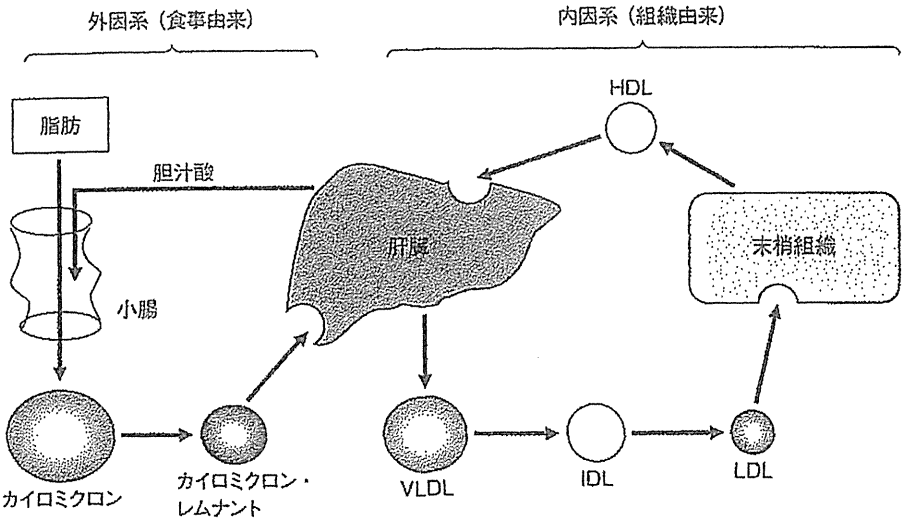

VLDL：超低比重リポ蛋白，IDL：中間比重リポ蛋白，LDL：低比重リポ蛋白，
HDL：高比重リポ蛋白

図1　リポ蛋白代謝

表2　脂質異常症：スクリーニングのための診断基準（空腹時採血）

LDLコレステロール	140mg/dL以上	高LDLコレステロール血症
	120～139mg/dL	境界域高LDLコレステロール血症
HDLコレステロール	40mg/dL未満	低HDLコレステロール血症
トリグリセライド	150mg/dL以上	高トリグリセライド血症

（文献1より引用）

2　診断基準

日本動脈硬化学会のガイドラインに基づく脂質異常症の診断を表2にまとめます[1]。LDLコレステロール（LDL-C）値はFriedewald式による計算値を推奨しています（LDL-C値＝総コレステロール－HDL-C－TG値/5）。しかし，この値はTG値が400mg/dL以上ではその精度に問題が生じるため，TGが400mg/dL以上または食後採血の場合はnon HDL-C値を用います。non HDL-C値は（総コレステロール－HDL-C値）で求め，その基準値はLDL-C＋30mg/dLとします[1]。

3　疾患と糖尿病との関係

糖尿病と脂質異常症は密接な関係にあり，とくに高LDL-C血症があると，虚血性心疾患の強いリスクになることが知られています。欧米また日本の疫学データによると糖尿病の存在は多因子で調整しても，冠動脈疾患，脳梗塞の2～3倍程度のリスクの上昇につなが

るとされています[2,3]。とくに女性の場合，糖尿病患者では動脈硬化性疾患発症リスクが著しく増加します[4]。したがって，日本動脈硬化学会のガイドラインでは，そのLDL管理目標において，糖尿病があれば，その他慢性腎臓病，非心原性脳梗塞，末梢動脈疾患と同様にカテゴリーⅢとされ，そのLDL-C管理目標値は120mg/dL未満としています。さらに糖尿病では，高TG血症，低HDL-C血症をともないやすく，それらも動脈硬化性疾患のリスクになります。

4 高齢者の特徴

高齢者では糖尿病ならびに脂質異常症罹患歴が長く，すでに動脈硬化性疾患を持っている，または動脈硬化自体が進行している症例が多いと思われます。また，脂質異常症，とくに高LDL-C血症に対しては，薬物療法としてスタチンによる治療が確立され，多くのエビデンスが存在します。しかし，高齢者に対しては，日本動脈硬化学会のガイドラインにおいても，前期高齢者では成人と同様の方針での治療を勧めてはいますが，後期高齢者（75歳以上）の冠動脈疾患の一次予防に対しては，この薬剤の予防効果の意義が確立されていないことから，主治医の判断で個々の患者に対応するとしています（冠動脈疾患の二次予防に対してはスタチンの使用を勧告しています）[1]。

（葛谷 雅文）

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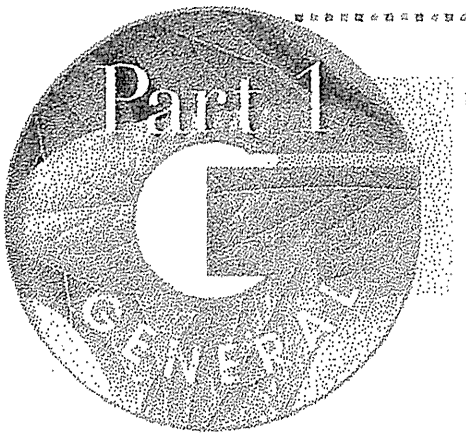

フレイルとは ——その概念と歴史

葛谷雅文　Kuzuya, Masafumi

はじめに

Frailty, frail elderly という言葉は日本の高齢者医療・福祉の研究者の間で使用されるようになってまだ日が浅いが，欧米では 1980 年代より盛んに使用されてきた言葉である．しかし，この言葉の意味するところは明確ではなく，さまざまな状態の高齢者をさすような状況が続いてきた．実際筆者らも米国の老年医学関連の雑誌に論文投稿をした際，調査対象を "frail elderly" としたところ，editor に「どのような対象者を "frail elderly" としているのか，明確にしろ」と指摘されたことが 2000 年代に入ってもあった．現在もなお単一の明確な定義は存在していないが，徐々に frailty, frail elderly の意味は集約されつつあるように思う．本稿では frailty（フレイル）の概念の変遷を中心に，文献的考察をしてみたいと思う．

多機能障害としてのフレイル

"Frail elderly" を PubMed で検索すると，多くは 1980 年代から関連論文がヒットする．80 年代初期の論文に frail elderly の明確な定義を示している論文は見つからないが，その多くは少なくともなんらかの介護が日常生活を送るうえで必要な高齢者として "frail elderly" が使用されている[1,2]．

1981 年に UCLA の Rubenstein は高齢者総合機能評価が必要な対象者を frail elderly とし，その特徴を「多くの慢性疾患と同時に精神心理問題を抱え，社会的な孤立を併せ持つ状態」とした[3]．また，Fisk は frail elderly を包括的な医療提供が必要となる対象者として，「著しく身体的，精神的，社会的に障害をもち，多くのサービス供給が必要な高齢者」としている[4]．また老年学の分野においても，種々の障害のため施設入所が必要な高齢者を "frail elderly" と一般的に呼称されていた．実際，Knight らは "Who are the frail elderly?" の問いに対して，「心身の障害があり，既存のサポートシステムでは在宅療養が困難であるような高齢者」としている[5]．1988 年に Woodhouse らも frail elderly を「移動に関しても自立しておらず，日常生活上でなんらかの介助を要し，多くは介護施設に入所している 65 歳以上の高齢者．そのような対象者の多くは重篤な心肺疾患，肝腎疾患，代謝疾患に罹患しているわけではないが，検査上は軽度のさまざまな異常が観察され，定期的な投薬が必要な状態にある．一般にアルツハイマー病，多発脳梗塞，パーキンソン症候群，骨粗鬆症，変形性関節症，骨折後などを基礎疾患としてもっていることが多

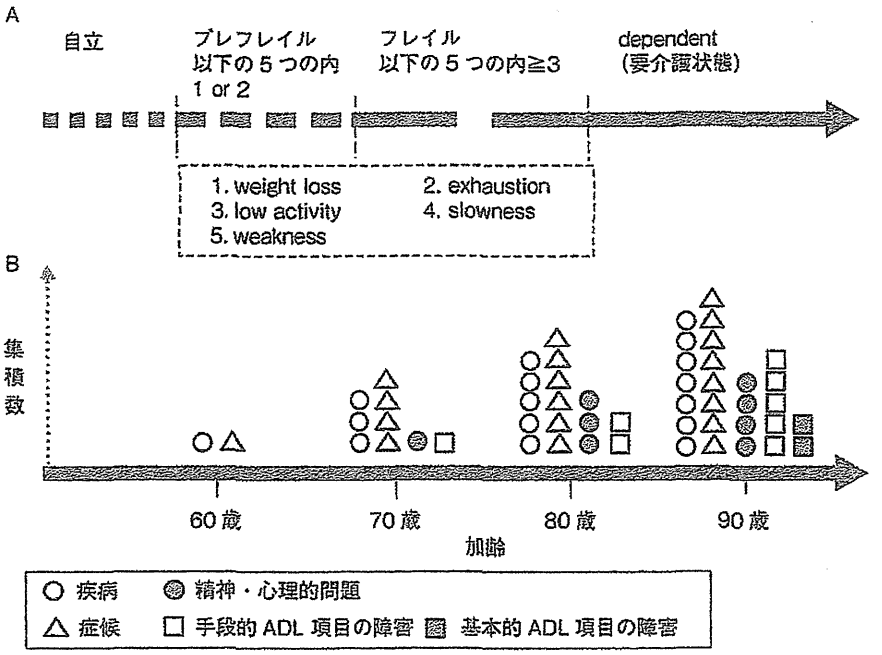

図1　2種類のフレイルの概念
A：Friedらの定義をもとにしたフレイルの概念
B：Rockwoodらの定義をもとにしたフレイルの概念

い」としている[6]．

このように，当時はfrailty，frail elderlyを基本的日常生活動作（ADL）障害があり，さまざまな基礎疾患を抱え，在宅療養の継続がむずかしい高齢者としてとらえられていた．

