Jpn J Rehabil Med 2015 ; 52 : 51-54

《教育講演》

フレイルの概念と予防*1

鳥羽 研二*2

はじめに

フレイルは老年医学の最も大事な概念の1つで，高齢者の中核症状である．フレイルは以前は「虚弱」と訳されてきたが，可逆性が高いことから，動揺性のニュアンスをもつフレイルという呼び方に日本老年医学会で決定された．

フレイルは身体的なもの（Physical Frailty）と精神的なもの（Cognitive Frailty，Mental Frailty）および社会的なもの（Social Frailty）に分かれる．これらの評価は高齢者総合的機能評価（CGA）の項目そのものである．

フレイルから要介護に至らぬように，介護予防事業が行われているが，内外のフレイルのエビデンスに基づき，科学的アプローチを行うことが必要である．回復期リハビリテーション（以下，リハ）や通院，通所リハは，フレイルが対象となることが多い．この場合CGA以外に，フレイルの臨床的表現形である老年症候群の理解が必要で，患者，家族にとってはリハによって副次的にこれらの改善がみられることが重要である．

フレイルの診断基準

以下の5項目で3項目以上がフレイル，1～2項目該当でフレイル予備軍（Prefrailty）と診断される．

1）歩行速度低下（<1 m/秒）
2）握力低下（<30 kg：男性，<20 kg：女性）
3）易疲労感（自己申告）
4）活力低下
5）体重減少（年間>5 kg）

#身体的フレイルを念頭においたLinda Friedの基準

認知機能を加味していない．

ロコモとフレイル

本邦では「ロコモティブシンドローム（通称ロコモ）」が次第に名称が浸透しつつあり，厚生労働省はこの概念の普及を目指している．国際的には身体的フレイルとほぼ同義語である（図1）．

フレイルの頻度（身体的フレイル）

西欧ではスイス，アメリカの6%と低いが，イギリスやフランスは10～15%，スペインは28%に達する．本邦は7～9%，アジアはほぼ同様となっている．

認知機能に関するフレイル（Cognitive Frailty）や社会的フレイルは20～30%あると推計されている．

特定高齢者の検診における基本チェックリストは，フレイルの頻度を調査するのに適切であると報告されている（佐竹，荒井：第8回国際フレイルサルコペニア研究会，2013）．

介護予防との関連

日本老年医学会にフレイル委員会が発足し，2014年2月に日本サルコペニア・フレイル研究会（世話人代表：荒井秀典京大教授）が発足した．介護予防という日本語として不適切な表現からようやく国際標準の「フレイル」の概念に移行できていくことが期待される．

介護保険におけるコンセプトは「地域における自立支援」と「地域で要介護者を支える」の2点に集約されてきた．

介護保険の開始前に，介護予防に関して異なった2つの見通しがあった．岡本は，「要支援に対する予防

2014年12月16日受稿
*1 本稿は第51回日本リハビリテーション医学会学術集会教育講演（2014年6月7日，名古屋）をまとめたものである．
*2 独立行政法人国立長寿医療研究センター/〒474-8511 愛知県大府市森岡町7丁目430番地

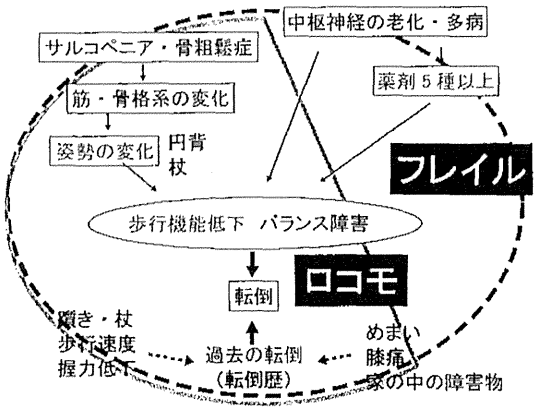

図1 ロコモとフレイル

給付は画期的で，介護予防がなされる」という明るい見通しを述べているが，同時に「寝たきり進行のプロセスは殆ど研究されていない」とも述べ，地道なプロスペクティブな研究の必要性を指摘した[1]．一方松林は，地域で予防介入を長く実践してきた立場から，介護に偏し，予防の比重が低くなる介護保険に危機感を表明していた[2]．既に筆者も予測していたところであるが[3]，残念ながら，危惧が現実のものとなった．介護保険制定後5年間に介護認定者が200万人から倍増し，特に要支援，要介護1といった，「自立支援」を図るべき対象であるフレイルが激増し，「介護保険料の値上げ」が避けられなくなり，2007年4月の「介護予防」の概念の導入と，「介護予防事業」の介護保険からの一部切り離しに関係していることはいうまでもない．

予防重視の改正の要点は，従来の要支援と要介護1に対し，認知症や脳血管障害，症状の不安定な対象を除き，筋力トレーニングや活力賦活（アクティビティーデイ）などを行う「要支援1，要支援2（新設）」を選別し「介護予防事業」で経費を賄うというものである．

新しい介護予防事業のサービスの選定根拠が十分科学的に担保されておらず，一部の少数例のデータによって，虫食い的なサービスモデルが提唱されている点が最も危惧される点である．

栄養，口腔ケア，筋力トレーニングなどはフレイル増悪の機序に沿った重要な視点であることは間違いないが，高齢者の多様な病態と機能低下の学問的関連を，十分反映した施策が求められる．

フレイルの生活機能への影響の多様性

介護保険の介護は，生活支援と身体介護に分けられる．

生活支援は，家事援助ともいい，独居あるいは，家族の家事代行が不十分な認定者に対して，買い物，掃除，洗濯，炊事，通院などを手助けするものであり，「手段的ADL」（表1）[4]の代行をしている．

身体介護には，寝返り，移動の介助や排泄支援，清拭などといった，「基本的ADL」（表1）の介助と，とこずれ処置，おむつ交換，摂食介助などといった，褥瘡，尿失禁，嚥下障害などの「老年症候群のケア」が含まれる．

従って，要介護予防という概念は，手段的ADL依存の予防，基本的ADL低下予防，および老年症候群の発症・悪化予防という極めて幅がひろい概念になる．

欠けている能力を賦活する介護サービスとして，共

表1 介護保険の介護内容（文献4より引用）

生活支援	身体支援	
独居高齢者の生活自立要因	最低限のセルフケア	移動の介護
＝手段的ADL	＝sADL	＝mADL
交通機関の利用	食事	寝返り
買い物	排尿・排便	起立
金銭管理	入浴	歩行屋内
料理	整容	歩行屋内
家事	更衣	階段昇降
洗濯	口腔衛生	
熱源の取り扱い		
服薬管理		
電話		

同生活，リハがあり，前者は手段的ADLを手助けを受けながら共同で行うことによって機能を維持し，後者は基本的ADLの改善，維持を主な目的としているが，認知症やうつなどにも効果が期待され，「認知機能・情緒」といった精神機能に対する介護の形態を含んでいる．

前フレイル者の早期発見というテーマが世界的に重要になってきており，フランスではツールーズに前フレイルセンターがオープンしている．

フレイルの悪化サイクルと介入の多様性

フレイルのモデルを1つの器官系に機能障害がある場合に限定するのは，全体を見損なう恐れがある．神経，内分泌，栄養，動脈硬化，炎症など多角的視点のなかで総合的に捉える必要がある．これはフレイルの悪化サイクルを理解する助けになる（図2）．

フレイルに対する詳細な検査方法

実際の測定方法としては，運動系機能として，握力，up&goテスト，トレッドミル，6分間歩行などを行い，認知機能として認知機能検査（MMSE），バランス機能として片足立ち試験，栄養状態として肥満指数（BMI），周囲径などが挙げられている．これらは，「高齢者総合的機能評価ガイドライン」に推奨した方法と図らずも一致している．同様の考え方に，フレイルは自立と終末期の中間点と見なす考え方で，ハイリスクの因子として，75歳以上の高齢，ADLおよびIADL障害・依存状態，転倒・骨折，多剤投与，慢性病，認知機能低下，抑うつ，栄養障害を指摘している．

表2 高知県香北町における総合機能評価と介入事業（文献2より引用）

1) 健康関連アンケート調査（65歳以上全高齢者）：ADL，視力，聴力，老研式活動能力，うつ，福祉サービス利用，QOL
2) 包括的機能健診（75歳以上全高齢者）：認知機能（MMSE），歩行能力，身体柔軟性，指先巧緻性
3) 運動教室
4) 家庭血圧測定
5) 定期健診，訪問看護
6) 保健・福祉・医療調整会議（現行のケアカンファランス）
7) 健康関連講演会（年2回）

フレイル予防

介護保険制度創設前の成功事例（香北町研究）によれば，健康予防活動（表2）による介入によって，基本的日常生活活動の増大と老人医療費の抑制という，理想的な結果が得られている[2]．

新しいフレイル予防のリハ

鳥羽，井形らは，均整柔軟体操の効果を大規模縦断的に検定し，自立高齢者を増やし，要支援への移行を予防阻止する観点（介護予防）から，開発したフレイル者の活力を測定する機能評価表を用いて，体操教室

