制度に関する基本方針」（高齢者医療制度改革会議提出資料，2010年12月20日）で提案された支援金比率に基づき現役世代の医療保険が負担するとの前提で，１人当たり後期高齢者支援金を推計する。

医療・介護保険財政モデルでの介護費用は，社会保障国民会議によるシミュレーションを再現する形で将来推計をおこなっている。この介護給付費を現行制度が予定する負担比率に基づき第２号被保険者が負担するとの前提で，１人当たり介護納付金を推計する。

国民健康保険特別会計のこれ以外の項目については，基準年度と推計年度で変化がないものとしている。特殊な要因や一時的な要因が影響している等，予測が難しいためである。

３．研究結果

１人当たり医療費の伸び率を全県で一律としたケース１では，福井県全域の医療費は2009年度から2015年度には13.9%，2020年度には22.8%，2025年度には23.8%伸びると予測される。2025 年度までの市町別の増加率は最小で-1.3%，最大で 35.0%となる。ケース２では最小で-2.8%，最大で 37.2%とばらつきの幅はケース１よりも若干大きい。増加率が小さい市町があるのは，人口減によって加入者数の減少が見込まれるからである。約４分の３の市町の増加率が県全域の増加率よりも小さくなっているのも，人口の伸びが県全域よりも低い市町が多いからである。

１人当たり医療費の推計結果は，医療費の伸び率を全県で一律としたケース１では，福井県全域の１人当たり医療費は2009年度から 2015 年度には 14.0%，2020 年度には 26.9%，2025 年度には 39.3%増加する。2025 年度までの市町別の増加率は，ケース１では最小で 26.5%，最大で 47.6%，ケース２では最小で 31.1%，最大で 47.1%となる。医療費増加率の格差が生じるケース２で最大と最小の幅が小さいのは，人口構成の変化による格差拡大と増加率の差による格差拡大が両端の市町で相殺する方向に働いたからだと考えられる。本研究では，このような現象はたまたま生じたと解釈することにする。他地域でも同様な現象が見られるならば，人口構成と医療費増加率の相関関係あるいは因果関係が存在するかもしれないが，現状の知見ではこれについて考察を加えることはできない。

１人当たり保険料の推定結果は，福井県全域の１人当たり保険料は，2009 年度から 2015 年度には 17.2%，2020 年度には 33.9%，2025 年度には 49.5%に増加する。市町別の増加率は，ケース１では2025年度には最小で35.0%，最大で57.7%になった。ケース２では最小で 36.6%，最大で 57.1%になる。１人当たり医療費と同様に，医療費増加率の格差を想定したケース２の方がばらつきが小さくなっている。

2025年度までの増加率のばらつきの具合を見ると，ケース１とケース２で顕著な違いはない。ケース１では７市町が 47.8%から 51.5%の範囲になるのに対して，ケース２では中心の７市町は 47.3%から 50.8%とわずかに縮小する。約半数が 10 ポイントの範囲におさまり，その他の半数が両端に散らばる形になる。

高額医療費共同事業と保険財政共同安定化事業の対象の医療費，前期高齢者医療費の増加額は県内で同じであるが，市町の高齢化の進展の違い等の要因によって，これだけの保険料の増加率の差が生じてくることがわかった。

４．考察

前期高齢者の医療費と高額医療費は市町村単独で財政運営されていたとすれば，財政の市町村格差に結びつくと考えられ

るが，これらはすでに県あるいは全国単位の財政運営になっている。しかし，それ以外の医療費の部分についても，人口構成の今後の変化によって市町村間に違いが生じることが確認された。ひとつの県のみの観察結果という限界はあるものの，人口構成の変化によって自治体間で将来の医療費や保険料水準が異なってくるという本研究の結果を踏まえると，後期高齢者医療制度の改革に合わせて目指されている国民健康保険の都道府県単位の統合は，こうした格差を縮小させることに貢献する可能性が示唆された。

５．結論

本研究は，福井県の 17 市町の国民健康保険加入者のレセプトデータ（2007 年４月から 2009 年９月分）を集計して，2015，2020，2025 年度の医療費と１人当たり保険料を推計する。国保では，高額医療費の再保険事業と全国的に財政調整がおこなわれる前期高齢者の医療費が大きな部分を占めている。レセプトデータを用いることで，費用負担方式が異なるこれらの医療費を制度に忠実な形で分類して集計することができる。

医療費の伸び率を全県で一律とした場合では，福井県全域の１人当たり保険料は，市町別の増加率は，2025 年度には最小で 35%，最大で 58%に散らばる。すでに市町村を超えた財政運営がされている部分が大きくても，市町間の人口構成の違いが今後の医療費の伸び率に大きな影響を与える。国民健康保険の都道府県単位の統合は，こうした格差の縮小に貢献することが示唆される。

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老人医療における社会的入院の規模
—福井県国保レセプトデータによる医療費からの推計

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医学的観点からは既に治療や看護継続の必要性が低いにも関わらず、患者や家族の事情によって、介護の代替策として医療機関に入院すると言う、いわゆる「社会的入院」が社会問題化して久しい。

介護保険が創設された理由の一つにも、社会的入院の解消という政策目的が存在していた。2000 年に介護保険が始まって以降、社会的入院が一定程度減少したとの研究結果もあるが、依然としてその解消にはほど遠い状況が続いている（畑農 2004、花岡・鈴木 2007、印南 2009、菊池 2010、徳永・橘本 2010）。例えば、畑農(2004)は、1999 年度と 2002 年度の患者調査を使って社会的入院の大きさを推計しているが、介護保険開始前の 1999 年度において 22.1 万人と推計された社会的入院者数は、2002 年度においても 21.5 万人と微減しているに過ぎない 。また、花岡・鈴木(2007)は、富山県における 1998 年度から 2002 年度までの国保レセプトデータを用いて、入院患者の在院期間の分析を行っている。log-logistic ハザードモデルによる推定の結果、介護保険導入による介護型療養病床の増加が、比較的医療行為の少ない入院患者や長期入院の傾向がある患者の退院確率を引き上げたことが報告されているが、その削減された医療費のインパクトは、2000 年度で 0.1%、2002 年度で 0.97%と非常に小さい 。