ストレスに対する脆弱性ならびに障害の前段階としてのフレイル

一方で，複数の老年医学者からはフレイルを「加齢にともなう症候群として，多臓器にわたる生理的機能低下やホメオスターシス（恒常性）低下を基盤として，種々のストレスに対して身体機能障害や健康障害を起こしやすい状態」，との概念が提唱された[7,8]．このコンセプトは明らかに上記の機能障害とは同一のものではなく，要因を考慮した異なる概念である．

これらの概念の提示にともない，1990年代になりフレイルを種々の介入が可能な状況，すなわち可逆的な状態ととらえ，老年医学的な介入により恩恵を受ける対象者をfrail elderlyとして定義づける流れが出はじめた．いい換えると，フレイルをphysically independent（自立）とdependent（要介護状態）の中間に位置する状態として定義する報告が出てきた．Winogradらは病院に入院した高齢患者を「自立している高齢者」「frail elderly」「重度の障害高齢者」と分別し，フレイルの存在と在院日数の延長，生命予後との関連を報告している[9]．BuchnerとWagnerは1992年にフレイルを「体の予備力が低下し，身体機能障害に陥りやすい状態」とし，障害のすでにある状態とは明確に区別し，ADL障害の前段階として定義づけた[10]．さらに，彼らはフレイルに関連する3つの前駆状態として，神経系の障害（複雑な仕事を

実行する能力の低下），動作能力の低下（筋力の低下），エネルギーの低下（心肺機能の低下により運動耐容能の低下）の関与を提案した[10]．フレイルの出現要素として疾病はもちろんであるが，それ以外に不活発な日常生活や疾病による過度な安静など身体活動の低下などによる要因も多く含まれている．したがって，フレイルは予防可能の要素が多く含まれ，その予防方策には 1）身体機能の定期的モニタリング，2）身体機能低下に直結する急性または亜急性のエピソード（疾病を含む）の予防，3）身体機能の低下が出現する前にその予測をする，4）身体機能障害が出現した後においても，回復を抑制する障害を排除する，としている[10]．

Fried らは身体的フレイルの定義として，1）体重減少，2）疲労感，3）活動量低下，4）緩慢さ（歩行速度低下），5）虚弱（握力低下），の 5 項目を診断基準として，3 つ以上に当てはまる場合はフレイルとして診断し，1 つまたは 2 つ該当する場合はプレフレイルとした[11]（図 1A）．このフェノタイプは明らかに先の 3 年間に起こる転倒，移動障害，ADL 障害，入院，生命予後に関連していることが明らかにされた．Fried はさらにこのフレイルをサルコペニア，予備力低下（恒常性低下）と関連させる理論を提示した[11]．

高齢者に出現しやすい疾病，症候，障害の集積としてのフレイル

一方，Rockwood らは 1999 年にフレイルを以下の 4 群（0 ～ 3）に群分けして施設入所や生命予後のリスクとの関係を報告している[12]．（0）介助なしで歩行や ADL が実施でき，失禁や認知機能障害がない；（1）尿失禁のみ存在；（2）以下のうち 1 つ以上が当てはまる場合（失禁の場合は尿便失禁の 2 つ），移動，ADL になんらかの介助が必要，認知症ではないが，認知機能障害が存在する，尿，便失禁がある；（3）2 つ以上（失禁の場合は 3 つ）が当てはまる場合，移動や ADL が全介助，または尿，便失禁，認知症が存在．

さらに Rockwood らは，フレイルを臨床的に介入法の選別，生命予後や施設入所のリスク予測することを目的として，包括的な因子（30 から 70 項目で症候，疾病，身体機能障害，検査異常なども含む）の存在（異常・不能の有無）をカウントし，Frailty Index を計算することを提唱している[13,14]（図 1B）．これは項目ごとに重みづけすることなく，たとえば合計 50 項目の評価で 10 項目が該当するなら Frailty Index は 10/50 ＝ 0.2 となる．この評価項目のなかには当然 ADL 障害や認知機能障害は含まれるし，慢性疾患などの疾病も含まれる．これらの能力障害，疾病，症候を重みづけなしに単純に加算して，フレイルの有無（あるかなしかの二分割ではなく）ではなく，インデックスとして連続的にフレイルの集積度を数値化し評価することは，臨床的には実際の高齢者の虚弱性評価としてわかりやすいものではある．

2 つの概念の相違

この Rockwood らの提唱する概念は，明らかに上記の Buchner と Wagner が提唱した「フレイルは障害の前状態である」との概念とは異なるものでものではあるが，高齢者の脆弱性，生命としての予備力の欠乏状態を評価するとの意味では理解しやすい．Rockwood らの提唱している疾患，ADL 障害を含めた多数の項目の有無または能力を評価する

Frailty Index は生命予後を含め，将来の健康障害の予測因子として有用なことは多くのデータの蓄積がある[15,16]．一方で，Frailty Index は高齢者包括的総合機能評価となにが異なるのだ，という批判も出てくる．

このようにフレイルの概念としては大きく分けて２つあり，繰り返しになるが１つはフレイルを身体障害の前段階としてとらえる考え方，もう１つは疾患，機能不全も含んだ多項目の包括的な異常（不能状態）の集積を評価する考え方である．欧米においてもこの定義の相違に関しては現在もなお盛んに論争が続いている．

昨年，計６つの国際学会（International Association of Gerontology and Geriatrics, Society on Sarcopenia, Cachexia, and Wasting Diseases, the International Academy of Nutrition and Aging），ヨーロッパ内の学会（European Union Geriatric Medicine Society），ならびに米国の学会（American Medical Directors Association と American Federation for Aging Research）ならびに有識者によりコンセンサス会議が開かれ，以下のような方針が打ち出されている[17]．

まずは，フレイルを「多因子が関与する症候群で生理機能の減退，体力，持久力の低下を基盤として，身体機能障害や死に対して脆弱性が増した状態」と定義した．

また，以下の４つのキーポイントを提唱している．

1. 定義によってはフレイルにすでに身体機能障害を抱える対象者が含まれている場合も，または含まれていない場合もありうるが，できるだけ障害にいたる前で，介護に依存していない対象者をターゲットにすべきである．このような症例をターゲットにすることにより，要介護に陥らないような介入ができる可能性がある．
2. サルコペニアはフレイルの構成成分であり，フレイルはサルコペニアそのものよりも，より多面的な広い概念である．
3. 多くの妥当性を検討されたフレイルモデルがすでに存在しており，老年内科医によりそれぞれのモデルに沿った評価基準を用いて種々の定義によるフレイルの診断がなされるべきである．これらの異なるモデルはいずれも健康障害や生命予後を予測することがわかっている．
4. 身体的フレイルとは多病状態とは異なる．両者とも高齢者にとっては珍しいことではないが，多疾患に罹患していることは65歳を超えた高齢者なら４人に３人は当てはまりフレイルより，より一般的である．フレイルは包括的なアプローチが求められる専門性の高い領域である．多疾患も包括的に評価管理されるのは重要ではあるが，個々の疾患に対して評価，治療管理することが基本であり，多病状態とフレイルとは根本的に異なる概念である．Rockwood らにより提唱されているようなより広範囲の臓器障害の集積としてとらえるフレイルは，軽度なストレスによっても障害を引き起こしやすくなった状態をさし，多疾患や認知機能障害や気分障害などに関連する中枢神経系の異常にも関連する．

というような報告をし，４つのフレイル評価法を提示している．この会議には Rockwood をはじめ，その４つの評価法にかかわる研究者が参加しており，意見の集約ができなかったということだろう．４つのうち３

つは，基本的にはBuchnerとWagnerの考え方に沿っており，Friedの定義をサポートしているようだがRockwoodらの定義を無視できず，無理やり組み込んだ感があり，歯切れがわるく，定義の統一ができていない．

おわりに

今後の日本においては「まえがき」で記載したように，要介護状態にいたる高齢者を少しでも減少させることがたいへん重要であり，介護予防をさらに推し進めることが喫緊の課題である．その意味でBuchnerとWagnerやFriedらの提唱しているフレイルの概念が現在の日本ではフィットするように思う．すなわち，要介護にいたる前のフレイルの状態で拾い上げ，適切な介入をすることにより，要介護状態にいたるプロセスをブロックする戦略である．フレイルの問題を押し進めるには今までの既存の臓器別分野では太刀打ちできない包括的問題の集合体であり，老年医学的ストラテジーが必要である．

なお，今回はphysical frailty（身体的フレイル）にフォーカスして議論を進めたが，これまた解決していない問題として，フレイルには身体的のみならず，精神心理的さらには社会的フレイル，たとえば認知機能障害，社会的孤立，家縛りなどの問題があり，今後フレイルをさらに広くとらえる必要性がある．

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RESEARCH

RELATIONSHIP BETWEEN LIGHT-INTENSITY PHYSICAL ACTIVITY AND COGNITIVE FUNCTION IN A COMMUNITY-DWELLING ELDERLY POPULATION—AN 8-YEAR LONGITUDINAL STUDY

To the Editor: There is considerable evidence suggesting the beneficial effects of moderate to vigorous physical activity (MVPA) and the negative effects of sedentary behavior on health outcomes.[1,2] A meta-analysis of 15 prospective studies showed a significant inverse relationship between high levels of physical activity and risk of cognitive decline in cognitively normal older adults,[3] but the contribution of light-intensity physical activity and sedentary time to cognitive function is less well known.