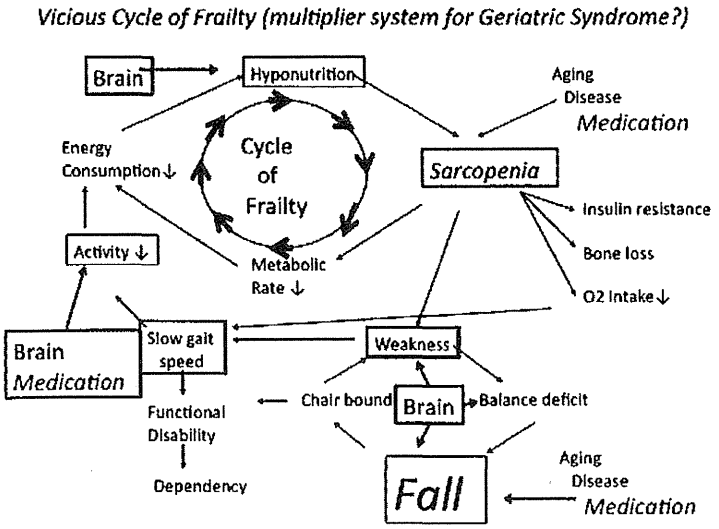

図2 フレイルの悪化サイクル（文献5より引用）

の全国的組織（三井島体操2600名：18～84歳）に対する大規模縦断研究1年面の成績で，運動による活力度（IADL，交流，運動機能，健康意識，うつ）の向上を示した[6]．この中で，後期高齢者では週2～3時間程度の運動が最適であることも示している．

Cognitive Frailty に対する認知症短期集中リハ

2006年の介護報酬改定で老健施設に認知症短期集中リハ実施加算（理学療法士，作業療法士，または言語聴覚士が1回20分以上の個人療法，1回60点，週3回までで，入所から3カ月以内まで請求できる）が軽症の認知症（MMSE，改訂長谷川式簡易知能評価スケール（HDS-R）が概ね15点以上）に認められ，リハ期間が規定されたために，効果の検証研究が容易になった．

2007年度で解析対象者を266人（対象者が203人，対照群が63人）を検証した．この結果，「ADL，活動，意欲」についてはっきり効果が出たばかりでなく，中核症状である認知機能に対しても有意な改善が認められ，薬物療法に匹敵する効果が得られた．

さらに，周辺症状に対しては，非定形精神病薬や漢方薬などの効果は知られているが，ほぼそれに匹敵する非常に強い改善効果が認められた．しかも頻度の高い周辺症状のその8割くらいに有効であるというインパクトのある成績である[7]．この成績は，認知症短期集中リハは身体的，精神的フレイルにきわめて有効な悪化予防の手段であることを示すものである．

2014年4月から，医療保険で認知症短期集中リハが認められることになった．当面進行した認知症に限定されるが，回復期リハや，フレイル悪化予防のリハとして拡大していくことが，高齢者の心身の健康維持に好影響をもたらし，結果的に医療費や介護費用の有効利用につながると確信している．

文　献

1) 岡本祐三：介護保険における評価法．高齢者の生活機能評価ガイド．医歯薬出版，東京，1999；pp 341-344
2) 松林公蔵：地域社会における寝たきり予防のための方策．高齢者の生活機能評価ガイド．医歯薬出版，東京，1999；pp 312-326
3) 鳥羽研二：老年科医の観点から見た介護サービス．Gerontology New Horizon 1998；10：39-44
4) 江藤文夫：ADL 20．日本老年医学会雑誌 1992；29：841-848
5) Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA；Cardiovascular Health Study Collaborative Research Group：Frailty in older adults：evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001；56：M146-M156
6) 鳥羽研二：厚生科学研究費補助金痴呆・骨折臨床研究事業「寝たきりの主要因に対する縦断介入研究を基礎にした介護予防ガイドライン策定に関する研究」平成16年度報告書
7) Toba K, Nakamura Y, Endo H, Okochi J, Tanaka Y, Inaniwa C, Takahashi A, Tsunoda N, Higashi K, Hirai M, Hirakawa H, Yamada S, Maki Y, Yamaguchi T, Yamaguchi H：Intensive rehabilitation for dementia improved cognitive function and reduced behavioral disturbance in geriatric health service facilities in Japan. Geriatr Gerontol Int 2014；14：206-211

Geriatrics Gerontology INTERNATIONAL ONLINE | Medline Indexed

Geriatr Gerontol Int 2014; **14 (Suppl. 2):** *77–86*

ORIGINAL ARTICLE

Association of grip strength and related indices with independence of activities of daily living in older adults, investigated by a newly-developed grip strength measuring device

Yasumoto Matsui,[1] Remi Fujita,[1] Atsushi Harada,[1] Takashi Sakurai,[2] Tetsuya Nemoto,[3] Nobuo Noda[4] and Kenji Toba[2]

[1]Department of Advanced Medicine (Orthopedic Surgery), [2]Center for Comprehensive Care and Research on Memory Disorders, [3]Department of Gerontechnology, National Center for Geriatrics and Gerontology, Obu, and [4]Eisyo Metal Co., Ltd, Tokyo, Japan

Aim: To investigate the association of grip strength and activities of daily living independence in older adults, using a newly-developed grip strength measuring device.

Methods: Patients who visited the clinic for memory disorders at the National Center for Geriatrics and Gerontology (142 men and 205 women, mean age 74.8 ± 8.8 years) were included in the present study. Their strength during gripping performance is described in detail, and following the indices were calculated: maximum strength (MS), response time (RT), time to MS, time to reach turning point (TP), strength at TP, inclination from start to TP, time from TP to reach MS, inclination from TP to MS and ratio of strength (TP/MS). Barthel Index (BI), total scores and scores of each subclass were used for evaluating activities of daily living independence. MS was compared between the independent and dependent groups. Correlations, using partial Pearson's coefficient adjusted for age, and Mini-Mental State Examination total score were analyzed between indices and BI by sex, side, and age groups.

Results: MS was significantly higher in the independent group. MS and RT were significantly related with BI total and certain subclasses in both hands, TP/MS was significantly related in the right hand of either sex, and strength at TP was significantly related in both hands in women and in the left hand in men. Time to reach TP was particularly correlated in both hands and time from TP to reach MS in the right hand, in men. The correlation of indices varied by sex, hand side and age group, especially in men aged in their 70s, and in women aged less than 70 years and women aged in their 80s.

Conclusion: MS was shown to be useful, but some of the newly defined indices, such as RT, strength at TP, and elements regarding before and after TP until reaching MS, were also suggested to be useful. **Geriatr Gerontol Int 2014; 14 (Suppl. 2): 77–86.**

Keywords: activities of daily living independence, association, detailed evaluation, grip strength, muscle contraction.

Introduction

In geriatric medicine, evaluations of physical ability and assessment as to whether elderly patients keep their independence in activities of daily living (ADL) are essential tasks. They are included in the comprehensive geriatric assessment (CGA),[1] the importance of which has been widely recognized.[2] For the evaluation of physical ability, the grip strength test is one of the most popular and widely utilized methods,[3–5] as it is considered to be an indication of the state of muscle function.[6–9] Grip strength has been reported to be correlated with ADL or physical performance,[10–14] or to predict disability or dependence in the future.[15–18]

In order to assess the gripping ability of physically weakened older adults more precisely, we have developed a new device to analyze the detailed way in which muscles contract during gripping performance.[19] This new device can accurately measure not only very weak peak values, but also the agility or the endurance in gripping by taking the time axis into consideration. Using the data obtained from the measurement by this

Accepted for publication 10 January 2014.

Correspondence: Dr Yasumoto Matsui MD, 35, Gengo, Morioka-cho, Obu, Aichi 474-8511, Japan. Email: matsui@ncgg.go.jp

© 2014 Japan Geriatrics Society

new device, we have proposed new indices and showed the difference by sex or hand side.[19]

In the present study, using the data from our newly-developed device, we investigated the association of gripping performance and independence of ADL in older adults, evaluated by total Barthel Index (BI) score and its subitems, and attempted to reveal the meaning of the newly proposed indices, as well as that of maximum grip strength.

Methods

Study population

The participants of the present analyses were recruited at the outpatient clinic for memory disorders at the National Center for Geriatrics and Gerontology, Japan at Obu City, Aichi Prefecture in Japan. The period of recruitment was from 18 October 2010 to 10 June 2011. Inclusion criteria were principally the patients who visited our memory disorder clinic for the first time and could understand the instructions on how to measure grip strength with the new device. Before the examination, their blood pressure was measured, and those with higher than 160 mmHg systolic pressure were excluded. The participants of the present study were 347 patients (142 men and 205 women, average age 75.0 ± 9.1 years).

Average Mini-Mental State Examination (MMSE) score was 21.1 ± 6.1 in men and 20. 2 ± 5.7 in women.

Evaluations of ADL independence by BI and participant grouping

Independence of the ADL was evaluated by BI[20] questionnaire. The index is composed of 10 items regarding bathing, grooming, feeding, dressing, toilet use, ascend/descend stairs, bowel management, bladder management, bed/wheelchair transfer and mobility (level surface), totaling 100 points as a full score. Participants were classified into two groups based on the total BI score. Those with a total score of 100 points were classified as independent, and those with less than 100 points as dependent. They were also classified by the scores on each of the 10 component subitems of BI (full score, less than full score).

Newly-developed device for measuring grip strength

Using the force-gauge (manufactured by IMADA, Toyohashi, Japan; product no. ZP-500N) for measuring industrial products, the signal output from the device is sent to a computer (Fig. 1). At the moment an LED lamp on the device lights up, the examinee is encouraged to grip the handle, and the grip strength is constantly recorded by the computer. How the gripping strength is produced can be automatically described on the computer monitor. Not only can it measure the maximum (peak) grip strength accurately, even very low levels of strength, but it can also measure the response time, agility (catching ability) or endurance (holding ability).