このように社会的入院が介護保険開始後も依然として残っている理由として、印南(2009)は、我が国の医療・介護保険制度が不適切なインセンティブを発生させている点を指摘している。すなわち、要介護者を抱える家族にとって、現金給付の無い我が国の介護保険制度は、自宅介護の負担が非常に大きく、相対的に安上がりな施設入所・入院を志向するインセンティブを発生させている。その際、介護保険に比べ、医療保険の方が手続き的に容易であり、医療機関の裁量余地も大きいため、介護施設入所よりも社会的入院が選ばれると言うのである。さらに、医療機関にとっても、低密度医療が評価され、過剰な病床を埋めることで収益が上がる構造となっている為、社会的入院を許容するインセンティブがあるとしている 。一方、菊池(2010)は、社会的入院が残る直接的な原因を、介護施設の整備が需要の拡大に追い付かず、施設に対する超過需要が解消されない点にあるとしている。実際、菊池(2010)が引用している厚生労働省調査(厚生労働省「特別養護老人ホームの入所申込者の状況」（2009 年 12 月 22 日）)によれば、特別養護老人ホームへの入所申込者数 42 万人のうち、約 5 万人が介護療養型医療施設を除く医療機関で生活している状況である。

このように、社会的入院は現在も継続している社会問題であり、印南(2009)が報告しているように療養型病床のみならず一般病床にも広範に存在している問題であるとすれば、現在、その規模はどの程度深刻なものになっているのであろうか。

社会的入院の規模に関して最近行われた研究としては、印南(2009)が急性期の一般病院、療養病床を対象に行った全国調査がほぼ唯一のものである。この調査では、短期入院も含め、「入院医療の必要性が小さいのに入院を継続している患者」を約 32 万人(療養病床約 15 万人、一般病床約 17 万人)と推計している。これは全国の 65 歳以上の入院患者総数 93.1 万人(平成 20 年度「患者調査」)のおよそ 34.4%に当たる数字である。

ただし、この印南(2009)が行ったアンケートでは、病院の MSW や看護師自身に、患者が社会的入院かどうかを判断させており、個人間の恣意性や病院間の判断の差がバイアスとなっている可能性が否定できない。また、アンケートの有効回答率も 5.1%とかなり低く、統計的な信頼性が低いという問題もある。一方、平成 17 年度「患者調査」でも、医療機関側が「受け入れ条件が整えば退院可能」と考えている患者数を調べているが、65 歳以上の入院患者数に占める割合は 21.9%である。ただし、この数字も医療機関側が判断しているという点で、印南(2009)同様のバイアスが生じている可能性が高い。

そこで本稿では、これらとは全く別のアプローチを採り、福井県全県の国保レセプトデータから社会的入院の規模を推計することにする。社会的入院の定義としては、入院期間に着目するもの(厚生省(1995)、二木(1995)、畑農(2004))と、入院医療費の金額に着目したもの(府川(1995))の 2 つが存在するが、入院期間だけで社会的入院と判断することは定性的に無理がある 。そこで、本稿では主に後者の費用ベースのアプローチを採用し、必要に応じて入院期間による定義も用いて比較を行っている。わが国で始めて費用ベースの社会的入院の分析を行った先駆的な研究が府川(1995)である。府川(1995)は、1993 年度における 11 県の国保における老人医療レセプトデータを収集し、社会的入院の規模を厳密に推計しており、本稿も基本的にその方法を踏襲した。また、府川(1995)のデータには、本稿と同じ福井県の分析結果が含まれており、福井県の過去と現在を比較することが可能である。これにより、介護保険開始前と開始後の社会的入院の規模について一定の知見を得ることが可能であると考えた。

本稿の分析で用いるデータは、2009 年度から、福井県と東京大学高齢社会総合研究機構が実施している共同研究によって収集された福井県内の各市町国保の医療保険レセプトデータ（業務支払データ）である。福井県及び福井県の各市町の協力の下に、各市町の個人情報保護審査会、東京大学倫理審査委員会で承認を受け、福井県国保連合会から提供を受けた。

本稿ではこのうち、2007 年 4 月から 2008 年 3 月までの 1 年間の月次データを年次データに集計し直して分析を行った。2008 年 4 月以降のデータも存在するが、75 歳以上の高齢者が後期高齢者医療制度に移行してレセプトデータから脱落している為 、やむを得ず 2008 年 3 月までを対象とした。分析対象者の年齢は、府川(1995)が対象とした当時の老人医療受給資格者と比較するために、70 歳以上の高齢者とした 。また、府川(1995)同様、無受診者除き、期間内の死亡者も除いて通年資格者のみのサンプルとした。分析対象者の人数は 79,477 であるが、このうち入院期間が 1 日でもある入院者数は 19,748 である。

国保レセプトデータは、月次データの他、毎年 5 月時点の 1 カ月分だけであるが、医療機関や疾病名などの詳細な属性データが入手できる。ただし、5 月時点で医療機関に受診していないとこの属性データは存在しなので、月次データと属性データがマッチングできるサンプルは全体の一部である。本稿では必要に応じてマッチング・データの分析も行っている。

一般に用いられる社会的入院の定義は入院期間の長さによるものであるが、これは定性的にやや無理がある。そこで、府川(1995)に従って、長期入院者の 1 日当たり医療費から「基本料」を算出し、その 1.1 倍を下回るものを社会的入院者と判定した。
基本料の定義によって 4 つのケースを算出しているが、「入院者計に占める社会的入院者の割合」は 7.5%～18.4%、「資格者に占める社会的入院者の割合」は 1.9%～4.6%、「入院医療費に占める社会的入院者の入院医療費の割合」は 6.9%～23.5%、「医療費計に占める社会的入院者の入院医療費の割合」は 3.2%～10.9%と、現在も決して少なくない規模の社会的入院が存在していることが明らかとなった。もっともこれらの割合は、府川(1995)が福井県について計算した 1993 年度の割合よりも、約半分～2/3 ほど低いものになっており、介護保険の導入などが社会的入院の減少に寄与した可能性が窺える。
それでは、この社会的入院にどのように対処してゆくべきか。本来、医療行為や看護行為を必要としていない高齢者に対しては、施設介護や在宅介護で対処する方が、医療費効率化や患者の生活の質、QOL からみて望ましいことは言うまでもない。印南(2009)が指摘しているように、制度上の不適切なインセンティブが社会的入院を誘発しているのであれば、それを正してゆくことが望まれる。
具体的には、世界的にも突出している医療機関の低密度を正し、急性期医療と在宅・施設介護の棲み分けを促進することが一つの方向性である。また、要介護者を抱える家族に対しても、在宅介護に対するインセンティブとしてドイツのような現金給付を検討すべきかもしれない 。また、退院の受け皿となる介護施設や在宅介護の支援体制の構築も急務であろう。ただし、社会的入院費を代替する介護費が、社会的入院を上回る高い費用となってはあまり意味がないから、現在の特別養護老人ホームを初めとする介護施設の高コスト構造は是正してゆく必要がある。一方、在宅介護に代替させるかどうかを判断する場合には、単純な介護費だけではなく、家族介護の機会費用も含めてコストを考えるべきである。
いずれにせよ、社会的入院の規模だけではなく、社会的入院が起きている背景・構造に対する分析や、代替策のコストベネフィット分析など、まだまだ社会的入院を巡る研究課題は多いと言えよう。