Light-intensity physical activity, which includes activities such as washing dishes, ironing, and other routine domestic or occupational tasks,[4] is the predominant determinant of variability in total daily energy expenditure.[5] Light-intensity physical activity is particularly important for older adults because they tend to spend a greater portion of their day performing light-intensity physical activity than any other age group.[6]

The purpose of the present study was to examine the relationship between light-intensity physical activity and sedentary time and cognitive decline independent of MVPA in a community-dwelling population aged 60 and older.

Participants were 550 (289 men, 261 women) adults aged 60 and older who completed the second (April 2000 to May 2002) and sixth (April 2008 to May 2010) wave of examinations of the National Institute for Longevity Sciences —Longitudinal Study of Aging (NILS-LSA)[7] in Aichi, Japan.

Trained interviewers asked subjects about time spent in physical activity for the past 12 months using a questionnaire developed by the Japanese Lifestyle Monitoring Study Group.[8] The questionnaire captured the duration of light-intensity physical activity, MVPA, and sedentary time determined by metabolic equivalent (MET) scores (a multiple of the resting metabolic rate) reported in the literature.[9]

Cognitive function was assessed using the Mini-Mental State Examination (MMSE). A decline of at least three points in MMSE score from baseline to follow-up was considered meaningful from a clinical point of view.[10]

Education level (>9, ≤9 yr), smoking status (current, former, never), occupation (working or not), depressive symptoms (Center for Epidemiologic Studies Depression

Table 1. Incidence and Odds of Significant Cognitive Decline During the Follow-Up Period According to Quartile of Light-Intensity Physical Activity and Sedentary Time per Day (N = 550)

	Second	Third	Highest	
Light Intensity and Sedentary Time	**Odds Ratio (95% Confidence Interval)**			***P* for Trend**
Light-intensity physical activity time per day (1.6–2.9 METs)				
Time, hours	1.4–2.3 (138)	2.4–3.6 (137)	≥3.7 (139)	
Model 1	0.59 (0.30–1.16)	0.60 (0.30–1.20)	0.50 (0.25–0.99)	.06
Model 2	0.58 (0.28–1.21)	0.53 (0.25–1.12)	0.39 (0.19–0.83)	.02
Model 3	0.58 (0.28–1.20)	0.53 (0.25–1.12)	0.39 (0.18–0.83)	.02
Working				
Yes (n = 155)	0.35 (0.08–1.58)	0.35 (0.09–1.41)	0.37 (0.10–1.47)	.18
No (n = 395)	0.63 (0.26–1.53)	0.61 (0.23–1.60)	0.26 (0.09–0.71)	.01
Education, years				
≤9 (n = 189)	0.30 (0.09–0.97)	0.50 (0.15–1.67)	0.26 (0.07–0.94)	.08
>9 (n = 361)	0.84 (0.32–2.26)	0.52 (0.19–1.43)	0.44 (0.17–1.18)	.07
Sedentary time (≤1.5 METs)				
Time, hours	11.5–13.0 (137)	13.1–14.2 (137)	≥14.3 (139)	
Model 1	1.45 (0.77–2.73)	1.22 (0.65–2.26)	1.97 (1.01–3.86)	.09
Model 2	1.47 (0.74–2.89)	1.37 (0.69–2.70)	2.66 (1.18–5.98)	.03
Model 3	1.57 (0.78–3.16)	1.51 (0.74–3.07)	3.03 (1.29–7.14)	.02
Working				
Yes (n = 155)	2.65 (0.79–8.85)	0.80 (0.27–2.39)	2.04 (0.55–7.65)	.66
No (n = 395)	1.13 (0.45–2.88)	1.85 (0.70–4.88)	3.74 (1.21–11.58)	.02
Education, years				
≤9 (n = 189)	2.67 (0.85–8.34)	1.99 (0.66–5.99)	3.90 (1.02–14.94)	.07
>9 (n = 361)	1.48 (0.58–3.79)	1.32 (0.52–3.38)	2.73 (0.87–8.55)	.12

The lowest quartile was used as a reference. Cognitive decline indicated as change of at least three points on the Mini-Mental State Examination. Model 1 was controlled for age, sex, and educational level; Model 2 was controlled as in Model 1 with further control for smoking status, self-rated health, Center for Epidemiological Studies—Depression Scale, sleep duration, whether participant was working, hypertension, myocardial infarction, hyperlipidemia, diabetes mellitus, stroke, and rheumatoid arthritis. Model 3 was controlled as in Model 2 with further control for moderate- to vigorous-intensity physical activity time. Subgroups were controlled as in Model 3 without control for educational level (education group) and occupational level (occupation group). METs = metabolic equivalents of a task.

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Scale (CES-D) score ≥16, <16), body mass index (BMI), self-rated health, sleep duration, and history of medical conditions (hypertension, myocardial infarction, hyperlipidemia, diabetes mellitus, stroke, rheumatoid arthritis) were based on answers to the questionnaire and interview.

For all logistic regression analyses, Model 1 was adjusted for age, sex, and educational level. Model 2 was further adjusted for BMI, initial MMSE score, smoking status, self-rated health, CES-D score, education level, sleep duration, occupation, hypertension, myocardial infarction, hyperlipidemia, diabetes mellitus, stroke, and rheumatoid arthritis. Model 3 was further adjusted for MVPA time. The odds of cognitive decline relative to light-intensity physical activity and sedentary time was also analyzed in subgroups of subjects (educational level ≤9 vs >9 years, working vs not). All analyses were performed using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC).

There were 96 cases of cognitive decline over a mean follow-up of 8 years in the 550 subjects. Compared with the lowest quartile, the odds of developing cognitive decline were lower (Model 1: odds ratio (OR) = 0.50, 95% confidence interval (CI) = 0.25–0.99; Model 2: OR = 0.39, 95% CI = 0.19–0.83; Model 3: OR = 0.39, 95% CI = 0.18–0.83) in the highest quartile of light-intensity physical activity time, and the dose-related response was significant in Models 2 and 3 (P for trend = .02 for each). In contrast, those in the highest quartile of overall sedentary time were more likely to show cognitive decline than those in the lowest quartile (Table 1). This tendency was also found in subjects who were not working and with lower education, regardless of multivariate control.

This study provides longitudinal evidence associations between light-intensity physical activity time and overall sedentary time and cognitive decline over an 8-year period in community-dwelling adults aged 60 and older. This association remained after controlling for covariates including baseline health status and MVPA time.

These findings have important implications because it may be easier for older adults to increase light-intensity physical activity than to increase vigorous or moderate structured exercise training. This could be particularly important for older adults who tend to spend more time participating in light-intensity physical activity than in more-vigorous activities. Light-intensity physical activity interventions may also be more likely to succeed across a variety of settings, including the workplace.

SungChul Lee, PhD
Atsumu Yuki, PhD
Yukiko Nishita, MD
Chikako Tange, PhD
Department for Development of Preventive Medicine, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, Morioka, Obu, Aichi, Japan

HeungYoul Kim, PhD
Department of Human Wellness, Tokaigakuen University, Ukigai-cho, Miyoshi, Aichi, Japan

Rumi Kozakai, PhD
Department of Sport Education, School of Lifelong Sport, Hokusho University, Hokkaido, Japan

Fujiko Ando, MD, PhD
Faculty of Health and Medical Sciences, Aichi Shukutoku University, Nagakute-cho, Aichi, Japan

Hiroshi Shimokata, MD, PhD
Department for Development of Preventive Medicine, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, Morioka, Obu, Aichi, Japan

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A Randomized Controlled Trial of Multicomponent Exercise in Older Adults with Mild Cognitive Impairment

Takao Suzuki[1]*, Hiroyuki Shimada[2], Hyuma Makizako[2], Takehiko Doi[2], Daisuke Yoshida[2], Kengo Ito[3], Hiroshi Shimokata[4], Yukihiko Washimi[5], Hidetoshi Endo[6], Takashi Kato[3]

1 Research Institute, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan, 2 Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan, 3 Department of Clinical and Experimental Neuroimaging, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan, 4 Department for Development of Preventive Medicine, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan, 5 Department of Cognitive Disorders, Hospital of National Center for Geriatrics and Gerontology, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan, 6 Department of Comprehensive Geriatric Medicine, Hospital of National Center for Geriatrics and Gerontology, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan

Abstract

Background: To examine the effect of multicomponent exercise program on memory function in older adults with mild cognitive impairment (MCI), and identify biomarkers associated with improvement of cognitive functions.