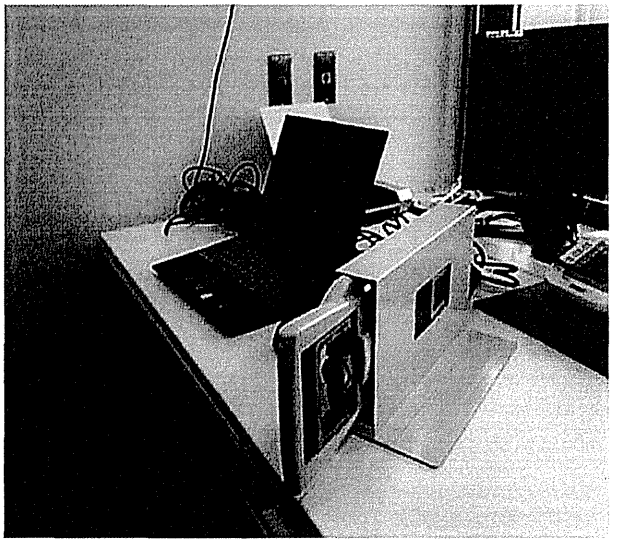

Figure 1 Newly-developed device for measuring grip strength. Force-gauge (made by IMADA, Toyohashi, Japan) can be used for measuring industrial products, such as the operation switch on a deluxe automobile. The gauge is equipped with an easy-grip handle. The signal output from the device is sent to the computer. The moment the LED lamp on the device lights up, the examinee grips the handle. Grip strength is constantly recorded by the computer. How the gripping strength is produced is automatically described on the computer monitor.

Method for measuring grip strength and items calculated

The participants were mostly elderly patients, whose grip strength was measured in the sitting position, with their elbows flexed approximately 90°. In the agility examination, the examinees were asked to grip the handle as soon as the lamp illuminated. The time and the pattern to reach the peak value were then evaluated.

For the analyses to assess agility in detail, from the graph showing the data output and recorded on the computer monitor, we selected four points: (i) lamp lights up; (ii) time to start gripping; (iii) turning point when curve inclination changes; and (iv) peak. We then defined nine indices, calculated with these four points as follows: (1) maximum strength; (2) response time; (3) time to reach maximum strength; (4) time to reach turning point; (5) strength at turning point; (6) inclination from start to turning point; (7) time from turning point to reach maximum strength; (8) inclination from turning point to maximum strength; and (9) ratio of strength (turning point/maximum); (Fig. 2).

© 2014 Japan Geriatrics Society

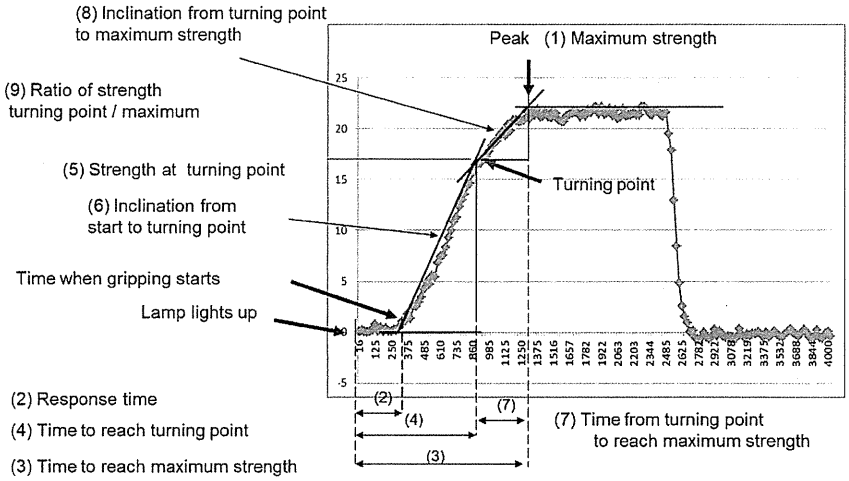

Figure 2 A graph showing nine detailed indices in the agility examination.

Statistical analyses

The average maximum grip strength was compared between the independent group and dependent group (both BI total score and each subclass item). Also, the average absolute values of each of the aforementioned nine items were calculated, and then the relationships were investigated between those items and BI scores of the total, and that of each subclass: bathing, grooming, feeding, dressing, toilet use, ascend/descend stairs, bowel management, bladder management, bed/wheelchair transfer and mobility were investigated with Pearson's coefficient, utilizing SPSS version 19 for Windows (SPSS, Chicago, IL, USA) was used. Partial correlations adjusted for age and total score of MMSE were also examined. Furthermore, the relationships between the nine grip strength measuring items and total BI scores of the three different age groups, below 70 years, 70s and 80s, were also investigated with partial Pearson's coefficient, adjusted for MMSE. *P*-values less than 0.05 were considered statistically significant. The study protocol was approved by the Committee on Ethics of Human Research of the National Institute for Longevity Sciences. Written informed consent was obtained from each participant.

Results

Participant characteristics

The demographic data of participants are listed in Table 1. There were significant differences between the independent group and dependent group in age, height, weight, and BI score (both total and each subclass item) in both sexes. Significant differences were seen in five of the nine newly advocated indices with the right hand in men, and in seven of the nine items in women. Significant differences were seen only in women regarding two indices: time to reach maximum strength and ratio of strength (turning point/maximum).

Comparisons of maximum grip strength

The partial correlation coefficients between the maximum grip strength and BI total score, after adjusting age and sex, were 0.296 for the right hand ($P < 0.001$) and 0.295 for the left hand ($P < 0.001$), showing significant relationships. Even after adjusting for MMSE total score, they were 0.228 for the right hand ($P < 0.001$) and 0.238 for the left hand ($P < 0.001$), and the relationships remained significant.

Comparisons among groups divided in terms of scores for total BI and each of the 10 subclass items in men showed significant differences between the full score (independent) group and those losing points (dependent) in total BI and all subitems. Similarly in women, except in one item of feeding, significant differences were shown between the independent and dependent group for almost all subitems, as well as for total BI (Table 2).

Correlations between nine grip strength items measured and BI

Partial correlations between the nine grip strength items measured and BI score (total score and each of 10 subitems), adjusted for age and MMSE, were examined for both hands in men (Table 3) and in women (Table 4). In men, maximum grip strength was significantly correlated with eight items in the left hand and five in the right, as well as with the total score in both hands. Response time was significantly correlated with five items in the left hand, four in the right hand and total score in both hands. Time to voach turning point was significantly correlared with five items and with total score in the left hand. Strength at turning point was significantly correlated with four items in the left hand

© 2014 Japan Geriatrics Society

Table 1 General characteristics of participants

	Men					Women			
		Independent (n = 87)	Dependent (n = 55)	P-value			Independent (n = 144)	Dependent (n = 61)	P-value
	Age (years)	72.6 ± 8.7	75.5 ± 10.5	0.073		Age (years)	74.2 ± 8.8	80.1 ± 6.6	<0.001
	Height (cm)	163.9 ± 5.7	160.2 ± 7.2	0.001		Height (cm)	149.8 ± 6.4	144.6 ± 7.1	<0.001
	Weight (kg)	61.2 ± 8.8	57.1 ± 11.2	0.017		Weight (kg)	47.9 ± 8.2	46.1 ± 9.1	0.154
	BMI (kg/m^2)	22.8 ± 2.9	22.1 ± 3.2	0.209		BMI (kg/m^2)	21.3 ± 3.1	22.0 ± 3.8	0.171
	MMSE score	23.0 ± 5.2	18.1 ± 6.3	<0.001		MMSE score	21.4 ± 5.4	17.3 ± 5.5	<0.001
Barthel Index	Total score	100.0 ± 0.0	78.9 ± 21.6	<0.001	Barthel Index	Total score	100.0 ± 0.0	80.7 ± 17.6	<0.001
	Feeding	10.0 ± 0.0	9.4 ± 2.0	0.002		Feeding	10.0 ± 0.0	9.4 ± 1.6	<0.001
	Bed/wheel-chair transfer	15.0 ± 0.0	13.9 ± 2.9	<0.001		Bed/wheel-chair transfer	15.0 ± 0.0	13.9 ± 2.3	<0.001
	Grooming	5.0 ± 0.0	3.8 ± 2.2	<0.001		Grooming	5.0 ± 0.0	3.4 ± 2.4	<0.001
	Toilet use	10.0 ± 0.0	8.3 ± 2.4	<0.001		Toilet use	10.0 ± 0.0	9.1 ± 2.0	<0.001
	Bathing	5.0 ± 0.0	3.5 ± 2.3	<0.001		Bathing	5.0 ± 0.0	2.8 ± 2.5	<0.001
	Mobility	15.0 ± 0.0	13.6 ± 3.7	0.001		Mobility	15.0 ± 0.0	13.8 ± 2.8	<0.001
	Ascend/descend stairs	10.0 ± 0.0	8.5 ± 2.7	<0.001		Ascend/descend stairs	10.0 ± 0.0	8.3 ± 2.9	<0.001
	Dressing	10.0 ± 0.0	8.0 ± 2.8	<0.001		Dressing	10.0 ± 0.0	8.4 ± 2.5	<0.001
	Bowel management	10.0 ± 0.0	6.6 ± 3.0	<0.001		Bowel management	10.0 ± 0.0	6.5 ± 3.0	<0.001
	Bladder management	10.0 ± 0.0	6.2 ± 2.9	<0.001		Bladder management	10.0 ± 0.0	6.2 ± 2.5	<0.001
Nine new indices	Response time (ms)	360.2 ± 153.6	425.6 ± 188.2	0.026	Nine new indices	Response time (ms)	388.6 ± 138.0	492.3 ± 186.7	<0.001
	Time to reach turning point (ms)	692.6 ± 252.2	807.8 ± 304.9	0.016		Time to reach turning point (ms)	761.8 ± 279.4	838.3 ± 273.4	0.077
	Strength at turning point (kg)	24.5 ± 8.3	18.3 ± 7.7	<0.001		Strength at turning point (kg)	16.7 ± 5.8	11.3 ± 4.7	<0.001
	Inclination from start to turning point (kg/ms)	0.082 ± 0.045	0.054 ± 0.037	<0.001		Inclination from start to turning point (kg/ms)	0.048 ± 0.027	0.031 ± 0.017	<0.001
	Time to reach maximum strength (ms)	1276.4 ± 464.6	1302.3 ± 422.1	0.740		Time to reach maximum strength (ms)	1261.2 ± 385.8	1397.4 ± 394.3	0.025
	Maximum strength (kg)	28.3 ± 8.2	21.6 ± 8.8	<0.001		Maximum strength (kg)	19.3 ± 6.0	14.0 ± 5.6	<0.001
	Time from turning point to reach maximum strength (ms)	583.8 ± 403.2	494.5 ± 362.5	0.186		Time from turning point to reach maximum strength (ms)	499.4 ± 331.5	559.2 ± 335.6	0.248
	Ratio of strength (turning point/maximum) (%)	85.7 ± 11.5	84.9 ± 11.3	0.663		Ratio of strength (turning point/maximum) (%)	86.1 ± 10.2	80.9 ± 12.9	0.003
	Inclination from turning point to maximum strength (kg/ms)	0.010 ± 0.010	0.009 ± 0.008	0.451		Inclination from turning point to maximum strength (kg/ms)	0.007 ± 0.005	0.005 ± 0.004	0.119

BMI, body mass index; MMSE, Mini-Mental State Examination.