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死亡前 1 年間における高齢者の医療費と介護費

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終末期を迎えた個人には集中的に医療サービスが投入されるため，それに応じて多額の医療費が発生することが知られているが，Lubits and Prihoda (1984)や Scitovsky（1984）などを嚆矢として，死亡前医療費をより詳細に検証している Garber et al. (1999)，Zweifel et al. (1999)，Seshamani and Gray (2004)，Stearms and Norton (2004)，Felder et al. (2010)などでは，死亡時年齢の上昇に伴って，死亡者の医療費が有意に減少することが確認されている。我が国でも，小椋（1994），府川・郡司（1994），府川（1998），大日（2002），鈴木（2007）などにおいて，大規模なレセプトデータを用いた分析が行われており，同様の傾向が確認されている 。しかしながら，終末期において集中的に投入されるサービスは医療サービスだけではない。この点に関して，Hoover et al. (2002) や Liu et al.(2006)，Polder et al.(2006)などでは，死亡前 1 年間における医療費と介護費の総支出は，年齢によって大きな差は存在しないが，死亡年齢の上昇に伴って医療費が下落，介護費が上昇していることを明らかにしている。こうした傾向は，日本の国民健康保険と介護保険のレセプトデータを接合させたデータを用いた阿和谷（2004），Hashimoto et al.（2010）でも報告されている。これらの分析結果は，終末期のケアのあり方をめぐる議論には，医療だけではなく介護にも焦点を当てるべきであることを示唆している。実際に，死亡前医療費に用いられているアプローチを拡張して，死亡前における介護サービス利用や介護費の決定要因の分析を行っている Werblow et al.(2007)，Weaver et al. (2009)，Meijer et al. (2011)などによれば，この期間における介護費の決定要因は，同期間における医療費の決定要因とは異なって，世帯属性の違いや病状，日常生活における身体的機能の衰え具合などといった要因が，介護費に有意な影響を与えていることが明らかにされている。

以上のような背景をふまえて，本研究では，福井県下全 17 市町の国民健康保険と介護保険のレセプトデータを用いて，死亡前 1 年間における個人レベルの医療費と介護費の特性を明らかにするとともに，同期間における医療と介護の関連性を検証している。特に，上述の先行研究とは異なって，個人のケアに対するニーズを考慮したうえで分析するともに，死亡前 1 年間における医療と介護の関連性を検証している。ケアに対するニーズは，期間内の介護サービス利用や介護費に反映されると考えられるため，それらの違いによって死亡前 1 年間の総費用に差が生じることが予想される。特に，日本の介護保険制度においては，介護サービスを利用する前に，全国一律の基準によって申請者の要介護度が定められる。こうした客観的な基準から判定された介護サービスに対する個人のニーズに応じて死亡前 1 年間の費用を分析した研究は我々の知る限り存在しない。

本研究で用いるデータは，2004 年 9 月から 2007 年 3 月における福井県下全 17 市町の国民健康保険レセプトデータ（以下，「国保レセプト」と記す）と介護保険給付費レセプトデータ（以下，「介護レセプト」と記す）である。国保レセプトからは，2003 年 10 月時点における国民健康保険被保険者 428,165 人の個人番号，保険者番号（市町村合併後），性別，年齢，診療区分，資格取得年月，資格喪失年月，資格喪失事由，件数，医療費，給付費，食事療養費，食事療養費標準負担額，一部負担金および薬剤一部負担金などが把握できる。一方で，介護レセプトからは，2003 年 4 月から 2009 年 10 月の間で要介護認定（更新も含む）を受けた 71,369 人の個人番号，国保レセプトとの共通番号，保険者番号（市町村合併前），性別，年齢，要介護度，資格取得年月，資格喪失年月，サービス種類コード，利用実日数，保険請求額，利用者負担額などが把握できる 。我々は，双方に共通の個人番号で，これらのデータをマージさせたうえで，サンプルを 65 歳以上の高齢者に限定して分析を行った。そのうえで， 2004 年 10 月から 2008 年 3 月までに死亡したもの 16,682 人を含むサンプルと，同時期に死亡しなかったもの（生存者）130,826 人を含むサンプルの 2 種類を作成した。しかしながら，このデータには，各個人の世帯属性や所得水準，消費行動，家族介護の有無，抱えている疾病，提供されている詳細な医療・介護サービスの項目，医療機関および介護サービス提供事業者に関する諸属性が含まれていない。これらの諸要因は，死亡者・生存者に関わらず，医療・介護需要に大きな影響を与えると考えられるため，本研究の分析結果や解釈には一定の留意が必要である。

詳細な分析に先立って，まずは死亡者と生存者の 1 年間の医療費と介護費を属性別に概観した。死亡者の総費用の平均は約 322 万円であり，医療費がその 77%（約 249 万円）を占め，残りの 23%（約 73 万円）が介護費となっている。これは生存者の平均費用（約 60 万円）のおよそ 5.3 倍である。性別で比較をしてみると，死亡者の総費用は女性の方がわずかに高いが，その内訳は対照的となっている。すなわち，医療費は約 58 万円女性の方が高いが，介護費は約 46 万円男性の方が高くなっている。また，生存者については，総費用は男性の方が高くなっており，特に介護費の差が顕著に存在している。年齢階級別に見てみると，死亡者の費用は，死亡時年齢の上昇に伴って，医療費は減少していくのに対して，介護費は着実に増加している様子が見られる。それらの総額は，死亡時年齢の上昇に伴ってゆるやかに減少している様子が見られる。一方で，生存者については，医療費は 50 万円前後でほとんど変化がないが，介護費は着実に増加をしており，それにともなって総額も死亡時年齢の上昇に伴って増加している様子が見られる。こうした傾向は，国内外の先行研究でも観察されている。