Methodology/Principal Findings: Subjects were 100 older adults (mean age, 75 years) with MCI. The subjects were classified to an amnestic MCI group (n = 50) with neuroimaging measures, and other MCI group (n = 50) before the randomization. Subjects in each group were randomized to either a multicomponent exercise or an education control group using a ratio of 1:1. The exercise group exercised for 90 min/d, 2 d/wk, 40 times for 6 months. The exercise program was conducted under multitask conditions to stimulate attention and memory. The control group attended two education classes. A repeated-measures ANOVA revealed that no group × time interactions on the cognitive tests and brain atrophy in MCI patients. A sub-analysis of amnestic MCI patients for group × time interactions revealed that the exercise group exhibited significantly better Mini-Mental State Examination ($p = .04$) and logical memory scores ($p = .04$), and reducing whole brain cortical atrophy ($p < .05$) compared to the control group. Low total cholesterol levels before the intervention were associated with an improvement of logical memory scores ($p < .05$), and a higher level of brain-derived neurotrophic factor was significantly related to improved ADAS-cog scores ($p < .05$).

Conclusions/Significance: The results suggested that an exercise intervention is beneficial for improving logical memory and maintaining general cognitive function and reducing whole brain cortical atrophy in older adults with amnestic MCI. Low total cholesterol and higher brain-derived neurotrophic factor may predict improvement of cognitive functions in older adults with MCI. Further studies are required to determine the positive effects of exercise on cognitive function in older adults with MCI.

Trial Registration: UMIN-CTR UMIN000003662

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* E-mail: suzutaka@ncgg.go.jp

Introduction

Alzheimer's disease (AD) places a considerable and increasing burden on patients, caregivers and society. The number of older adults living with AD is predicted to increase from the current 26.6 million to 106.2 million by 2050 globally. [1] The current standard of care for mild to moderate AD involves treatment with acetylcholinesterase inhibitors to improve cognitive function. The N-methyl-d-aspartate antagonist memantine has also been reported to improve cognitive function in patients with moderate to severe AD. [2] While these drugs improve the symptoms of AD, they do not have substantial disease-modifying effects. [3] Thus, attempts have been made to identify individuals at increased risk of AD, and to test interventions that might delay the progression of prodromal symptoms of dementia.

An association has been proposed between regular participation in physical activity, especially aerobic exercise, and a variety of cognitive benefits. [4,5,6,7,8] Several meta-analyses have reported that physical activity is associated with improvements in attention, processing speed, and executive function in older adults with and without cognitive impairments. [9,10,11] However, these studies produced some inconsistent findings, with some reporting

cognitive gains in memory function [10,11] and other study reporting equivocal results. [9]

Evidence from neuropsychological and neuroimaging studies has suggested that mild cognitive impairment (MCI) represents a clinical prodrome to degenerative dementias such as AD. [12] For example, a population-based study in Sweden reported that the relative risks of progression to dementia in a 3-year follow-up in subjects with mild, moderate, and severe cognitive impairment (without dementia), were 3.6, 5.4, and 7.0, respectively. [13] However, of the individuals with MCI, 11% remained stable, and 25% exhibited an improvement in cognitive function between baseline and follow-up observation. [13] This variation in MCI populations should be examined to facilitate the development of interventions for inhibiting the progression of dementia. Several randomized controlled trials (RCTs) have been conducted to investigate the effects of exercise or physical activity on cognitive function in older adults with MCI. [4,5,6,7,8] These studies have revealed the effects of exercise or physical activity on cognitive function, including executive function, in older adults with MCI. However, the effect of exercise on memory function in this population remains unclear.

The precise neurobiological mechanism for the improvement of cognitive functions remains unknown, however a large number of rodent studies suggest a central role of certain molecules such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1), and vascular endothelial growth factor (VEGF). The molecules have been shown to facilitate neurogenesis in the hippocampus, promote synaptic plasticity in the hippocampus and cerebral cortex, and angiogenesis and enhance growth and protection of neurovasculature. [14,15] In fact, some neuroimaging studies of human subjects revealed that aerobic exercise increased hippocampal volume, [16] and gray and white matter regions including the cingulate cortex, supplementary motor cortex, inferior frontal gyrus, and superior temporal gyrus. [17]

The present randomized trial was designed to test whether a 6-month supervised multicomponent exercise program could reduce the rate of cognitive decline, especially in memory function, and reduce the rate of brain volume decline among older adults with MCI. The multicomponent exercise program included aerobic exercise, muscle strength training, and postural balance retraining, because previous reviews suggested that combined aerobic exercise and strength training interventions improved attention and working memory to a greater extent than aerobic exercise alone. [11,18] We explored the biomarkers for identifying improvement of cognitive functions. Serum total cholesterol (T-cho), hemoglobin A1c (HbA1c), BDNF, and VEGF levels at baseline were used as potential predictors.

Methods

CONSORT checklist and the protocol for this trial is available as supporting information; see **Checklist S1** and **Protocol S1**.

Participants

Subjects in this study were recruited from two volunteer databases (n = 1,543), which included elderly individuals (65 years and over) selected either by random sampling or when they attended a medical check-up in Obu, Japan. Inclusion criteria specified that prospective participants were community-dwelling individuals aged 65 years and over. A total of 528 prospective participants with a Clinical Dementia Rating (CDR) of 0.5, or who complained of memory impairment, were recruited in the first round of eligibility assessments. Of these, 135 subjects satisfied the requirements of the second round of eligibility assessments, which included neuropsychological tests, which included language and memory tests, attention and executive function tests, clinical diagnosis, activities of daily living (ADL), educational level, and magnetic resonance imaging. Thirty-five subjects were excluded, meaning that a total of 100 subjects took part in the study (mean age, 75.4±7.1 years; 65–95 years, men n = 55, 51%). All subjects met the definition of MCI as per the Petersen criteria. [19] All MCI subjects had objective impairments in either episodic memory and/or executive functioning at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. Final classification of subjects was based on the above factors and consensus of a team of neuroscientists. Exclusion criteria included a CDR = 0, or a CDR of 1–3, a history of neurological, psychiatric, or cardiac disorders or other severe health issues, use of donepezil, impairment in basic activities of daily living (ADL), and participation in other research projects. Subjects were classified to an amnestic MCI group (aMCI) (n = 50) with neuroimaging measures, and other MCI group (n = 50) before the randomization. Then, the subjects in each group were randomly assigned to either a multicomponent exercise or an education control group using a ratio of 1:1. Participant characteristics at the beginning of the study are shown in **Table 1**. We confirmed that there were no significant differences in demographic characteristics, physical performance, or instrumental ADL levels between the exercise and control groups. Fifty subjects with aMCI (mean age, 76.0±7.1 years; 65–92 years, men n = 27, 54%) were selected from among the subjects to participate in a sub-analysis. All subjects included the aMCI group agreed to measure functional neuroimaging tests. This sub-analysis was limited to aMCI patients because aMCI is most likely to progress to AD.[20] Objective memory impairment to determine aMCI was defined as a lower memory score on the Wechsler Memory Scale-Revised (WMS-R) Logical Memory II. [21]

Ethics

The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol. The purpose, nature, and potential risks of the experiments were fully explained to the subjects, and all subjects gave written, informed consent before participating in the study. The subjects had the capacity to consent because they maintained general cognitive function and daily activities.

Interventions

The six-month, multicomponent exercise program included biweekly 90-minute sessions involving aerobic exercise, muscle strength training, postural balance retraining, and dual-task training. In addition, the exercise program included a focus on promoting exercise and behavior change. Two trained physiotherapists involved in geriatric rehabilitation conducted each intervention. Each exercise class contained 16 17 participants, and each supervised session began with a 10-min warm-up period and stretching exercise, followed by 20 min of muscle strength exercise. The subjects then practiced aerobic exercise, postural balance retraining, and dual-task training for 60 min. In the aerobic exercise and postural balance retraining, subjects underwent circuit training, including stair stepping, endurance walking, and walking on balance boards. The mean intensity of the aerobic exercise was approximately 60% of maximum heart rate which was similar to the intensity used in previous studies. [4,6] Eleven of the 40 classes during the six-month intervention period included approximately 20 30 minutes of consecutive outdoor walking. In the dual-task training sessions, subjects performed concurrent cognitive tasks during exercise. For example, the subjects in the

Table 1. Characteristics of the subjects.