© 2014 Japan Geriatrics Society

© 2014 Japan Geriatrics Society

Table 2 Comparisons of maximum grip strength between independent and dependent groups of total Barthel Index score and each Barthel Index subitem

		Men			Women		
		Independent (*n*)	Dependent (*n*)	*P*-value	Independent (*n*)	Dependent (*n*)	*P*-value
Total score	Right	28.3 ± 8.2 (87)	21.6 ± 8.8 (54)	<0.001	19.3 ± 6.0 (142)	14.0 ± 5.6 (59)	<0.001
	Left	27.3 ± 8.0 (87)	21.1 ± 8.6 (55)	<0.001	17.9 ± 5.7 (143)	12.9 ± 5.4 (60)	<0.001
Feeding	Right	26.3 ± 8.8 (134)	15.4 ± 5.4 (6)	0.003	17.9 ± 6.3 (194)	14.0 ± 4.7 (7)	0.11
	Left	25.4 ± 8.7 (135)	15.9 ± 4.9 (6)	0.009	16.5 ± 6.0 (196)	13.2 ± 6.9 (7)	0.15
Bed/wheelchair transfer	Right	26.3 ± 8.8 (130)	17.5 ± 7.7 (9)	0.004	18.1 ± 6.2 (189)	11.4 ± 5.0 (11)	<0.001
	Left	25.4 ± 8.6 (131)	17.3 ± 8.1 (9)	0.006	16.9 ± 5.9 (190)	10.3 ± 3.9 (12)	<0.001
Grooming	Right	26.8 ± 8.7 (126)	16.1 ± 5.9 (13)	<0.001	18.4 ± 6.2 (181)	12.2 ± 4.3 (20)	<0.001
	Left	25.8 ± 8.3 (127)	15.5 ± 7.0 (13)	<0.001	17.0 ± 6.0 (183)	10.9 ± 3.6 (20)	<0.001
Toilet use	Right	26.9 ± 8.8 (121)	18.4 ± 6.5 (18)	<0.001	18.1 ± 6.3 (190)	12.5 ± 4.5 (10)	0.007
	Left	26.0 ± 8.5 (122)	17.4 ± 6.5 (18)	<0.001	16.8 ± 6.0 (191)	11.4 ± 4.3 (11)	0.004
Bathing	Right	27.0 ± 8.6 (122)	15.7 ± 6.1 (15)	<0.001	18.5 ± 6.1 (175)	12.6 ± 5.1 (25)	<0.001
	Left	26.1 ± 8.3 (123)	14.7 ± 5.6 (15)	<0.001	17.1 ± 5.9 (176)	12.2 ± 5.3 (26)	<0.001
Mobility	Right	26.4 ± 8.8 (131)	16.0 ± 5.6 (8)	0.001	18.0 ± 6.2 (190)	12.8 ± 6.7 (10)	0.01
	Left	25.4 ± 8.6 (132)	16.1 ± 6.3 (8)	0.003	16.7 ± 5.9 (191)	11.7 ± 6.0 (11)	0.006
Ascend/descend stairs	Right	26.8 ± 8.7 (125)	16.9 ± 6.8 (14)	<0.001	18.3 ± 6.2 (183)	12.4 ± 5.0 (17)	<0.001
	Left	25.8 ± 8.4 (126)	16.3 ± 7.1 (14)	<0.001	17.0 ± 5.9 (184)	11.2 ± 4.5 (18)	<0.001
Dressing	Right	26.9 ± 8.6 (121)	17.8 ± 7.7 (18)	<0.001	18.3 ± 6.2 (183)	12.4 ± 4.7 (17)	<0.001
	Left	25.8 ± 8.5 (121)	18.9 ± 8.1 (19)	0.0001	17.0 ± 5.9 (184)	11.0 ± 4.0 (18)	<0.001
Bowel management	Right	27.4 ± 8.3 (108)	20.0 ± 9.1 (32)	<0.001	18.8 ± 6.1 (163)	13.1 ± 5.3 (37)	<0.001
	Left	26.3 ± 8.1 (108)	19.8 ± 9.2 (33)	<0.001	17.5 ± 5.8 (164)	11.8 ± 4.6 (38)	<0.001
Bladder management	Right	27.3 ± 8.7 (104)	20.8 ± 8.3 (35)	<0.001	18.9 ± 6.2 (158)	13.6 ± 5.1 (42)	<0.001
	Left	26.6 ± 8.5 (104)	19.8 ± 7.7 (36)	<0.001	17.6 ± 6.0 (159)	12.4 ± 4.4 (43)	<0.001

Table 3 Partial correlations between nine grip strength items measured and Barthel Index (total score and each sub items) adjusted for age and Mini-Mental State Examination total score in men

			Total score	Feeding	Bed/wheel-chair transfer	Grooming	Toilet use	Bathing	Mobility	Ascend/ descend stairs	Dressing	Bowel management	Bladder management
Response time	Right	*r*	−0.22*	−0.22*	−0.12	−0.10	−0.16	−0.25**	−0.22*	−0.15	−0.19*	−0.14	−0.04
	Left	*r*	−0.24**	−0.29**	−0.16	−0.12	−0.13	−0.27**	−0.23**	−0.18*	−0.25**	−0.06	−0.07
Time to reach turning point	Right	*r*	−0.22*	−0.30**	−0.13	−0.12	−0.13	−0.15	−0.28**	−0.12	−0.12	−0.09	−0.14
	Left	*r*	−0.25**	−0.29**	−0.14	−0.06	−0.15	−0.10	−0.25**	−0.12	−0.20*	−0.19*	−0.18*
Strength at turning point	Right	*r*	0.17	0.12	0.07	0.13	0.10	0.23*	0.10	0.10	0.14	0.16	0.09
	Left	*r*	0.26**	0.15	0.13	0.22*	0.16	0.32**	0.17	0.21*	0.16	0.14	0.18*
Inclination from start to turning point	Right	*r*	0.18*	0.16	0.09	0.12	0.10	0.13	0.15	0.08	0.07	0.11	0.22*
	Left	*r*	0.20*	0.15	0.08	0.16	0.09	0.11	0.16	0.07	0.07	0.20*	0.26**
Time to reach maximum strength	Right	*r*	0.13	−0.10	0.06	0.06	0.14	0.09	0.04	0.12	0.21*	0.14	0.07
	Left	*r*	−0.01	−0.08	0.00	−0.06	0.08	0.11	−0.05	0.02	−0.06	−0.05	0.00
Maximum strength	Right	*r*	0.26**	0.15	0.12	0.18*	0.18*	0.31**	0.16	0.17	0.22*	0.20*	0.16
	Left	*r*	0.30**	0.17	0.15	0.25**	0.23*	0.36**	0.20*	0.23**	0.17*	0.18*	0.23**
Time from turning point to reach maximum strength	Right	*r*	0.30**	0.10	0.17	0.15	0.25**	0.21*	0.24**	0.23*	0.33**	0.22*	0.18*
	Left	*r*	0.15	0.11	0.10	−0.03	0.19*	0.20*	0.10	0.11	0.07	0.07	0.13
Ratio of strength (turning point/maximum)	Right	*r*	−0.22*	−0.07	−0.17	−0.14	−0.20*	−0.19*	−0.20*	−0.17	−0.18*	−0.06	−0.18*
	Left	*r*	−0.09	−0.06	−0.07	−0.02	−0.17*	−0.07	−0.06	0.04	−0.01	−0.12	−0.09
Inclination from turning point to maximum strength	Right	*r*	0.06	0.11	0.09	0.03	0.02	0.12	0.09	0.06	−0.07	−0.04	0.06
	Left	*r*	0.07	0.08	0.08	0.12	−0.06	−0.05	0.09	−0.03	−0.01	0.12	0.10

**$P < 0.01$, *$P < 0.05$.

Table 4 Partial correlations between nine grip strength items measured and Barthel Index (total score and each sub items) adjusted for age and Mini-Mental State Examination total score in women