また，要介護状態別に比較をしてみると，死亡者の総費用は，要支援，要介護 1，要介護認定なし（非認定者）の順に高くなっており，その後は要介護度の上昇とともに単調に増加している。しかしながら，その内訳を見てみると，要介護度の進展とともに，医療費は下がっていき，要介護 3 からはほぼ横ばいとなっている一方で，介護費は要介護度の上昇とともに単調に上昇している。このことは，死亡前費用は，多くの先行研究が明らかにしてきた死亡時年齢との関係のみならず，介護に対するニーズによっても大きく変動しうることを示唆している。また，生存者に関しては，総費用は非認定者よりも認定者の方が高く，また，要介護度の上昇とともに単調に増加している様子が見られる。

加えて，死亡前 1 年間という期間において，医療費と介護費の相互依存関係や他の要因がそれらの費用に与える影響を検

証するために，連立トービットモデル（Simultaneous Tobit Model）を用いた実証分析を行った。その結果，介護費が医療費に対して負で有意な影響を与えており，介護費の増加は医療費を有意に減少させることが確認された。しかし，その限界効果は-0.023 であった。この限界効果の値は，他の条件を一定とした場合，介護費を 1000 円増加させることによって医療費を 23 円抑えることができることを意味しているが，この効果は極めて微少であるといえよう。また，医療費が介護費に与える有意な影響は確認されなかった。これらの結果は，医療機関では医療サービスと介護サービスが併用されているが，介護施設では医療サービスがあまり利用されていないことを示唆しているものと考えられる。

（※本報告の内容は，2012 年 2 月 3・4 日に名古屋ガーデンパレスにて開催された「レセプト分析報告会」における報告に基づいている。）

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通所リハビリテーションのアクセス改善が介護費用に与える影響

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1. はじめに

介護保険の財政状況の悪化や、施設での社会的入院、住み慣れた地域での継続的な生活を望む高齢者のニーズにより、施設系サービスから居宅系サービスへと、利用する介護サービスを転換させる制度設計が重視されている。2012 年度の介護保険制度改正と介護報酬改定でも、地域社会での生活を充実させるための地域包括ケアシステムの構築や、施設系サービスを補完的な存在とする計画が盛り込まれるなど、高齢者がより居宅系サービスを効率的に利用するための環境整備が急がれている。

公的介護保険制度は全国一律の制度として導入されたが、介護提供体制には地域差がある。居住する地域に希望する介護サービスの提供主体がない場合には、別の地域の提供主体に依存するか、利用そのものをあきらめる、という選択が求められる。前者の場合には、遠くになればなるほど地理的なアクセスが悪くなるため、それだけ多くの移動時間や機会費用が発生する。

提供主体が少ないことで介護サービスの種類の選択に制約がある地域では、提供されない介護サービスに対する潜在的な需要や、本来の最適な介護サービスの選択が実現しないことによる損失の存在が考えられる。損失の対象として、費用面での節約の機会や、より良好な健康状態の実現などがあげられる。居住する地域に提供主体が現れれば、需要が顕在化した場合、他の介護サービスへの需要にも影響を与える可能性がある。今後、居宅系サービスへの転換により、過疎地域などで提供主体や介護サービスの種類に変化が起これば、新たな介護サービス需要や新たな介護サービス利用の組み合わせが顕在化することも考えられる。

本研究の目的は、特定の地域で起きている介護提供体制の変化に着目し、それによって生じる介護費用・医療費の変化を定量的に把握することである。イベント部分に着目することで因果関係が特定化することができるとともに、介護サービス間や、介護サービスと医療サービス間の代替関係や補完関係を知ることができる。

本研究では、介護と医療のレセプトデータを使用する許可が得られた福井県に焦点を当て、県内で起きた提供主体による介護サービスの提供開始の影響を分析する。

ここでは特に、居宅系サービスの一つである通所リハビリテーションを分析対象とする。通所リハビリテーションとは、居宅要介護者の心身の機能の維持回復を図り、日常生活の自立を助けるために行われる医学療法や作業療法、その他の必要なリハビリテーションを指す（介護保険法第 8 条第 8 項）。サービスの提供主体には、基準省令によって医師やコメディカルの配置が課されている。通所リハビリテーションを分析対象とする理由として、2012 年の介護報酬改定の議論において、利用者の自立支援の促進が求められているとともに、医療保険の維持期のリハビリテーションの受け入れ先として期待されている点があげられる。介護報酬改定で通所リハビリテーションが重視される一方、地域間で提供主体数の格差が大きいのも事実である。2011 年 10 月 31 日の社会保障審議会の介護給付費分科会の資料では、要介護者 1000 人あたりの請求事業所数が最も少ない県と最も多い県が比較されており、約 4.4 倍の差があることが『介護給付費実態調査』（平成 21 年度）のデータから示されている 。

福井県では、2007 年 3 月まで複数の町（永平寺町・池田町・美浜町・おおい町）に通所リハビリテーションの提供主体がなかったが、2007 年 4 月以降、おおい町で、従来からあった介護老人保健施設が通所リハビリテーションと介護予防通所リハビリテーションのサービス提供を開始した。このような場合、提供が始まった町の住人の介護サービス需要の変化は、サービスの提供開始と外部要因の影響を受けるが、提供がない町の住人の介護サービス需要の変化は、外部要因の影響のみを受けると推察される。

そこで本研究では、永平寺町・池田町・美浜町をコントロールグループ（非介入群）、おおい町をトリートメントグループ（介入群）とみなし、それぞれのグループで生じる介護費用の変化や医療費の変化を分析する。具体的には、2006 年度と 2007 年度の介護費用と医療費の平均値の比較や「差の差分(Difference-In-Differences: DID)」による推定から、通所リハビリテーションの提供開始がもたらす影響を把握する。使用するデータは、介護保険のレセプトデータと国民健康保険のレセプトデータである。

本研究と関連する先行研究として、地域内での医療機関の密度と医療需要の関係を検討している研究があげられる(Stano (1985), Carlsen and Grytte (1998))。いずれも医師誘発需要仮説を検証することを目的とした論文である。Zweifel, Breyer, and Kifmann (1997) が指摘するように、医療機関の密度が高ければ、移動時間や待ち時間が短く、機会費用が低下するため、医師が誘発する需要とは別に、患者が医療需要を増加させる「利用可能性効果(availability effect)」の影響も考える必要がある。Stano (1985)と Carlsen and Grytte (1998)は、利用可能性効果によるバイアスを考慮した上で医師誘発需要部分を計測した研究である。本研究は利用可能性効果が介護費用や医療費にもたらす影響を計測している。