	All subjects		aMCI subjects	
	Exercise (n=50)	Control (n=50)	Exercise (n=25)	Control (n=25)
Age, mean (SD), y	74.8 (7.4)	75.8 (6.1)	75.3 (7.5)	76.8 (6.8)
Men, No. (%)	25 (50.0)	26 (52.0)	13 (52.0)	14 (56.0)
Educational level, mean (SD), y	10.9 (2.8)	10.4 (2.4)	11.1 (2.4)	10.8 (2.7)
Diagnosis, No. (%)				
Hypertension (3*, 1†)	23 (46.9)	22 (45.8)	13 (52.0)	11 (45.8)
Heart disease (4*, 1†)	5 (10.2)	1 (2.1)	2 (8.0)	0 (0)
Diabetes Mellitus	8 (16.0)	3 (6.0)	5 (20.0)	3 (12.0)
Medication, 3 and over (2*, 1†)	22 (44.0)	19 (39.6)	10 (40.0)	11 (45.8)
Blood pressure, mmHg				
Systolic, mean (SD)	144.6 (21.6)	142.4 (19.4)	152.2 (21.0)	143.7 (21.3)
Diastolic, mean (SD)	74.6 (11.7)	75.1 (11.2)	77.3 (11.1)	74.3 (10.1)
Blood test				
Total cholesterol, mean (SD), mg/dL	211.7 (36.2)	200.5 (34.5)	212.6 (36.9)	202.8 (32.2)
HbA1c, mean (SD), %	5.6 (0.8)	5.4 (0.5)	5.6 (0.6)	5.4 (0.5)
BDNF, mean (SD), ng/mL	12.1 (10.0)	13.5 (10.4)	11.9 (11.3)	14.4 (12.2)
VEGF, mean (SD), pg/mL	97.6 (19.7)	103.5 (22.2)	95.9 (18.4)	96.7 (15.4)
Physical performances				
Grip strength, mean (SD), kg	24.7 (8.1)	23.5 (7.3)	25.2 (7.3)	23.1 (8.4)
One legged standing, mean (SD), s	34.6 (24.6)	31.2 (23.9)	34.0 (25.1)	29.3 (23.6)
Timed up & go, mean (SD), s	8.8 (2.5)	9.2 (2.1)	9.0 (2.2)	9.1 (2.0)
IADL subscale of TMIG index, mean (SD), score	4.8 (0.9)	4.9 (0.3)	5.0 (0.2)	4.9 (0.3)
GDS, mean (SD), score	3.8 (3.1)	3.3 (2.8)	3.0 (2.1)	2.6 (2.0)
Cognitive functions, score				
MMSE, mean (SD)	26.8 (2.3)	26.3 (2.7)	26.8 (1.8)	26.6 (1.6)
ADAS-cog, mean (SD)	6.0 (2.8)	6.5 (2.8)	6.3 (2.2)	6.8 (2.2)
WMS-LM I, mean (SD)	14.6 (6.9)	13.8 (7.4)	12.5 (5.9)	12.0 (4.9)
WMS-LM II, mean (SD)	10.5 (7.4)	9.4 (7.4)	8.2 (5.4)	6.9 (5.0)
Clinical subtype, No. (%)				
Amnestic MCI	34 (68.0)	37 (74.0)		
Non-amnestic MCI	16 (32.0)	13 (26.0)		
VSRAD				
MTA-ERC atrophy, mean (SD) (1*)	1.3 (0.9)	1.5 (1.0)	1.4 (1.0)	1.4 (1.0)
WBC atrophy, mean (SD) (1*)	7.3 (4.7)	8.3 (4.6)	7.9 (3.9)	7.4 (3.3)

Abbreviations: IADL subscale of TMIG index, instrumental activities of daily living subscale of Tokyo Metropolitan Institute of Gerontology index; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; WMS, Wechsler Memory Scale; MCI, mild cognitive impairment. *missing value in all subjects. †missing value in the aMCI subjects.

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exercise group were asked to walk while inventing their own poem, as aerobic exercise. In the ladder training exercise, subjects learned to step in consecutive square segments, and were instructed to step as quickly and accurately as possible. Before and after each session of the program, physiotherapists conducted a health check of each subject. The physiotherapists and a well-trained instructor implemented risk management for accidents and other adverse events during the program. The subjects were instructed to carry out daily home-based muscle strength exercises and walking, which were self-monitored using a booklet and pedometer based on the concept of promoting exercise and behavior change. Attendance at each session was recorded and a transportation service was provided for participants, if necessary, to help subjects maintain their participation in the program.

Subjects in the education control group attended two education classes about health promotion during the 6-month study period. The class provided information regarding healthy diet, oral care, prevention of urinary incontinence, and health checks. However, the group did not receive specific information regarding exercise, physical activity, or cognitive health.

Outcomes

Cognitive Functions. The Mini-Mental State Examination (MMSE) [22] and Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog) [23] were used to assess general cognitive function.

Modified versions of the logical memory subtest from the WMS-R [21] was used to assess memory function. In the WMS-R, two short stories (Story A and B) were read aloud to the subject, who was then instructed to recall details of the stories immediately (LM I, immediate recall) and after 30 min (LM II, delayed recall; each total recall score = 50). [21]

MRI. MRI was performed with a 1.5-T system (Magnetom Avanto, Siemens, Germany). Three-dimensional volumetric acquisition with a T1-weighted gradient echo sequence was then used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (repetition time, 1700 ms; echo time, 4.0 ms; flip angle 15°, acquisition matrix 256×256, 1.3-mm slice thickness).

In analysis of brain volume, we used the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD), which enables the examination of atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) using voxel-based morphometry. [24] The VSRAD has been shown to achieve high accuracy (87.8%) in discriminating patients in the very early stages of AD with MCI from normal control subjects using Z scores. [24] A previous VSRAD study reported that atrophy of the MTA-ERC exhibited a clear functional relationship with blood flow changes in the hippocampus, thalamus and temporal lobe, which were suggested to be closely related to inter-regional anatomical and physiological connections. [25]

Acquired MRI images were formatted to gapless, transaxial images, followed by extraction of the gray matter images using SPM2. Anatomical standardization was used to fit each individual brain to standard template MRIs in the common coordinate system of the MNI T1 MRI template. [26] The segmented gray matter images were then subjected to affine and nonlinear standardization using a template of prior gray matter. The anatomically standardized gray matter images were then smoothed again using an isotropic Gaussian kernel 12 mm in full width at half maximum, to determine the partial volume effect and create a spectrum of gray matter intensities. Gray matter intensities were equivalent to the weighted average of gray matter voxels located in the volume fixed by the smoothing kernel. Regional intensity was considered equivalent to gray matter concentration. We compared the gray matter image of each patient with the mean and standard deviation (SD) of gray matter images of healthy volunteers using voxel-by-voxel Z score analysis. In the final step, the Z score was calculated according to the following equation: (Z score = ((control mean) − (individual value))/control SD). The Z score thus reflected the degree of atrophy in bilateral MTA-ERC. Higher Z scores indicated clearer MTA-ERC atrophy. VSRAD also automatically measured the degree of atrophy in the whole brain cortices (WBC), including the hippocampus: if the Z-score was more than 2.0 within a voxel, the area was considered to exhibit atrophy. [24] Thus, the proportion of atrophic area in the whole brain (%) was measured in the following way: 100×{[the number of voxels with Z-score≥2.0]/[the number of whole brain voxels]}.

Biochemical measures3. T-cho, HbA1c, BDNF, VEGF receptor 1 (VEGFR1) were used as biomarkers. Blood samples were collected between 11 am and 4 pm in a non-fasting state. The blood samples were kept at room temperature for 30 min to allow for clotting, after which the samples were centrifuged for 15 min. Serum was then harvested and stored at −25 °C until analysis. Analyses were carried out centrally in one laboratory (Special Reference Laboratories, Tokyo, Japan). BDNF and VEGFR1 were measured with the Quantikine Human kit (R&D systems, Inc. Minneapolis, MN, USA). Coefficients of variation (CVs) of BDNF in intra-assay and inter-assay precision were 2.6 3.2 and 5.5–9.8, respectively. Those of VEGFR1 were 3.8–6.2 for intra-assay and 7.6–11.3 inter-assay precision.

Sample size

Since participants were selected on the basis of memory impairments, memory was considered the most important cognitive outcome in our study. Therefore, sample size calculations were based on AVLT data. [27] A previous study reported that a sample of 34 participants per group to detect a clinically relevant effect, with 80% power. [6] To allow for a dropout of 25%, the final sample size was 85 participants.

Randomization–Sequence generation

Subjects were randomly assigned after completion of baseline assessments. Subjects were classified to an amnestic MCI group (n = 50) with neuroimaging measures, and other MCI group (n = 50) before the randomization. The subjects in each group were randomized to either a multicomponent exercise or an education control group using a ratio of 1:1. The subjects were further randomized and dichotomized into two groups, an amnestic MCI group (n = 50) with neuroimaging measures, and other MCI group (n = 50).

Randomization–Implementation and concealment

After the baseline assessment, subjects were randomized using the option "random sample of cases" in IBM SPSS statistics software (Version 19; SPSS Inc., Chicago, IL, USA). A researcher who was not aware of the aims of the study performed the randomization procedure.

Blinding

Study personnel involved in the collection of outcome measures were blinded to the randomization assignment. Several trained speech therapists blinded to group status conducted the cognitive tests, and one speech therapist recalculated all of the results.

Statistical methods

Statistical analysis was performed using IBM SPSS statistics software. For the baseline comparisons between exercise and control groups for all subjects, and for the amnestic MCI (aMCI) sub-analysis, Pearson's method, together with Chi square analysis with Fisher's exact test was used to investigate the categorical data. Kolmogorov-Smirnov tests confirmed that all continuous variables followed a normal distribution. Basic characteristics of patients were compared between the two groups using *t*-tests.