			Total score	Feeding	Bed/wheel-chair transfer	Grooming	Toilet use	Bathing	Mobility	Ascend/ descend stairs	Dressing	Bowel management	Bladder management
Response time	Right	*r*	−0.14	0.26	−0.05	−0.12	−0.02	−0.16*	0.04	−0.17*	0.07	−0.19*	−0.14
	Left	*r*	−0.16*	−0.10	−0.07	−0.22**	−0.06	−0.16*	0.02	−0.11	0.07	−0.15*	−0.18*
Time to reach turning point	Right	*r*	0.01	0.10	0.10	0.04	0.04	0.03	0.07	−0.03	0.04	−0.12	−0.05
	Left	*r*	0.02	0.03	0.05	−0.07	0.02	0.02	0.09	−0.04	0.08	−0.02	−0.03
Strength at turning point	Right	*r*	0.26**	0.09	0.20**	0.16*	0.11	0.22**	0.12	0.21**	0.15*	0.22**	0.23**
	Left	*r*	0.23**	0.04	0.17*	0.17*	0.09	0.13	0.14	0.15*	0.16*	0.24**	0.25**
Inclination from start to turning point	Right	*r*	0.14	−0.10	0.07	0.02	0.07	0.04	0.10	0.12	0.06	0.20**	0.17*
	Left	*r*	0.11	−0.04	0.09	0.03	0.06	0.02	0.05	0.12	0.03	0.15*	0.16*
Time to reach maximum strength	Right	*r*	−0.11	−0.02	0.04	−0.02	−0.07	−0.01	−0.05	−0.10	−0.08	−0.20**	−0.15*
	Left	*r*	−0.04	0.00	0.01	0.02	−0.05	0.07	−0.02	−0.02	0.01	−0.13	−0.09
Maximum strength	Right	*r*	0.22**	0.06	0.20**	0.15*	0.06	0.19**	0.12	0.17*	0.13	0.18*	0.20**
	Left	*r*	0.23**	0.03	0.19**	0.18*	0.08	0.15*	0.13	0.16*	0.16*	0.19**	0.22**
Time from turning point to reach maximum strength	Right	*r*	−0.14	−0.10	−0.04	−0.06	−0.11	−0.04	−0.11	−0.09	−0.13	−0.12	−0.14
	Left	*r*	−0.06	−0.02	−0.02	0.03	−0.07	0.08	−0.08	−0.01	−0.04	−0.15*	−0.09
Ratio of strength (turning point/maximum)	Right	*r*	0.24**	0.13	0.18*	0.18*	0.25**	0.19**	0.15*	0.18*	0.19*	0.13	0.14
	Left	*r*	0.11	0.08	0.02	−0.01	0.06	−0.04	0.10	0.00	0.09	0.22**	0.17*
Inclination from turning point to maximum strength	Right	*r*	0.04	0.01	−0.01	−0.03	−0.04	−0.02	0.05	0.02	0.01	0.10	0.12
	Left	*r*	0.12	0.02	0.09	0.08	0.07	0.07	0.05	0.08	0.09	0.11	0.12

**$P < 0.01$, *$P < 0.05$.

© 2014 Japan Geriatrics Society

and with total score. Different from the results before adjustment, in the right hand only one index gained significance. Time from turning point to reach maximum strength and ratio of strength (turning point/maximum strength) were significantly related to seven and five items, respectively, as well as to the total score in the right hand. Inclination from start to turning point was significant only in total score and some subclass items in both hands (Table 3). In women, maximum grip strength was significantly related to seven items in the left hand and six in the right, as well as with the total score in both hands. Response time was significantly related to four items in the left hand and three in the right, whereas the total score was significant only in the left hand. Strength at turning point, differing slightly from men, was significant in seven items in the right hand and six in the left, as well as in the total score in both hands. The ratio of strength (turning point/maximum strength) was significant in seven items and the total score in the right hand (Table 4).

Correlations between nine grip strength items measured and total BI scores in three different age groups

In men aged in their 70s, six out of nine items, namely, response time, time to reach turning point, strength at turning point, maximum grip strength, time from turning point to reach maximum strength and ratio of strength (turning point/maximum), were correlated with total BI score in the right hand, whereas five items, response time, time to reach turning point, strength at turning point, inclination from start to turning point and maximum grip strength, were related with total BI score in the left hand (Table 5). In the age group below 70 years, just two items, strength at turning point and ratio of strength (turning point/maximum), were related in both hands (Table 5). In the 80s age group, no item was correlated in the right hand, and response time and inclination from start to turning point were correlated in the left hand (Table 5).

Much different from men, in women aged in their 70s only one item, strength at turning point, was correlated in the right hand, and also only one item, response time, was correlated in the left (Table 5). In the age group below 70 years, no item was correlated in the right hand, whereas four items, response time, time to reach turning point, time to reach maximum strength and time from turning point to reach maximum strength (all of these were time-related items), showed significant correlations in the left hand. In women aged in their 80s, strength at turning point and maximum strength were correlated in both hands, and time from turning point to reach maximum strength was correlated in the right hand (Table 5).

Discussion

The grip strength test is one of the most popular and widely utilized methods for evaluating muscle strength.[3-5] It is doubtful, however, whether a grip strength device, originally made for young people, is suitable for measuring very weak strength, because average grip strength of female residents (mean age 83.2 years) in a nursing home was reported to be as low as 8.7 kg.[21] We have developed a new grip-strength measuring device that not only measures small values accurately, but also evaluates muscle contraction in detail, by taking a time axis into consideration, and defined various indices, which were shown to be different by sex or side in a previous study.[19]

In the present study, we have investigated the association of grip strength and independence of ADL in older adults, comparing the data from our newly-developed device and the internationally utilized BI to determine whether the newly advocated indices are associated with limitations in ADL. Maximum grip strength was proved to be a very good index, which could be shown with precise values; however, response time, values at the turning point and ratio of strength (turning point/maximum strength), although correlated with the indices, varied by sex or hand side (Tables 3 and 4). When we first introduced this device, we thought that not only measuring the maximum strength, but also the time to reach maximum strength, would be important. The time to reach maximum strength, however, was not found to be significant in either sex or in total BI score, or in most of the subclass indices. As a matter of fact, although no association was seen in time to reach maximum strength, some relationships were seen in time to reach turning point and time from turning point to reach maximum, especially in men (Tables 3 and 4). Therefore, the meaning of time might not be the same before and after the turning point. Also, strength at turning point was found to be correlated with total BI score and several subclass items, especially in women.

From the aforementioned, turning point was suggested to be worth measuring, although its meaning warrants further investigation; it could have something to do with the proportional change of the fast and slow twitch fiber contraction, or something else, such as the relative involvement of flexors and extensors in gripping performance. In order to determine this with greater certainty, further studies should be carried out, such as simultaneous electromyography measurement. In the analyses of the separate age groups, particularly in the group of men aged below 70 years, the strength at turning point was associated with total BI scores, although maximum grip strength was not. In the group of women aged below 70 years, in the left hand, neither maximum grip strength nor strength at turning point was related with total BI scores, and some other indices,

© 2014 Japan Geriatrics Society

Table 5 Partial correlations between nine grip strength items measured and total BartheI Index scores in three different age groups, adjusted by Mini-Mental State Examination score

Age		Men			Women		
		Below 70 years (n = 38)	70s (n = 67)	80s (n = 36)	Below 70 (n = 45)	70s (n = 71)	80s (n = 85)
Response time	Right hand	−0.12	−0.34**	−0.14	0.20	−0.08	−0.07
	Left hand	−0.12	−0.33**	−0.40*	−0.33*	−0.27*	−0.09
Time to reach turning point	Right hand	0.16	−0.42**	−0.11	0.01	−0.01	0.08
	Left hand	0.15	−0.27*	−03.2	−0.34*	−0.01	0.06
Strength at turning point	Right hand	0.41*	0.25*	0.26	0.07	0.26*	0.30**
	Left hand	0.35*	0.36**	0.31	0.11	0.22	0.35**
Inclination from start to turning point	Right hand	0.16	0.21	0.31	0.18	0.15	0.14
	Left hand	−0.16	0.28*	0.37*	0.22	0.07	0.18
Time to reach maximum strength	Right hand	0.08	0.06	0.07	−0.10	−0.15	−0.16
	Left hand	−0.23	0.04	−0.1	−0.48**	0.11	−0.02
Maximum strength	Right hand	0.24	0.35**	0.28	0.08	0.16	0.29**
	Left hand	0.09	0.43**	0.30	0.12	0.20	0.35**
Time from turning point to reach maximum strength	Right hand	0.03	0.36**	0.19	−0.11	−0.16	−0.25*
	Left hand	−0.32	0.22	0.16	−0.38*	0.13	−0.07
Ratio of strength (turning point / maximum)	Right hand	0.39*	−0.29*	0.17	0.02	0.23	0.21
	Left hand	0.52**	−0.20	0.22	−0.02	−0.02	0.18
Inclination from turning point to maximum strength	Right hand	−0.07	0.12	0.06	0.15	0.02	0.12
	Left hand	0.07	0.07	−0.03	0.25	0.02	0.17

$^{**}P < 0.01$, $^{*}P < 0.05$.

© 2014 Japan Geriatrics Society

involving time elements rather than strength were significant. These time-related items were influenced by sex or by side (right or left). This could be as a result of the changes of the quality of the muscle,[22] such as the rates of fast and slow twitch fiber, respectively, or the proportion of the fat infiltration.

As the participants of the present study were assumed to have cognitive problems, we adjusted for MMSE score in the analyses (Tables 3–5). Even after that, however, the results were almost the same in men, with a difference becoming apparent in only one item – inclination from start to turning point. In women, differences became apparent in five items (data not shown), suggesting that cognitive function might be influenced more in women. Further detailed analyses will have to be carried out to elucidate the associations between cognitive function, grip strength and the related new indices. With regard to the association between dementia and gripping performance in particular, further careful studies are required with separation of dementia into vascular, Alzheimer type, Lewy body disease or other types.

So far there have been several studies expressing the association between grip strength and ADL.[11–18] All but one related to ADL performance as a whole.[13] Although most of the studies compared the sex difference, none of them focused on the side difference nor differentiated the subjects by age groups. Thus, to our knowledge, the present study carried out the most detailed analyses to date, such as the subclass items of ADL or the influences of sex, side, or age. Furthermore, we investigated the detailed items during muscle contraction, which were shown for the first time while taking the time axis into consideration. Thus, it has become possible to analyze such detailed items by utilizing our elaborate new device equipped with a machine for quality control in the industrial product field. The detailed indices showed the difference, not only when comparing the difference between an independent group and those with clearly lower levels of ADL, but also with those who require only light assistance (group with total BI score of 95 or 90). This was suggested by the finding that right hand inclination from start to turning point was significantly lower in the 95 and 90 point group than in the 100 point group, although a significant difference was not seen in maximum strength (data not shown), which an ordinary device can measure as a solitary index.