また、利用者と提供主体の間の地理的なアクセスに関する研究として、北島・北澤・曹・野山 (2001)と高橋・小田切・内田 (2006) があげられる。それぞれ八王子市と甲府市に着目し、地理情報システム(GIS)を用いて高齢者の居住地域から通所介護施設までの距離を計測している。その結果、同じ市内であっても居住地域から通所介護施設までの距離にばらつきがあり、優先的な設置が求められる地域があることを指摘している。

2. データ

本研究では、介護給付と医療給付のレセプトデータを使用する。前者は、福井県国民健康保険団体連合会が共同電算処理で管理する調査客体の介護給付等レセプトデータである。このレセプトデータは、介護保険の被保険者番号をもち、かつ介護保険の介護認定を受けている人によって構成されている。それぞれの個人について、サービスの提供年月、性別、年齢、要介護

度、資格取得年月、資格喪失年月、サービス種類コード、サービス実日数、計画点数、保険請求額、利用者負担額、公費本人負担額、出来高医療費利用者負担額、公費出来高医療費利用者負担額などの情報が含まれている。分析では1ヶ月あたりの保険請求額を使用する。2007年4月に通所リハビリテーションの提供がおおい町で始まっていることから、その前後1年に着目するため、2006年4月から2008年3月の給付分の月次データを使用する。

後者は、福井県国民健康保険団体連合会が共同電算処理で管理する調査客体の医科・歯科・調剤分のレセプトデータのうち、医療情報・月別受診動向調査を使用する。2003年10月から2008年9月までに1ヶ月でも国保加入者であった人がすべて抽出されているデータで、ここでは2006年4月から2008年3月のレセプトデータを使用する。特に入院外データの入院外（診療区分）の医療費に着目する。

分析では、要介護1から要介護5の利用者を対象とする通所リハビリテーションとそれ以外の介護サービス、参考として要支援1と要支援2の利用者を対象とする介護予防通所リハビリテーションとそれ以外の介護サービスに焦点を当てる 。通所リハビリテーション以外の介護サービスとして、通所リハビリテーションと同様に、日常的に利用される介護サービスを考える。対象とするのは、訪問介護、訪問入浴介護、訪問看護、訪問リハビリテーション、通所介護、短期入所生活介護、短期入所療養介護（介護老人保健施設）、短期入所療養介護（介護療養型医療施設等）、居宅療養管理指導、夜間対応型訪問介護、認知症対応型通所介護である。また、介護予防通所リハビリテーション以外の介護サービスも同様で、対象とするのは、介護予防短期入所生活介護、介護予防短期入所療養介護（介護老人保健施設）、介護予防短期入所療養介護（介護療養型医療施設等）、介護予防居宅療養管理指導、介護予防訪問介護、介護予防訪問入浴介護、介護予防訪問看護、介護予防訪問リハビリテーション、介護予防認知症対応型通所介護である。

分析では、おおい町の標本をトリートメントグループとし、永平寺町・池田町・美浜町の標本をコントロールグループとして扱う。また、65歳以上の標本に限定して分析する。

3. 分析結果のまとめ

分析の結果、大きく二つの点が観察された。第一に、通所リハビリテーションのサービス提供が始まることで、提供されたおおい町では、通所リハビリテーションの保険請求額が増加する一方、他の日常的な介護サービスの合計の保険請求額が減少することがわかった。提供されていない永平寺町・池田町・美浜町では、このイベントの前後での変化が小さかったことから、おおい町での増額・減額は、通所リハビリテーションの提供開始の影響を受けていると考えられる。

2006年度と2007年度の比較において、おおい町では、通所リハビリテーションは1ヶ月あたり平均して約1000円の増加があったが、他の介護サービスの総額は平均して約4000円の減少があった。そのため、通所リハビリテーションと他の介護サービスの合計をみた場合には約3000円の減額が起きたことになる。また、医療費は、おおい町と永平寺町・池田町・美浜町とでは、いずれも約1000円程度の増額が起きており、通所リハビリテーションのサービス開始とは独立した変動であると考えられる。通所リハビリテーションと通所リハビリテーション以外については、トービットモデルによる推定も行っており、それらの推定結果も、平均値データで観察された事実と同様のことを示している。

第二に、通所リハビリテーション以外の介護サービスでは、通所リハビリテーションと同様に保険請求額が増加した介護サービスと、逆に減少した介護サービスがあることが観察された。増加したものは短期入所療養介護（介護老人保健施設）であり、減少したものは訪問介護、訪問看護、通所介護、短期入所生活介護、居宅療養管理指導である。減少したもののうち、通所介護は通所リハビリテーションと部分的にサービス内容が近いことが影響していると考えられる。そのため、両者は利用者にとっては代替財としての性格をもっていることが推測される。

以上のことより、新たな提供主体が介護サービスの提供を開始することで地理的アクセスが改善されると、新たな介護サービスの費用が増えるとともに、費用を減らす介護サービスがあり、介護費用全体でみた場合には、費用が減少していることがわかった。これは、選択可能な介護サービスの種類が増えたことで、利用者がより自分にとって適切な組み合わせになるよう利用する介護サービスの種類を変化させたため、全体の費用が減少したと考えられる。

研究上の今後の課題としては、大きく3点ほどあげることができる。第一に、医療費に関してはより正確さを向上させるため、個人 ID をマッチングさせて厳密に議論する必要がある。第二に、今回の保険請求額の変動が一時的なものなのか、継続的なものなのか、識別する必要性がある。たとえば、2006年度と 2008 年度以降のデータの検証をすることで、持続性について議論することができる。そして第三に、利用する介護サービスの変化がその後の健康状態に与える影響についても議論していく必要があると考えられる。

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特定健康診査結果からみた福井県民の健康度

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福井県の平均寿命は男女ともに全国トップクラス であり、日本を代表する健康長寿県として知られている。その健康長寿の要因を探るため、これまで様々な側面から分析がなされてきたが、客観的な健康診査データからの評価としては、限られた対象地域、限られたサンプル数で行われた国民健康・栄養調査（福井県分）、県民健康・栄養調査の調査報告があるのみで、必ずしも十分なものとは言えなかった(福井県(2005)) 。
本稿は、平成 20 年度より 40 歳から 74 歳の全県民が特定健康診査（以下、特定検診）の対象となり、大規模なデータが収集可能となったことに着目し、特定検診結果からの健康度の評価を行なうことにした。分析対象となるサンプルは、各市町の国民健康保険加入者のうち、平成 20 年度に特定検診を受診した全数（31,870 人）である。