A general linear model for repeated-measures analysis of variance (ANOVA) was used to determine the group difference for the cognitive tests and VSRAD measurements. Two time points were treated as the within-subjects factor (effect over time) and the differences between the exercise and control groups were treated as the between-subjects factor. When the repeated-measures ANOVA indicated that the group × time interaction was significant, tests of simple main effects were performed to determine which group or groups differed significantly across the intervention period. Alpha level of the post-hoc analyses were adjusted for the Bonferroni method, i.e. corrected alpha = .025.

Multiple logistic regression models were used to determine the predictors of improvements in cognitive function. Dependent variables were the cognitive tests which showed significant improvements in the comparison between before and after the intervention of all subjects. Based on the results from the cognitive tests, the subjects were dichotomized into two categories; the subjects who improved their cognitive test scores (improvement

group) and the subjects who showed no improvement, or who exhibited a deterioration in their cognitive test scores (no improvement group). Biochemical variables at baseline measurements were treated as independent variables. Covariates such as age, sex, educational level, and the intervention group were included in the logistic model.

The univariate analyses and repeated-measures ANOVA were performed with all subjects grouped together as well as with a subgroup that was limited to older adults with aMCI. The logistic regression analysis was performed to determine the predictors of improvement of cognitive functions in all subjects. All statistical significance tests were two-sided, and an alpha-level of .05 was considered statistically significant.

Results

Participant flow

Figure 1 shows the flow of participants from the time of screening to study completion at 6 months. Ninety-two (exercise group, n = 47) subjects completed the 6-month follow-up. Of the 50 aMCI subjects, 47 (94%) completed the 6-month follow-up. Two of the remaining 47 subjects in the exercise group (one male, one female) missed all exercise programs, but completed the examinations before and after the intervention. The two subjects were included in the following analyses. Mean adherence to the exercise program, including the remaining 47 subjects, was 85.9%, and 38 subjects (80.9%) in the exercise group attended our intervention program with greater than 80% adherence.

Baseline data

There were no significant differences in baseline characteristics between all subjects grouped together and the aMCI group alone (**Table 1**).

Participants analyzed

Our primary analysis of cognitive function included all patients who remained at the end of the study (total n = 92; exercise group, n = 47; control group, n = 45). A total of 90 subjects (exercise group, n = 46; control group, n = 44) completed MRI scanning. When the analyses were limited to subjects with aMCI, the exercise and control groups included 24 and 23 subjects in assessments of cognitive function and MRI, respectively.

Outcomes in all MCI subjects

Table 2 shows changes in cognitive scores over the 6-month period by group. There were main effects of time in ADAS-cog ($p = .01$), WMS-LM I ($p < .01$), WMS-LM II ($p < .01$), and WBC atrophy level ($p = .03$), although no main effects of group and group × time interactions were detected on the cognitive tests and brain atrophy (**Table 2**).

Outcomes in aMCI subjects

When the analyses were limited to subjects with aMCI, the repeated-measures ANOVA for MMSE showed a significant effect of group ($p = .03$) and there was a group × time interaction in MMSE ($p = .04$) indicating benefit of the exercise over time. Tests of simple main effects revealed that the control group decreased in MMSE score ($p = .015$) after intervention. A repeated-measures ANOVA showed a significant effect of time ($p < .01$) and group × time interaction ($p = .04$) in WMS-LM I. Tests of simple main effects showed that the exercise group exhibited better WMS-LM I ($p < .01$) scores compared to baseline, but not in the control group. The repeated-measures ANOVA for WMS-LM II ($p < .01$) and MTA-ERC atrophy ($p = .03$) showed a significant effect of time. However, there were no main effects of group and no group × time interactions. A repeated-measures ANOVA showed a significant group × time interaction ($p < .05$) in WBC atrophy level. There were no main effects of group or time. Tests of simple main effects revealed that the subjects in the control group showed increased WBC atrophy ($p = .01$) after intervention, compared with their baseline scores (**Table 2, Figure 2**).

Relationships between cognitive functions and biomarkers

Paired *t*-tests revealed significant improvements in ADAS-cog ($p = .01$), WMS-LM I ($p < .01$), and WMS-LM II scores ($p < .01$) after the intervention. Multiple logistic regression analysis revealed that low T-cho level before the intervention was associated with improvement in WMS-LM I (odds ratio (OR) 0.98, 95% confidence interval (95% CI) 0.96–1.00, $p = .02$). Higher BDNF level at baseline was significantly related to improvements in ADAS-cog (OR 1.07, 95% CI 1.02–1.13, $p = .01$) independent of age, sex, educational level, and intervention (**Table 3**).

Adverse events

Four subjects (exercise group, n = 2; control group, n = 2) experienced adverse events (hospitalization for illness). Falls (as a type of minor adverse event) over a 6-month period were reported by 23/90 (26%) of subjects, with no significant differences among groups. There were no other adverse events during exercise intervention for 6-months.

Discussion

Evidence of exercise on cognitive function

Older adults with MCI have been found to exhibit greater decreases in memory function than in other cognitive functions, relative to healthy older adults. [28] The enhancement of cognitive function, especially memory function, in individuals with MCI may play a crucial role in preventing the progression from MCI to AD in older adults. Klusmann et al. reported significant effects of a multifaceted exercise program on cognitive function, finding that a 6-month exercise program resulted in improvements in delayed story recall. [29] However, their sample consisted of healthy, well-functioning females without any signs of cognitive impairment. In addition, previous studies reported that aerobic exercise or other physical activity can increase executive function in older adults with cognitive impairments, but the effects of exercise on memory function in this population remain unclear. [4,5,6,7,8] To our knowledge, this is the first study to demonstrate an improvement in logical memory following multicomponent exercise training among older adults with aMCI. The exercise group showed significant differences not only in WMS-LM I scores, but also in MMSE scores compared to the control group in aMCI populations. Our intervention study extends the results of previous studies with healthy samples, indicating the potential for an increase in memory performance and maintenance of general cognitive function in subjects exhibiting signs of cognitive decline.

A meta-analysis of aerobic exercise and neurocognitive performance demonstrated that interventions combining aerobic exercise and strength training, similar to our program, improved attention, processing speed and working memory to a greater extent than aerobic exercise alone. [11] However, the mechanism underlying this improvement remains unclear. A previous study reported that subjects with MCI improved their episodic memory performance when they were exposed to a multifactorial cognitive intervention program that included dual-task attentional and memory training. [30] Dual-task deficit is recognized as a potential