Notwithstanding, the number of participants in the present study might not be large enough to confirm the significance of these indices, as the results on the significance of some of the indices changed when the participants were divided into three different age groups, particularly in women. This was seen in the ratio of strength (turning point/maximum).

There were some limitations to the present study. First, the analyses were carried out only in a Japanese population, and in participants with some cognition problems. Also, although we found some relationships between grip strength and BI scores, they remained rather weak. This might derive from the fact that the distribution of the BI was not even, shifting towards the full or nearly full score group. To more properly assess the influence of gripping performance and ADL, therefore, it might be necessary to use other indices, such as instrumental ADL, or gain a greater number of patients. These are issues to be investigated in future.

For hand side we used right versus left, but it would be more appropriate to consider this based on the hand dominance. However, it was not easy (or simple) to separate the participants by hand dominance, because when asked about their dominancy, 134 male patients replied right, three replied left, three replied both, two replied right but switched from left and eight did not answer. In women, 195 replied right, four replied left, six replied both, one replied right but switched from left and 20 did not answer. We therefore carried out the investigation with the classification of right and left. Nevertheless, for ratio of strength (turning point/maximum), significant correlations were seen with many subitems only in the right hand in both sexes, as was the case for time from turning point to reach maximum strength in men (Tables 3 and 4).

The device itself is still also limited to research purposes, and further improvements must be made to adapt it for more practical use, both in software so that the detailed indices are read automatically, and in hardware, including the handle section, for more comfortable gripping by older adults.

Despite those limitations, however, we will carry out further analyses on the various functions of older adults, by increasing the number of study population, and show the effectiveness of these indices, as the measuring method has advantages: it can be carried out safely and in a very short time with subjects in a sitting position, and can measure isometric contractions that are considered to be proper in measuring strength in elderly people. The device is accurate, of which measuring values (maximum strength) accorded quite well with those of Jamar Hydraulic Hand Dynamometer (data not shown).

In summary, we investigated the association of grip strength and the independence of ADL in older adults, using the data from a newly-developed grip strength measuring device. The maximum grip strength was shown to be associated with ADL in many items of the BI, but some of the newly defined indices, such as response time, strength at turning point, elements regarding before and after turning point until the strength reaches maximum, were shown to be associated with some ADL-related items. Some of the associations were different from those with the maximum grip strength, and they varied by sex, hand side or age groups. This new device, considering the time axis and

© 2014 Japan Geriatrics Society

novel items for measuring, could possibly be used effectively for applications in evaluating the functions of older adults, although further investigations will be required in order to determine the meaning or usefulness of the newly advocated indices.

Acknowledgments

This work was supported by The Research Funding for Longevity Sciences (23-24) from the National Center for Geriatrics and Gerontology (NCGG), Japan. We also thank the BioBank at the NCGG for quality control of clinical data.

Disclosure statement

The authors declare no conflict of interest.

References

1 Stuck AE, Iliffe S. Comprehensive geriatric assessment for older adults. *BMJ* 2011; **343**: d6799.
2 Arai H, Ouchi Y, Yokode M *et al.* Members of subcommittee for aging. *Geriatr Gerontol Int* 2012; **12**: 16–22.
3 Cruz-Jentoft AJ, Baeyens JP, Bauer JM *et al.* Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; **39**: 412–423.
4 Forrest KY, Bunker CH, Sheu Y, Wheeler VW, Patrick AL, Zmuda JM. Patterns and correlates of grip strength change with age in Afro-Caribbean men. *Age Ageing* 2012; **41**: 326–332.
5 Schlussel MM, dos Anjos LA, de Vasconcellos MT, Kac G. Reference values of handgrip dynamometry of healthy adults: a population-based study. *Clin Nutr* 2008; **27**: 601–607.
6 Lauretani F, Russo CR, Bandinelli S *et al.* Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol* 2003; **95**: 1851–1860.
7 Leal VO, Mafra D, Fouque D, Anjos LA. Use of handgrip strength in the assessment of the muscle function of chronic kidney disease patients on dialysis: a systematic review. *Nephrol Dial Transplant* 2011; **26**: 1354–1360.
8 Moriya S, Tei K, Murata A, Muramatsu M, Inoue N, Miura H. Relationships between Geriatric Oral Health Assessment Index scores and general physical status in community-dwelling older adults. *Gerodontology* 2012; **29**: e998–1004.
9 Patel HP, Syddall HE, Jameson K *et al.* Prevalence of sarcopenia in community-dwelling older people in the UK using the European Working Group on Sarcopenia in Older People (EWGSOP) definition: findings from the Hertfordshire Cohort Study (HCS). *Age Ageing* 2013; **42**: 378–384.
10 Laukkanen P, Era P, Heikkinen RL, Suutama T, Kauppinen M, Heikkinen E. Factors related to carrying out everyday activities among elderly people aged 80. *Aging (Milano)* 1994; **6**: 433–443.
11 Rantanen T, Era P, Heikkinen E. Maximal isometric strength and mobility among 75-year-old men and women. *Age Ageing* 1994; **23**: 132–137.
12 Rantanen T, Era P, Heikkinen E. Physical activity and the changes in maximal isometric strength in men and women from the age of 75 to 80 years. *J Am Geriatr Soc* 1997; **45**: 1439–1445.
13 Simard J, Chalifoux M, Fortin V, Archambault MJ, St-Cerny-Gosselin A, Desrosiers J. Could questions on activities of daily living estimate grip strength of older adults living independently in the community? *J Aging Res* 2012; **2012**: 427109. doi: 10.1155/2012/427109
14 Young DR, Masaki KH, Curb JD. Associations of physical activity with performance-based and self-reported physical functioning in older men: the Honolulu Heart Program. *J Am Geriatr Soc* 1995; **43**: 845–854.
15 Al Snih S, Markides KS, Ottenbacher KJ, Raji MA. Hand grip strength and incident ADL disability in elderly Mexican Americans over a seven-year period. *Aging Clin Exp Res* 2004; **16**: 481–486.
16 Nishiwaki T, Nakamura K, Ueno K, Fujino K, Yamamoto M. Health characteristics of elderly Japanese requiring care at home. *Tohoku J Exp Med* 2005; **205**: 231–239.
17 Rantanen T. Muscle strength, disability and mortality. *Scand J Med Sci Sports* 2003; **13**: 3–8.
18 Sarkisian CA, Liu H, Ensrud KE, Stone KL, Mangione CM. Correlates of attributing new disability to old age. Study of Osteoporotic Fractures Research Group. *J Am Geriatr Soc* 2001; **49**: 134–141.
19 Matsui Y, Fujita R, Harada A *et al.* A new grip-strength measuring device for detailed evaluation of muscle contraction among the elderly 2014 (in press).
20 Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? *Int Disabil Stud* 1988; **10**: 64–67.
21 Harada A, Mizuno M, Takemura M, Tokuda H, Okuizumi H, Niino N. Hip fracture prevention trial using hip protectors in Japanese nursing homes. *Osteoporos Int* 2001; **12**: 215–221.
22 Doherty TJ. The influence of aging and sex on skeletal muscle mass and strength. *Curr Opin Clin Nutr Metab Care* 2001; **4**: 503–508.

© 2014 Japan Geriatrics Society

Geriatrics Gerontology International — Medline Indexed

Geriatr Gerontol Int 2014; **14 (Suppl. 2):** *62–70*

Differential subtypes of diabetic older adults diagnosed with Alzheimer's disease

Takashi Sakurai,[1] Shuji Kawashima,[1] Shosuke Satake,[1] Hisayuki Miura,[1] Haruhiko Tokuda[2] and Kenji Toba[1]

[1]Center for Comprehensive Care and Research on Memory Disorders, and [2]Department of Diabetes and Endocrinology, National Center for Geriatrics and Gerontology, Obu, Japan

Aim: The clinical management of diabetic elderly patients with Alzheimer's disease (AD) is hindered by several difficulties. The present study aimed to clarify the clinical characteristics and pathophysiological properties of AD in diabetic older adults.

Methods: A total of 91 patients with type 2 diabetes mellitus and 161 non-diabetic individuals who were diagnosed with AD were recruited. Diabetic patients were classified into two groups with glycated hemoglobin (HbA1c) <7.0% or ≥7.0%. The demographics, cognition, daily-life function, metabolic changes, treatment, and behavioral and psychological symptoms of dementia (BPSD), as well as brain pathophysiology, were compared among the three groups.

Results: Patients with higher HbA1c had increased diabetic vascular complications and impaired activities of daily living with decreased levels of serum high-molecular-weight adiponectin and 25-hydroxyvitamin D. Although cognitive status was similar among the three groups, BPSD, including apathy, overeating and excessive daytime sleeping appeared to be increased in the patients with HbA1c ≥7.0%. The frequency of apolipoprotein E4 carriers and of posterior cerebral hypoperfusion (AD-pattern) on single-photon emission computed tomography in poorly controlled diabetic subjects was similar to that in non-diabetic AD patients, whereas diabetic patients with HbA1c <7.0% included fewer apolipoprotein E4 carriers and fewer patients with an AD pattern on single-photon emission computed tomography.

Conclusion: Subtypes of older diabetic patients with AD were identified based on clinical features and brain pathophysiology. Physical and psychological complications of dementia are prevalent in patients with higher HbA1c. It seems likely that difficulties in the management of diabetes with AD are due not only to non-adherence to diabetes treatment, but also several symptoms and pathophysiological characteristics of dementia. **Geriatr Gerontol Int 2014; 14 (Suppl. 2): 62–70.**

Keywords: Alzheimer's disease, behavioral and psychological symptoms of dementia, diabetes, glycemic control, pathophysiology.