用いるデータは、福井県各市町の国民健康保険（以下、国保）加入者のうち、平成 20 年度に特定検診を受診した人々の検査値データである。平成 20 年度受診者の全数分を、各市町のご協力・ご許可の下に、福井県国民健康保険団体連合会よりデータの提供を受け、分析を行った。また、必要に応じて、対象者の医療保険レセプトデータをマッチングさせ分析した。
医療保険レセプトデータは、具体的に、「新共電・月別受診動向調査（以下、A データ）」、「新共電・傷病別等受診動向調査（以下、B データ）」の 2 種類がある。前者の A データは毎月の国保加入者の支払い請求書をデータ化したもので、入院、外来、歯科、調剤の各医療費が細目にわたって収集可能である。サンプル対象は平成 19 年 1 月に国保加入者であった人々を追跡しているため、平成 20 年度の国保加入者全員ではない。分析では平成 20 年の 1 年分の医療費を合算して用いている。後者の B データは、平成 20 年 5 月に医療機関を受診した国保加入者について、疾病名などの詳細を調査したデータである。サンプル対象は平成 19 年 5 月に国保加入者であった人々を追跡しているため、平成 20 年度の国保加入者全員ではないし、平成 20 年 5 月の無受診者分は除かれている。

分析結果は、次の 5 つにまとめられる。

(1)検査値の全国との比較
全体として全国に比してリスク群の割合は低く、福井県民の健康度が高いことがわかる。特徴としては、血圧関連、糖尿関連の検査値の良さが際立つ一方、コレステロール、血液関係の検査値に若干の課題あることがわかった。
また、若い世代では全国よりもリスク群の割合が高い項目がやや多く、総じて見て、年齢層が高いほうが、全国比での健康度が高いといえる。

(2)疾病リスク群の全国との比較
検査値から、メタボリックシンドローム、糖尿病、高血圧、脂質異常症の判定者の割合を計算し、全国と比較すると、福井県の健康度が際立って高いことがわかる。
あえて注意を要するとすれば、70 歳代でのメタボリックシンドローム判定者がやや全国を上回ることと、脂質関係でやや服薬率が高い年齢層があるといった点程度である。

(3)市町別の検査値の比較
判定リスク群の割合が高い地域は、各検査値ごとに、地域的な偏りが見られることがわかった。
また、全ての検査値で判定リスクが高いという市町があるというわけではなく、それぞれの市町で一長一短があることがわかった。

(4)検査値と医療費の関係の分析
医療費と健康度の間の統計的な関係（回帰分析）から、福井県民の健康度が全国に比較して良いことによって、どの程度、医療費が縮減されているのか、その節約額を評価することが出来る。
これをもとに、各年齢層の総医療費をどの程度押し下げているか定量化すると、40 歳代の医療費を－7.5%、50 歳代の医療費を－13.9%、60 歳代の医療費を－10.9%、70-74 歳の医療費を－10.1%と、それぞれ 1 割程度削減できていることがわかる。

(5)特定健診未受診者と受診者における医療費比較
一人当たり年間総医療費について、受診者と未受診者の差を比較すると、未受診者の総医療費は平均で 360,705 円であるのに対して、受診者は 237,403 円であり、未受診者が 5 割近く上回っていることがわかった。 これは、入院、外来といった細目に分けても、歯科以外は同様の傾向となっている。

特定健診未受診者の方が、受診者よりも医療費が高いという点については、解釈にやや注意する必要がある。
一つの解釈は、未受診者は健康状態が悪いことを知らずに、状況を悪化させて多額の医療費を発生しているというものであるが、それ以外にもさまざまな可能性がある。例えば、未受診者には入院患者が元々多いので（平均入院日数、入院確率が受診者よりも高い）、①健診に行くことができない、もしくは②入院で検査を行なって健康状態がよく分かっているから、健診に行かないという可能性もある。そこで、長期入院のサンプルを除いたデータの分析を行ったが、やはり 3 割程度未受診者の医療費が高いことは変わらないことがわかった。したがって、未受診者の医療費が高いことは、入院で時間的制約があるという面からだけでは解釈できず、やはり、健康状態を把握せずに重篤化している患者がいる可能性を否定することは出来ない。
そのほか、特定健診受診者と未受診者で、それぞれどのような疾病が多いのかを分析すると、入院、外来ともに未受診者の方が重篤な疾患の割合が高いことがわかった。

さて、本分析から得られる結論をまとめると、概ね次のようになろう。特定健診の検査値におけるリスク群の割合、メタボリックシンドロームなどの判定者の割合を、福井県の平成 20 年の特定健診受診者（全数）における検査値と、全国（18 年度国民健康・栄養調査結果）とで比較したところ、福井県の健康度の高さが際立っていることがわかった。特に、血圧や糖尿病、メタボリックシンドロームなどに対するリスクは、福井県で非常に低い。一方で、コレステロール等の脂質関係や赤血球数、

ヘマトクリットといった血液関係の値はやや全国を下回るものも存在している。また、どちらかといえば若い年齢層よりも年配の年齢層の方が全国と比較した健康度は高い傾向にある。さらに、市町別のリスクにはかなり地域的な特徴がみられており、今後の健康増進政策の課題を浮かび上がらせることになった。

次に、福井県の健康度が高いことによって、福井県の医療費をどの程度縮減できているかという点を定量的に評価したところ、各年齢層ともに1割程度、医療費を節約できていることがわかった。今後さらに健康度を高めれば、医療費を縮減することが可能であろう。

最後に、特定健診の受診者と未受診者の医療費を比較した結果、未受診者の方が 5 割 程度、医療費が高いことがわかった。入院が長いことによって特定健診が受けられない人を除いても、この結果は頑健な傾向を持っている。国保の健診受診率は一般的に低いが、未受診者はかならずしも健康な人ばかりではなく、疾患を持っている人々も含んでおり、健康状態を把握しないばかりに未受診者の病状が重篤化する可能性も否定できない。国保の健診受診率を高める努力は、今後、継続的に行なってゆくべきものと考えられる。