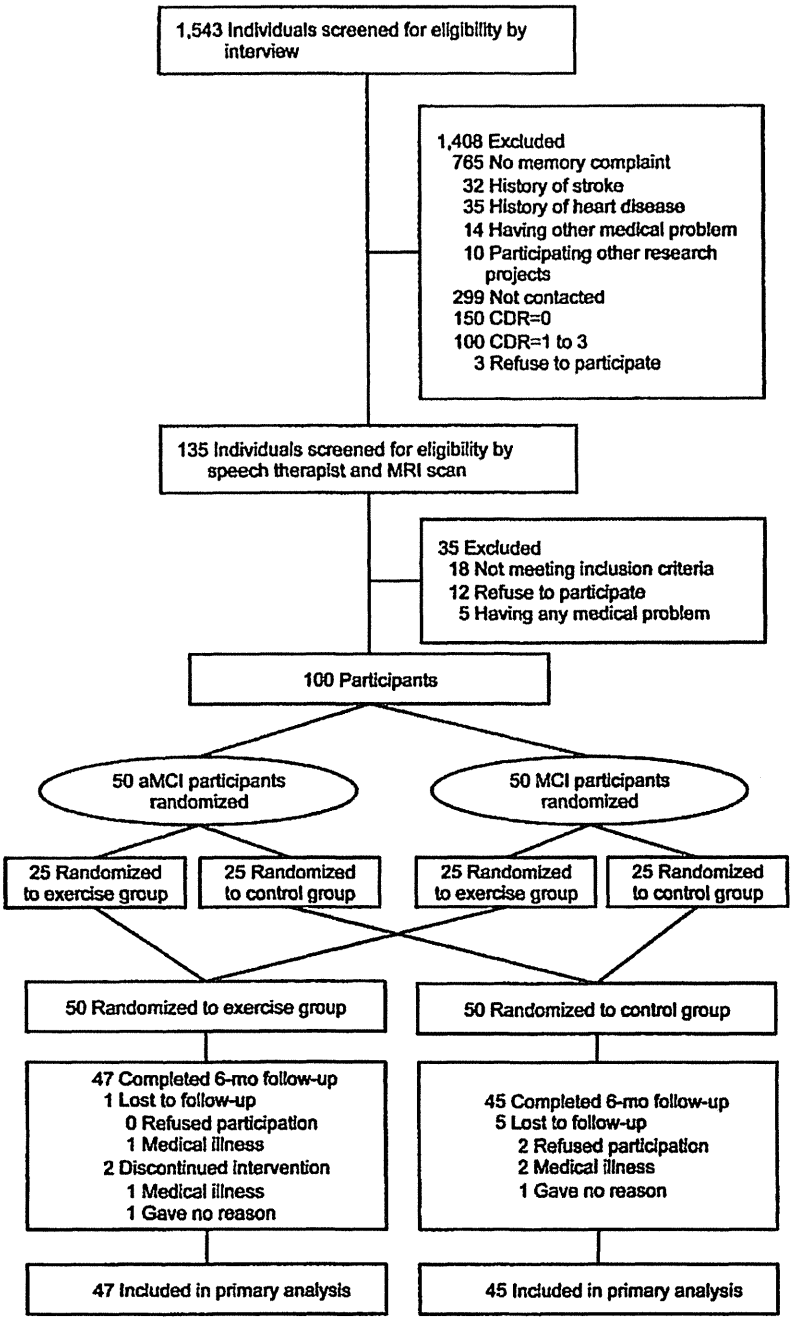

Figure 1. Subject flow diagram from initial contact through to study completion.
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early marker for dementia, [31,32] and dual-task-related changes in performance were greater in subjects with MCI compared with cognitively normal age-matched controls. [33,34] Our multicomponent program involved changes in cognitive load using dual-task stimulation and learning tasks. We believe that dual-task training may have a greater effect on various cognitive functions, for example, general and memory functions, than interventions that only focus on aerobic exercise. [7,10] However, the results from the present study do not provide direct evidence for the positive effect of dual-task training. Future studies are required to investigate the effects of dual-task training on cognitive function in the older adults with MCI.

Lautenschlager et al. reported that physical activity and behavioral intervention improved general cognition among adults with MCI. [4] The multicomponent exercise training in the current study also included encouragement for subjects to engage in more physical activity. Our results further support the notion that training involving physical activity can have a beneficial effect

Table 2. Comparison of Cognitive Function between the Exercise and Control Group.

	All subjects (n = 100)						aMCI subjects (n = 50)					
	Mean Difference From Baseline (95% CI) in All Subjects		P Value ANOVA for Repeated Measures			ES	Mean Difference From Baseline (95% CI) in aMCI Group		P Value ANOVA for Repeated Measures			ES
	Exercise Group (n = 47)	Control Group (n = 45)	Group	Time	Group × time interaction	r	Exercise Group (n = 24)	Control Group (n = 23)	Group	Time	Group × time interaction	r
MMSE	0.2 (−0.5, 0.9)	−0.3 (−1.1, 0.4)	0.18	0.79	0.32	0.11	0.3 (−0.8, 1.3)	−1.4 (−2.5, −0.3)	0.03	0.14	.04[b]	0.31
ADAS-cog	−0.8 (−1.4, −0.2)	−0.2 (−0.8, 0.4)	0.17	0.01	.16 (1)[c]	0.15	−1.2 (−2.1, −0.3)	−0.1 (−1.0, 0.8)	0.1	0.06	0.1	0.24
WMS-LM I	2.8 (1.4, 4.2)	1.0 (−0.5, 2.4)	0.29	<.01	0.08	0.19	3.8 (1.6, 5.9)	0.5 (−1.6, 2.7)	0.14	<.01	.04[a]	0.31
WMS-LM II	3.4 (2.0, 4.8)	1.9 (0.4, 3.4)[b]	0.28	<.01	0.15	0.15	3.8 (1.8, 5.7)	2.1 (0.1, 4.2)	0.11	<.01	0.26	0.17
MTA-ERC	0 (−0, 0.1)	0 (0, 0.1)	0.18	0.08	0.89	0.02	0.1 (0, 0.2)	0 (−0.1, 0.1)	0.91	0.03	0.27	0.17
WBC	0.1 (−0.4, 0.7)	0.7 (0.1, 1.2)	0.08	0.03	0.16	0.15	−0.1 (−0.8, 0.6)	0.9 (0.2, 1.6)	0.86	0.08	<.05[b]	0.29

Abbreviations: MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; WMS, Wechsler Memory Scale; MTA-ERC, medial temporal areas including the entorhinal cortex; WBC, whole brain cortices; ES, effect size.

[a]$p<.025$; significant differences before versus after intervention in the exercise group

[b]$p<.025$; significant differences before versus after intervention in the control group

[c]Missing value

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not only on memory function, but also on general cognitive function in people with aMCI. General cognitive function can be used to discriminate between people who progress to AD and those who do not. [35] Improvements of memory function and maintenance of general cognitive function suggest that multicomponent exercise can help prevent progression from MCI to AD. However, despite significant interactions, the effect sizes in general cognitive function and logical memory were small. Moreover, these interactions would not become significant if the p-values were adjusted for multiple comparisons. Further studies are required to determine the positive effects of exercise on cognitive function in older adults with MCI.

Relationship between exercise and brain atrophy

It is well established that structures in the medial temporal lobe, particularly the hippocampus and ERC, are essential for normal memory function. There is an emerging literature describing baseline structural MRI correlates of cognitive impairment in elderly adults with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Some studies have identified relationships between aerobic exercise and increased brain volume [16,17] and functional connectivity between parts of the frontal, posterior, and temporal cortices [36] in healthy older adults. For example, Erickson et al. found that the hippocampus remains plastic in late adulthood and that a 1-year period of aerobic exercise was sufficient for enhancing volume. [16] Our 6-month multicomponent exercise program with MCI subjects revealed that exercise did not have a significant group × time interaction on MTA-ERC scores or WBC atrophy compared to the control group. However, there was significant group × time interaction in WBC atrophy level, when tested in a sub-analysis restricted to aMCI subjects. Post-hoc analyses revealed that the control group exhibited increased WBC atrophy after intervention, compared with their baseline scores. These results suggest that older adults with aMCI may exhibit high levels of plasticity in WBC atrophy. Further study is needed to establish our findings using large samples and detailed neuroimaging analysis.

Predictors of increasing of cognitive function

In the relationships between cognitive function and biochemical measures, low T-cho and high BDNF serum levels at baseline were associated with increased memory and general cognitive function in the MCI subjects, respectively. Serum lipoprotein levels may be a common and potentially modifiable risk factor for AD. [37] For example, a prospective study reported that lower serum levels of LDL and T-cho were associated with better cognitive performance and a lower risk of cognitive impairment in 1,037 women with cardiovascular disease. [38] Our finding extends knowledge about the relationships between T-cho and cognitive function to older adults with MCI. Animal studies have revealed that the structure and function of the hippocampus, a brain region critical for certain forms of cognition, is adversely affected by hyperlipidemia. (e.g. [39]) Abnormal lipid metabolism may be undesirable status for improvement cognitive functions, especially memory. Exercise is also a valid and feasible way to manage lipoprotein levels and regular activity may be potential strategies for preventing cognitive decline in elderly individuals. [40]

One of the main determinants of cell size is cell growth, which is modulated by certain growth factors, such as BDNF. The levels of BDNF-associated gene expression have been found to increase with physical activity. [14] BDNF expression has also been suggested to play a role in learning and synaptic plasticity. [41]