Introduction

Diabetes increases the risk of dementia, including Alzheimer's disease (AD) and vascular dementia.[1] Once an older diabetic patient begins to experience cognitive decline, treatment of diabetes becomes difficult despite intensive care and education. Physical exercise and dietary changes are feasible treatment options, but adherence to diabetic medicine is usually impaired, even in the early course of AD. When serious hyperglycemia continues, the more powerful antidiabetic medicines are prescribed, which in turn increases the risk of hypoglycemia. Hyperglycemia and hypoglycemia, as well as acute fluctuation of glucose, further worsen cognitive impairment.[2–4] Behavioral and psychological symptoms of dementia (BPSD) also cause difficulties in the management of diabetes. To overcome these problems, a coordinated treatment plan that addresses both the AD and diabetes is required.

There is currently no consensus as to the pathophysiology of AD in diabetes; studies have alternatively reported that AD-associated pathology is increased,

Accepted for publication 26 December 2013.

Correspondence: Dr Takashi Sakurai MD PhD, 35 Gengo, Morioka-cho, Obu, Aichi 474-8511, Japan. Email: tsakurai@ncgg.go.jp

© 2014 Japan Geriatrics Society

unchanged or even decreased in diabetic older adults.[5–8] Other studies have found that cerebral vascular disease (CVD) is more likely to be involved in diabetes.[9,10] Metabolic factors of diabetes might have a profound impact on the clinical course of AD, resulting in a variety of clinical pictures.[11–14] Because of the complex nature of AD, the true reasons for the difficulties in managing diabetic elderly patients with AD have remained unclear.

The purpose of the present study was to clarify the clinical characteristics of diabetic older adults with AD from the standpoint of demographics, cognition, activities of daily living (ADL), complications of dementia, metabolic changes, treatment and pathophysiology of the brain. We hypothesized that clinical symptoms related to AD would depend largely on glycemic control and brain pathophysiology. We therefore compared these variables among three patient groups: diabetic patients with AD and good glucose control, diabetic patients with AD and poor glucose control, and non-diabetic patients with AD. The present study was designed to identify subtypes of dementia with differential clinical properties and pathophysiology in diabetic patients with AD.

Methods

Participants

The study protocol was approved by the institutional review board of the National Center for Geriatrics and Gerontology (NCGG), Japan. Candidate patients and their caregivers submitted informed consent before participation in the study.

A total of 252 elderly patients (age 65–85 years) who had been diagnosed with AD and treated in the NCGG were enrolled consecutively. The total Barthel Index score for each of the 252 patients was 80 or over.[15] Patients with severe cardiac failure, renal disorder, liver dysfunction or other neurological and psychiatric disorders, such as depression or alcohol abuse, and patients with symptomatic cerebral infarction or cortical lesions on brain magnetic resonance imaging (MRI) were excluded from the present study.

The final participant groups thus consisted of 91 patients with type 2 diabetes and 161 non-diabetic individuals. Diabetic patients were classified into two groups based on whether their glycated hemoglobin (HbA1c) was <7.0% or ≥7.0%. All diabetic participants had a history of diabetes, and were receiving pharmacological treatment for diabetes that included oral antihyperglycemic agents and/or insulin.

All participants underwent the standardized and reliable diagnostic procedures for dementia disorders.[16] AD was diagnosed as probable AD or possible AD according to the criteria from the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association.[17]

Comprehensive assessment

Information about previous diseases and medication was obtained from the clinical charts. Polypharmacy was defined as taking five or more types of oral medicine.[18] The Barthel Index and the Lawton Index were used to evaluate basic and instrumental ADL, respectively.[15,19] Cognitive status was measured by using a psychiatric assessment battery that included the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (ADAS), Digit Span Forward and Backward trials, Frontal Assessment of the Brain (FAB), Raven's Colored Progressive Matrices (RCPM), and Logical Memory I and II subtests from the Wachster Memory Scale-Revised.[20–24] Depressive mood and BPSD were estimated by the Geriatric Depression Scale-15 (GDS) and Dementia Behavior Disturbance Scale (DBD), respectively.[25,26] The Zarit burden interview (ZBI) was used for measurement of the caregivers' burden.[27] Risks for falls were evaluated by the Fall Risk Index (FRI).[28] Geriatric syndrome was assessed by administering a questionnaire to patients and their caregivers; the questionnaire included questions on dyspnea, cough, chest oppression, edema, fatigue, nausea, abdominal pain, diarrhea, constipation, dysphasia, numbness, tremor, syncope, dizzying, chewing troubles, polyuria, incontinence of urine, decubitus ulcer, itching, lumbago, back pain, lower limb pain, upper limb pain and sleeping problems.

Laboratory measurements

Apolipoprotein (Apo) E phenotypes were determined in plasma specimens by using isoelectric electrophoresis and immunoblotting methods.[29] Vitamin D insufficiency was assessed by the serum concentration of 25-hydroxyvitamin D, as currently recommended.[30] Levels of high-molecular-weight adiponectin were analyzed by enzyme immunoassay as described elsewhere.[31]

Neuroimaging studies

Brain MRI and single-photon emission computed tomography (SPECT) were used to elucidate the pathophysiology of dementia. A standard series of axial T1-weighted (repetition time [TR], 485 ms; echo time [TE], 11 ms), T2-weighted (TR, 3800 ms; TE, 93 ms) and fluid-attenuated inversion recovery (TR, 8000 ms; TE 101 ms; inversion time, 2500 ms; a 256 × 256 matrix). MR sequences were carried out in a 1.5T MR system (Siemens Avanto, Munich, Germany). Scans were in parallel with the anterior commissura–posterior commissura line, with 6-mm thick slices and an interslice gap of 1.2 mm.

© 2014 Japan Geriatrics Society

MRI data were processed to measure the total volumes of the intracranial space (IC), parenchyma, ventricles and white matter regions (WML) by a fully automatic segmentation program (Software for Neuro-Image Processing in Experimental Research: SNIPER), which was developed at the Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands. Detailed procedures of the MRI post-processing by SNIPER have been described elsewhere.[32]

SPECT scanning was carried out by using a two-head rotating GCA 7200DI gamma-camera (Toshiba, Otabara, Japan). Imaging was started 15~45 min after injection of 222 MBq (6 mCi) of N-isopropyl-p-[^{123}I] iodoamphetamine (Nihon Mediphysics, Tokyo, Japan), while the participants rested in a supine position with their eyes closed. The data were acquired in 128 × 128 matrices through an 18° rotation at an angle interval of 4°. The projection data were prefiltered and reconstructed, and Chang's attenuation and scattering corrections were applied.[33]

SPECT data were processed using the three-dimensional stereotactic surface projection (3D-SSP) method (Neurostat Software Library; Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA).[34] To assess perfusion deficits, the normalized brain activity of each patient was compared with that of 18 normal participants by using a pixel-by-pixel z-score analysis.[33] Qualitative z-score image analysis was carried out by two specialists without any knowledge of the clinical data. An image was defined as showing an AD pattern if the perfusion was decreased in the bilateral parietal association areas and posterior cingulate cortices, with relative sparing of the sensorimotor cortex, occipital cortex and cerebellum. The 3D-SSP technique, together with SPECT and positron emission tomography, provide a high diagnostic accuracy for AD.[34]

Statistical analysis

Statistical analysis was carried out using SPSS 19.0 for Windows (SPSS, Chicago, IL, USA). Comparisons of variables among the three patients groups were carried out by χ^2-test and analysis of covariance (ANCOVA), followed by post-hoc analysis (Bonferroni) to detect statistically significant differences. The association between BPSD and HbA1c was analyzed by Spearman's correlation analysis. Independent risks for BPSD were analyzed by multivariate logistic regression. Differences were considered significant at $P < 0.05$.

Results

Clinical profiles of the study participants

Age and education level were similar among the three groups of patients, whereas male sex was more prevalent in diabetic patients with HbA1c <7% (Table 1). The Barthel Index was lower in diabetic patients with HbA1c ≥7.0% than those with HbA1c <7.0%. Impaired dressing ability and urinary incontinence were apparent in diabetic patients with higher HbA1c (data not shown). Depressive mood and vitality, as well as caregivers' burden were not different among the three patient subgroups. The FRI was significantly increased in diabetic individuals with HbA1c ≥7.0%, although the incidence of falls in the previous year was unchanged. Polypharmacy was prevalent in diabetic participants. Use of sulfonylurea and insulin was increased in patients with HbA1c ≥7.0%, whereas biguanide was used more frequently in patients with HbA1c <7.0% (Table 1).

Apo E4 carriage, a genetic risk for AD, was seen in 52.5% (n = 122) of non-diabetic AD patients, which was compatible with the previous reports. However, among diabetic patients, the frequency of Apo E4 carriage was 39.4% and 47.7% in those with HbA1c <7% (n = 33) and ≥7.0% (n = 44).

As for physical complications, numbness was significantly increased in patients with HbA1c ≥7.0%, compared with non-diabetic individuals (25.0% and 11.8%, respectively). Dysphagia and diarrhea/constipation were also increased in poorly controlled diabetic participants (data not shown).

Biochemical properties

Blood glucose and HbA1c were significantly elevated in diabetic individuals (Table 2). Serum alkaliphosphatase tended to be increased in diabetic patients, and a significant increase was seen in diabetic patients with HbA1c ≥7.0%. Serum creatinine and estimated glomerular filtration rate were not changed among the three subgroups, whereas persistent proteinuria (>1 g protein/gCr) tended to be prevalent in patients with higher HbA1c (P = 0.056). The serum level of adiponectin was significantly reduced in patients with HbA1c ≥7.0%. 25-Hydroxyvitamin D, which reflects the activity of vitamin D, was significantly decreased in poorly controlled diabetic participants.