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４．メンバリスト

4.メンバリスト

4.1　機構専任

機構長・教授　　鎌田　実（総長裁量ポスト）
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4.4　客員研究員

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５．付録

5. 付録

5.1　規則等

5.1.1　東京大学高齢社会総合研究機構内規
（平成２１年 ２月 ３日　総長裁定）

（趣旨）

第１条 この内規は、東京大学高齢社会総合研究機構（以下「機構」という。）の組織及び運営について定めるものとする。

（目的）

第２条 機構は、国 内外に散在する個人のエイジング(加齢)や人口の高齢化に関する知見や技術を「ジェロントロジー」という知識体系に集約・構造化すると共に、新たに創成すること、それにより産み出される新しい価値を社会に還元し、高齢社会の諸課題を学際的に解決することを目的とする。

（業務）

第３条 機構においては、前条の目的を達成するため、次の各号に掲げる業務を行う。

(1) エイジングや高齢化に関する学際的研究の推進

(2) 高齢社会を俯瞰的視野から支える人材育成を目的とした教育プログラムの運営

(3) 機構における研究及び教育に必要な会議の開催

(4) 機構における研究成果の社会への還元

(5) その他前条の目的達成のために必要な業務

（組織等）

第４条 機構に、室員として専任教員、兼任教員、特任教員、特任専門員等を置くことができる。

２ 前項の教員の選考は、東京大学総長室総括委員会内規及び東京大学総長室総括委員会教員選考に関する申し合せによるものとする。

（機構長）

第５条 機構に、機構長を置く。

２ 機構長は、本学の教授のうちから総長が指名する。

３ 機構長の任期は、２年とする。ただし、再任を妨げない。

（副機構長）

第６条 機構に、副機構長を置くことができる。

２ 副機構長は、機構長を補佐するものとし、本学の教授のうちから機構長が指名する。

３ 副機構長の任期は、２年とする。ただし、再任を妨げない。

（運営委員会）

第７条 機構に、その管理及び運営に関する重要事項を審議するため、運営委員会を置く。

２ 運営委員会に関し必要な事項は、別に定める。

（事務）

第８条 機構に関する事務は、工学系・情報理工学系等事務部で行う。

（補則）

第９条 この内規に定めるもののほか、機構の運営に関し必要な事項は、別に定める。

附 則

この内規は、平成21年4月1日から施行する。

5.1.2 東京大学高齢社会総合研究機構運営委員会内規 （平成 21 年 4 月 28 日、機構長 裁定）

（趣旨）

第１条 この内規は、東京大学高齢社会総合研究機構内規（以下「機構内規」という。）第７条第２項の規定に基づき、東京大学高齢社会総合研究機構運営委員会（以下「運営委員会」という。）の組織及び運営について定めるものとする。

（任務）

第２条 運営委員会は、機構内規第２条に定める目的を達成するために、東京大学高齢社会総合研究機構（以下、「機構」という。）の管理及び運営に関する重要事項を審議する。

（組織）

第３条 運営委員会は、委員長及び委員 20～30 名をもって組織する。

（委員長）

第４条 委員長は、委員の中から選任する。

２ 委員長は、運営委員会を招集し、その議長となる。

３ 委員長に事故があるときは、あらかじめ委員長の指名した委員がその職務を代行する。

（委員）

第５条 委員は、東京大学総長室総括委員会の同意を得て、次に掲げる者に機構長が委嘱する。

（１）　機構の専任教員　若干名
（２）　その他総長が必要と認めた本学教職員
（任期）
第６条　前条の委員の任期は、２年とする。ただし、再任を妨げない。
２　補欠の委員の任期は、前任者の残任期間とする。
（議事）
第７条　運営委員会は、委員の過半数の出席を必要とするが、委任状の出席も可とする。またメールでの審議も可とする。
２　運営委員会の議事は、出席委員の過半数をもって決し、可否同数のときは、委員長の決するところによる。
（執行委員会）
第８条　運営委員会は、機構の円滑な運営を行うために、執行委員会を設ける。
２　執行委員会の委員は、運営委員会の議を経て機構長が委嘱する。
３　執行委員会は、機構の日々の業務にまつわる案件を審議し、運営委員会へ報告して了承をもらうこととする。
（補則）
第９条　この内規に定めるもののほか、運営委員会及び執行委員会に関し必要な事項は、別に定める。

附則
この内規は、平成 21 年 4 月 1 日から施行する。

5.1.3　高齢社会総合研究機構客員研究員及び協力研究員受入内規
（制定　平成２１年４月２８日　執行委員会）

第１条　高齢社会総合研究機構において一定期間､国内外の研究者と共同研究等の必要がある場合は客員研究員を、国内外の研究者と研究上の協力等を必要とする場合は協力研究員を置くことができる。

第２条 客員研究員及び協力研究員は、原則として、国内外の教育・研究機関に所属している常勤の研究者とする。

第３条 客員研究員は博士の学位を有するか、それに相当する研究歴を有する者、又は、これと同等以上の研究能力を有する者とし、協力研究員は博士の学位取得以前の研究者で、修士課程修了の者、又は、これと同等以上の研究能力を有する者とする。