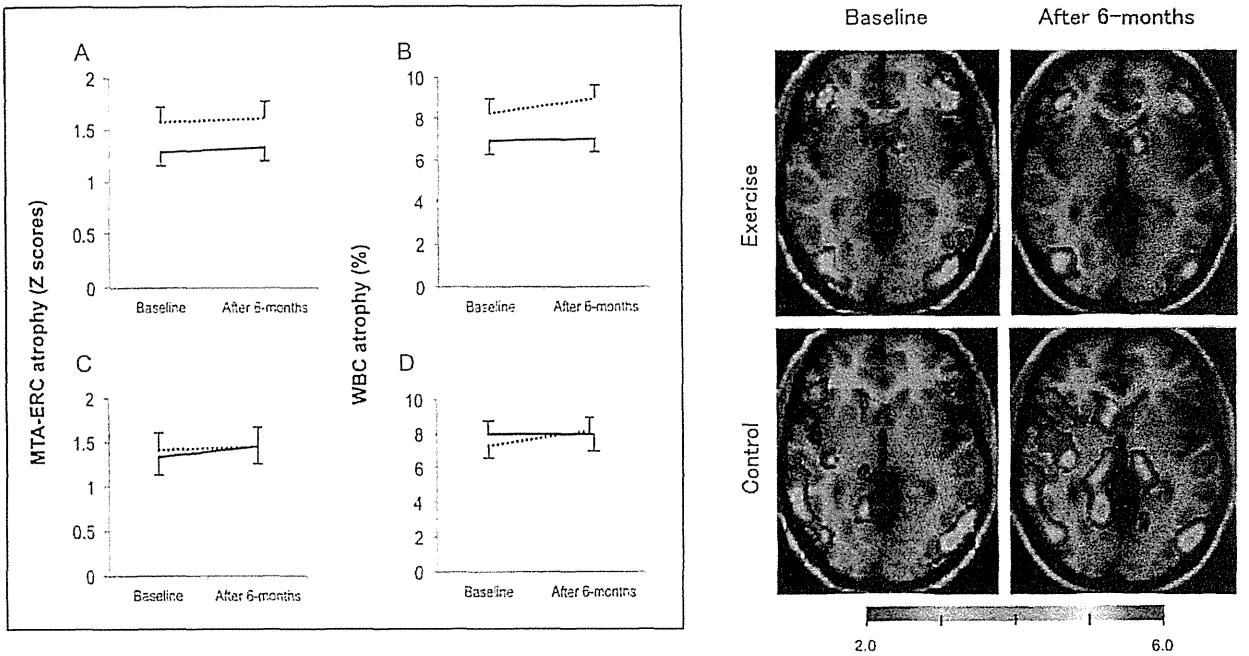

Figure 2. Change in MTA-ERC and WBC volumes in response to the 6-month intervention. Abbreviations: MTA-ERC, medial temporal areas including the entorhinal cortex; WBC, whole brain cortices. Left panel shows change in MTA-ERC and WBC volumes before and after the 6-month intervention. Solid and dashed lines indicate the exercise and control groups, respectively. Group mean differences and standard errors for MTA-ERC and WBC atrophy are shown in panels A and B, respectively, for all subjects. Panels C and D show mean differences and standard errors for MTA-ERC and WBC atrophy, respectively, for older adults with aMCI. The repeated-measures ANOVA revealed that there was a significant group × time interaction on WBC atrophy level ($p<.05$) in older adults with aMCI. Right panel shows typical images for VSRAD, indicated atrophy region, in subjects with aMCI in the exercise and control groups. The upper panel shows WBC atrophy in a man (81 years old) with aMCI who completed the 6-month exercise program. The rate of WBC atrophy decreased after the intervention (8.74% at baseline to 6.39% after the intervention). The lower panel shows WBC atrophy of a man (80 years old) with aMCI in the control group. The rate of WBC atrophy increased after the 6-month intervention period (7.19% at baseline to 10.48% after the intervention).
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The present results indicate that high serum BDNF levels have a beneficial effect on general cognitive function in older adults with MCI.

Limitations

The present study involved several limitations. The small sample size should be addressed by replication with a larger group of adults with MCI. Of the 135 potential subjects screened for eligibility in our study, 35 were excluded for not meeting inclusion criteria, refusal to participate, or medical reasons (**Figure 1**). This

Table 3. Predictors of Improvements in Cognitive Function.

	ADAS-cog	*P*	WMS-LM I	*P*	WMS-LM II	*P*
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
Age, years	0.97 (0.91–1.05)	.44	0.95 (0.89–1.03)	.22	0.96 (0.90–1.04)	.34
Sex, women/men	1.00 (0.35–2.82)	1.00	0.74 (0.26–2.13)	.57	2.56 (0.85–7.66)	.09
Educational level, years	0.85 (0.70–1.04)	.11	0.93 (0.76–1.13)	.45	1.01 (0.83–1.22)	.96
Intervention, exercise group/control group	2.85 (1.10–7.37)	.03	2.27 (.90–5.72)	.08	1.98 (.77–5.12)	.16
T-cho, mg/dl	1.00 (0.98–1.02)	.96	**0.98 (0.96–1.00)**	**.02**	0.99 (0.97–1.01)	.18
HbA1c, %	0.53 (0.25–1.14)	.10	1.20 (0.57–2.53)	.64	0.61 (0.29–1.30)	.20
BDNF, ng/ml	**1.07 (1.02–1.13)**	**.01**	1.00 (0.95–1.05)	.94	1.02 (0.97–1.08)	.39
VEGFR1, pg/ml	0.99 (0.97–1.01)	.39	0.99 (0.96–1.01)	.32	1.00 (0.98–1.03)	.74

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; WMS, Wechsler Memory Scale; T cho, total cholesterol; HbA1c, hemoglobin A1c; BDNF, brain-derived neurotrophic factor (BDNF); VEGFR1, vascular endothelial growth factor receptor 1.
Missing values: ADAS-cog (n = 10), WMS-LM I (n = 9), WMS-LM II (n = 9)
doi:10.1371/journal.pone.0061483.t003

selection bias may have affected the generalizability of our findings to population-based samples. Other limitations include unknown group differences in risk factors of cognitive decline and AD, such as apolipoprotein E ε4 genotype, and inflammation, although there were no significant differences between groups in terms of hypertension, diabetes mellitus, medications, biomarkers of lipid metabolism, physical performance, instrumental ADL functioning, or depressive mood. In addition, it is possible that the improvement in the exercise group resulted from the social contact to which the intervention group was exposed. This possibility cannot be completely excluded with the present design, and should be addressed in future studies.

Conclusion

The current results indicate that a multicomponent exercise program can provide cognitive benefits for older adults with aMCI. The effects of exercise were most pronounced for logical memory and general cognitive function in older adults with aMCI. Exercise was found to maintain the atrophy levels of the whole brain cortex in older adults with aMCI. Improvement of cognitive function was associated with low T-cho and high BDNF levels at baseline. A future follow-up investigation is required to determine whether the observed effects are associated with prevention or delayed onset of AD in older adults with MCI.

Supporting Information

Checklist S1 CONSORT Checklist.
(DOC)

Protocol S1 Trial Protocol.
(DOCX)

Acknowledgments

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Author Contributions

Conceived and designed the experiments: TS H. Shimada. Performed the experiments: H. Shimada HM TD DY TK. Analyzed the data: H. Shimada. Contributed reagents/materials/analysis tools: KI H. Shimokata YW HE. Wrote the manuscript: TS H. Shimada HM TD DY. Review of manuscript: KI H. Shimokata YW HE TK.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

High prevalence of sarcopenia and reduced leg muscle mass in Japanese patients immediately after a hip fracture

Tetsuro Hida,[1,3] Naoki Ishiguro,[3] Hiroshi Shimokata,[2] Yoshihito Sakai,[1] Yasumoto Matsui,[1] Marie Takemura,[1] Yasuto Terabe[1] and Atsushi Harada[1]

[1]Department of Orthopedic Surgery, [2]Department for Development of Preventive Medicine, National Center for Geriatrics and Gerontology, and [3]Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

Aim: Sarcopenia-related falls and fractures are becoming an emerging problem as a result of rapid aging worldwide. We aimed to investigate the prevalence of sarcopenia by estimating the muscle mass of the arms and legs of patients with and without hip fracture.

Methods: This cross-sectional study examined 357 patients immediately after a hip fracture (the HF group) and in 2511 patients from an outpatient clinic who did not have a hip fracture (the NF group) at single institution in Japan. We carried out whole-body dual energy X-ray absorptiometry to analyze body composition with skeletal muscle mass index (SMI; lean mass / height^2) and bone mineral density (BMD). We carried out stepwise logistic regression analysis to determine the factors associated with a hip fracture.

Results: Lower appendicular SMI ($P < 0.001$), leg SMI ($P < 0.001$), and higher prevalence of sarcopenia ($P < 0.001$) were observed in the HF group after controlling for age and sex. The arm SMI was similar in both groups ($P > 0.95$). In multivariate analysis, the presence of sarcopenia, older age and lower BMD were associated with the occurrence of a hip fracture (OR 1.476, $P = 0.002$; OR 1.103, $P < 0.001$; OR 0.082, $P < 0.001$; respectively).

Conclusion: This study showed a higher prevalence of sarcopenia and more reduced leg muscle mass in patients after a hip fracture than in the outclinic patients who did not have hip fractures. The results imply sarcopenia can be a risk factor for a hip fracture. **Geriatr Gerontol Int 2013; 13: 413–420.**

Keywords: dual energy X-ray absorptiometry, hip fracture, osteoporosis, sarcopenia, skeletal muscle mass.

Introduction

As populations are aging worldwide, the number of patients with osteoporotic fracture is increasing. Hip fracture, which is the most common osteoporotic fracture, is one of the most serious and unavoidable medical and social concerns.[1] A fracture of the hip results in increased mortality, persistent physical morbidity[2] and limited activities of daily living (ADL).[3] It is also associated with a high risk of institutionalization,[4,5] readmission[6] and reduction of the quality of life for caregivers.[7] The financial burden on society is becoming more and more critical.[8] Prevention of hip fracture is essential for maintaining a good quality of life for the elderly.

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Correspondence: Dr Tetsuro Hida MD, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, 35, Tsuruma, Showa-ku, Nagoya 466-8550, Japan. Email: hidat@med.nagoya-u.ac.jp

The role of muscles in maintaining functional performance and preventing falls has been an emphasis in recent years. The mass and strength of skeletal muscles decrease with age, and this loss accelerates after 65 years-of-age with a risk of adverse outcomes, such as physical disability, poor quality of life and death.[9] This condition, called sarcopenia, has received particular attention in recent years.[10,11] In addition to a decrease of physical performance, the elderly with sarcopenia have increased risk of age-related diseases, such as decreased swallowing function[12] or urinary disorder, as a result of muscle dysfunction.[13] Consequently, sarcopenia is regarded as an indicator of development of frailty[14] and loss of independence in the elderly. Furthermore, this condition is also associated with increased physical disabilities, resulting in the risk of falls.[15] However, the impact of sarcopenia on osteoporotic fractures has rarely been reported.

The aim of the present study was to estimate the muscle volume of the extremities and investigate the prevalence of sarcopenia in patients immediately after the occurrence of a hip fracture.

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