第４条 研究期間は、原則として１４日以上１年未満とする。

第５条 客員研究員及び協力研究員を受け入れようとする教員（以下「受入教員」という。）は、１ヶ月前までに別紙様式１により、機構長あて申請しなければならない。

第６条 客員研究員及び協力研究員の受入れは、機構長が決定する。

第７条 受入教員は、必要に応じて旅費、滞在費、謝金を客員研究員及び協力研究員に支給することができる。

第８条 客員研究員及び協力研究員の受け入れ承認後、研究期間に変更が生じた場合、受入教員は別紙様式２により、速やかに機構長あて申請しなければならない。

第９条 この内規に定めるもののほか、必要な事項は機構長が別に定める。

附則

この内規は平成21年4月1日から施行する。

5.2 執行委員会、運営委員会の開催実績

5.2.1 執行委員会の開催実績

2011 年 5 月 9 日、8 月 22 日、9 月 22 日、10 月 7 日、11 月 23 日

2012 年 1 月 22 日、2 月 6 日

（メール審議も含む）

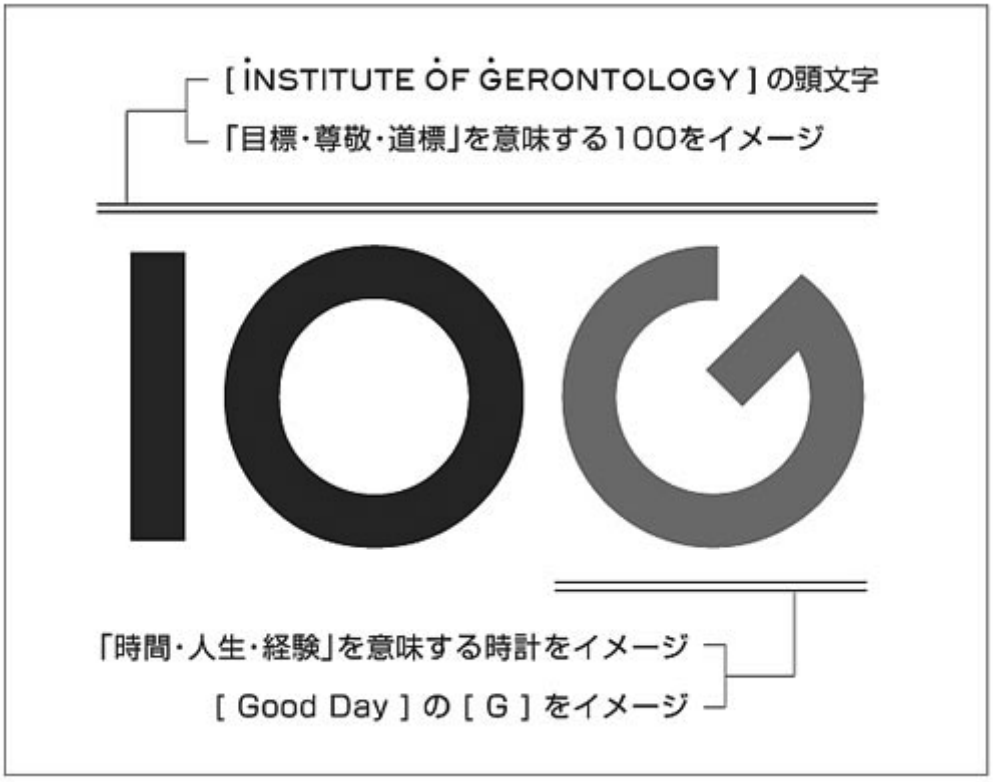
5.2.2 運営委員会の開催実績

2011 年 7 月 22 日・23 日

2012 年 3 月 24 日

5.3　ロゴデザインの紹介

機構の英語名（Institute of Gerontology）の頭文字「IOG」をモチーフにしたロゴを、ユニバーサルデザイン、サスティナブルデザインで日本の第一人者である、中川聰氏（トライポッド・デザイン株式会社代表、東京大学大学院工学系研究科機械工学専攻デザインイノベーション社会連携講座　特任教授）に作成していただきました。
このデザインには、「１００」「時間・人生・経験」「Good の G」という、たくさんの思いが詰まっており、「高齢社会、そして長寿を尊び豊かなものとしたい」という、機構の理念が反映されています。



100

Design concept-❶

「100」という数は、時に「満」を意味し、
ひとつの到達値として用いられます。
年齢における「100」年という歳月は、
さらなる特別な価値を生むものです。
「100歳まで元気でいたい」
「100歳になっても楽しく暮らしたい」
「100歳をきっかけに何かを始める」
「100年の経験で見えてくる事もある」
100歳とは私たちにとって、ひとつの
「目標」であり、「夢」であり
人生の大きな「道標」でもあるのです。

Design concept-❷

「人生は時の旅人」
"G"は刻み続ける時の振り子を象徴し、
100までの時の流れ、そして100から新たに始まる時間、一刻一刻を表現しています。

「IOG」と100歳が重ねて見えるデザインであり、100歳に見る「人生における夢としての道標」をヴィジュアライズ(可視化)したイメージを訴求しました。

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100 + GOOD DAY

IOG

Design concept-❸

「100歳までの素敵な人生」
そして「100歳からの幸せな時間」
100歳まで、100歳から
<Good Day！>をいつまでも。

5.4　掲載記事

＜掲載記事例（一部）＞

【2011.05.17／読売新聞･朝刊】

車イス移動楽々
介護拠点も併設

岩手県釜石市は16日、東京大学と連携し、東日本大震災で被災した高齢者らが入居する新タイプの仮設住宅を建設することを決めた。〝長屋〟のように近所づきあいが可能な住宅を約100戸作り、孤独死の防止を目指すほか、介護拠点や託児所を併設する。住戸配置、人的支援などの総合的な対策で、ケアの必要な人を支える初の仮設住宅となる。

「コミュニティケア型仮設住宅」と名付けた仮設住宅の建設が予定されているのは、市内の平田総合公園。同市が近く県に申請、23日

（東大高齢社会総合研究機構の資料をもとに作成）

ケア重視の仮設住宅

阪神大震災では、仮設住宅に移った後に地域のつながりが薄れたことなどから、高齢者を中心に2000人以上が孤独死した。今回の震災の被災地は高齢化率が全国平均より高いため、東大高齢社会総合研究機構が新型仮設住宅を提案した。

同機構の辻哲夫教授は「復興には高齢者が孤立しない環境が必要だ。安心できる生活を仮設住宅の段階から実現し、今後の地域作りに生かせれば」と話している。

釜石市設置へ

高齢者のほか、障害者やひとり親世帯などが対象で、車いすでも移動しやすいように、住戸をウッドデッキでつなぐ。さらに住戸の配置を変更、通常はすべて北側に面している玄関を互いに向き合うようにし、住民が交流しやすい環境を作る。併設された介護拠点ではデイサービスなどを行う。

【2011.05.24／建通信新聞】

【2011.07.10／日経新聞･朝刊】

SUNDAY NIKKEI

理想の高齢社会像探る

65歳以上が40%

千葉・柏「豊四季台地域」

千葉・船橋「高根台団地」

子ども拠点で指導役
在宅のまま効率的に
公園に住民の声反映

働く場提供
介護・医療
まちづくり

住民主導で対応

多機能型介護施設
URに要望し実現

介護に高齢者活躍

【2011.08.01／日経ホームビルダー】

東日本大震災のいま

復旧
復興

仮設高齢者の孤立を防げ

岩手県遠野市設町

【2011.08／スウェーデンの新聞】

Japaner nyfikna på svensk äldrevård

Uppsala universitet. Forskare på studiebesök • Den svenska modellen lockar