Cognitive impairment

Global brain function as measured by MMSE, ADAS and RCPM was substantially impaired in all three groups, but the degree of impairment was not significantly different among them (Table 3). Verbal fluency was significantly impaired in diabetic patients with HbA1c ≥7.0%. Performance on the recent memory and digit span tests, the latter of which is used as a measure of attention, was not different among the groups.

BPSD

The total score of DBD was significantly elevated in patients with HbA1c ≥7.0% (Table 4). DBD is a

© 2014 Japan Geriatrics Society

Table 1 Clinical profiles of study participants

	Diabetes HbA1c <7.0% (n = 39)		Diabetes HbA1c ≥7.0% (n = 52)		Diabetes total (n = 91)		Non-diabetes (n = 161)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	76.9	4.7	76.7	5.3	76.8	5.0	77.1	5.3
Male (%)	53.8*		40.4		46.2*		24.8	
Education (years)	10.5	2.6	10.4	2.7	10.5	2.7	10.2	2.7
BMI (kg/m^2)	23.4*	3.4	22.7	3.4	23.0*	3.4	21.8	3.1
Heart rate (b.p.m.)	80.0*	13.0	80.2*	15.4	80.1*	14.3	75.4	14.1
Systolic blood pressure (mmHg)	158.9	24.3	158.0	24.9	158.4	24.5	158.2	25.0
Diastolic blood pressure (mmHg)	80.5	10.7	81.8	13.5	81.3	12.3	85.2	13.7
Barthel Index	98.8	3.1	95.7**	7.9	97.0	6.5	97.3	6.1
Lawton Index								
Male	3.2	1.3	3.2	1.4	3.2	1.3	3.3	1.4
Female	5.7	1.9	5.3	2.0	5.4	1.9	5.8	1.8
Geriatric depression scale	3.9	2.2	3.9	2.7	3.9	2.5	4.6	2.7
Zarit burden interview	17.8	13.1	21.2	14.8	19.8	14.1	19.6	14.6
Fall risk index	5.3	3.4	5.5*	3.6	5.4	3.5	4.9	3.6
Polypharmacy (%)	63.2*		54.9*		58.4*		32.5	
Insulin user (%)	0.0		21.2**		12.1		–	
Use of sulfonylurea (%)	25.6		51.9**		40.7		–	
Use of biguanide (%)	33.3		13.5**		22.0		–	
Use of thiazolidines (%)	25.6		23.1		24.2		–	
Apoprotein E4 carrier (%)	39.4		47.7		44.2		52.5	

*P < 0.05 versus non-diabetes, **P < 0.05 versus glycated hemoglobin (HbA1c) <7.0%, ANCOVA adjusted for age and sex.

Table 2 Biochemical and metabolic analysis

	Diabetes HbA1c <7.0%		Diabetes HbA1c ≥7.0%		Diabetes total		Non-diabetes	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Blood glucose (mg/dL)	141.4*	38.6	197.7*,**	102.0	174.4*	86.2	105.9	15.4
HbA1c (%)	6.5*	0.4	8.7*,**	1.5	7.7*	1.5	5.5	1.2
Serum albumin (g/dL)	4.3	0.3	4.4	0.3	4.4	0.3	4.4	0.3
ALP	274.3	59.4	332.5*,**	136.6	307.7*	113.7	244.4	69.3
AST (IU/L)	25.5	7.5	26.2	14.4	25.9	11.9	24.9	8.6
ALT (IU/L)	21.6	9.6	27.0*	22.5	24.7*	18.3	19.4	11.2
γ-GT (IU/L)	31.7	30.4	42.2*	61.2	37.8*	50.5	26.0	22.0
Creatinine (mg/dL)	0.9	0.3	0.8	0.3	0.8	0.3	0.7	0.2
eGFR (mL/min/1.73m^2)	59.6	17.5	67.0	19.7	63.8	19.1	67.3	17.8
Total cholesterol (mg/dL)	194.6*	40.7	211.2	46.0	204.2*	44.4	221.7	37.2
HDL cholesterol (mg/dL)	51.4*	13.4	54.1*	14.4	52.9*	14.0	66.7	16.7
Non-HDL cholesterol (mg/dL)	140.3*	35.0	158.2	44.8	150.7	41.7	158.2	32.8
LDL cholesterol (mg/dL)	109.6	31.2	125.4	37.6	118.7	35.7	127.7	31.1
Triglyceride (mg/dL)	138.9	70.5	164.7*	120.2	153.8*	102.5	117.4	64.8
Adiponectin (mg/mL)	8.2	8.5	6.0*	3.8	7.0	6.5	9.0	5.4
25-Hydroxyvitamin D (ng/mL)	27.1	8.8	21.0*,**	6.9	23.9	8.4	23.9	6.7
Persistent proteinuria (%)	16.7		18.4		17.6*		7.6	

*P < 0.05 versus non-diabetes, **P < 0.05 versus glycated hemoglobin (HbA1c) <7.0%, ANCOVA adjusted for age and sex. γ-GT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

© 2014 Japan Geriatrics Society

Table 3 Neuropsychiatric assessment

	Diabetes HbA1c <7.0%		Diabetes HbA1c ≥7.0%		Diabetes total		Non-diabetes	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MMSE	18.7	3.8	19.6	4.1	19.2	4.0	19.3	5.1
ADAS	19.0	5.6	17.8	7.1	18.4	6.4	16.8	6.1
RCPM	21.2	5.3	23.5	4.8	22.3	5.1	22.4	6.3
FAB	8.8	2.3	9.2	2.6	9.0	2.5	9.6	2.5
Verbal fluency	2.6	2.1	2.3*	2.1	2.4*	2.1	3.2	2.0
Digit span: Forward	4.9	1.0	5.1	1.0	5.0	1.0	5.1	1.0
Backward	3.1	1.0	3.1	1.0	3.1	1.0	3.2	1.1
Logical memory 1	2.8	2.8	3.0	2.8	2.9	2.8	3.5	3.6
Logical memory 2	0.3	0.7	0.5	1.4	0.4	1.1	.4	1.1

*$P < 0.05$ versus non-diabetes, ANCOVA adjusted for age, sex and education. ADAS, Alzheimer's Disease Assessment Scale; FAB, Frontal Assessment of the Brain; HbA1c, glycated hemoglobin; MMSE, Mini-Mental State Examination; RCPM, Raven's Colored Progressive Matrices.

Table 4 Dementia Behavior Disturbance scale

	Diabetes HbA1c <7.0%		Diabetes HbA1c ≥7.0%		Diabetes total		Non-diabetes	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total score of DBD	12.8	8.3	20.1*,**	11.1	17.0	10.6	15.9	10.6
Exhibits lack of interest in daily activities	1.5*	1.4	2.1*	1.2	1.9	1.3	1.8	1.3
Sleeps excessively during the day	1.5	1.5	1.8*	1.3	1.7*	1.4	1.1	1.2
Is verbally abusive, curses	0.4	0.8	0.8*	1.2	0.6	1.1	0.4	0.9
Dresses inappropriately	0.3	0.6	0.9**	1.0	0.6	0.9	0.6	0.9
Hoards things for no obvious reason	0.5	1.1	1.2**	1.4	0.9	1.3	0.8	1.2
Overeats	0.7	0.9	1.3*,**	1.4	1.0*	1.3	0.5	0.9
Is incontinent of urine	0.2	0.6	0.7**	1.1	0.5	0.9	0.5	0.9

*$P < 0.05$ versus non-diabetes, **$P < 0.05$ versus glycated hemoglobin (HbA1c) <7.0%, ANCOVA adjusted for age and sex. DBD, Dementia Behavior Disturbance scale.

questionnaire composed of 28 items and similar comparisons were carried out for each subitem. Lack of interest, excessive daytime sleeping, verbal abuse, inappropriate dress, hoarding, overeating and urinary incontinence were significantly elevated in diabetic individuals with higher HbA1c. Significant correlations were observed between HbA1c and each of inappropriate dress, hoarding and urinary incontinence ($P = 0.023$, $P = 0.031$, $P = 0.014$, respectively). Because overeating is a crucial problem that can induce hyperglycemia in diabetes, we attempted to identify factors that might have been independently associated with hyperphagia by multivariate logistic regression. The results showed that male sex, excessive daytime sleeping, elevated levels of HbA1c and elevated triglyceride were independently associated with overeating ($P = 0.013$, $P = 0.005$, $P = 0.007$ and $P = 0.005$, respectively). Interestingly, overeating was significantly increased in patients with daytime sleep >3 h (38.5%), and also in those with daytime sleep of 0–3 h (16.0%), compared with those without daytime sleep (7.2%) (ANOVA).

Brain MRI and SPECT

Finally, we evaluated the morphological and functional changes of the brain (Table 5). The total volumes of the IC, parenchyma, ventricles and WML were determined by automatic segmentation on brain MRI. We found that the parenchyma/IC ratio, as an index for brain atrophy, was significantly decreased in patients with HbA1c ≥7.0%, whereas the WML/IC ratio was unchanged.

The 3D-SSP technique with SPECT provides a high diagnostic accuracy for AD.[34] Posterior cerebral hypoperfusion on SPECT (AD pattern) was observed in 60.6% of diabetic patients with HbA1c <7.0% ($n = 36$), which was significantly smaller than the percentage of

© 2014 Japan Geriatrics Society

Table 5 Magnetic resonance imaging and single-photon emission computed tomography analysis

	Diabetes HbA1c <7.0%		Diabetes HbA1c ≥7.0%		Diabetes total		Non-diabetes	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MRI								
Parenchyma (mL)	1040.1	105.4	1028.0	112.0	1032.7	108.9	1024.8	101.0
WML (mL)	21.5	24.6	14.7	13.8	17.4	18.9	19.7	20.7
IC (mL)	1418.4	133.5	1400.4	140.3	1407.4	137.0	1377.9	125.6
Parenchyma/IC	73.3	3.3	73.4*	3.0	73.4	3.1	74.4	3.2
WML/IC	1.5	1.8	1.1	1.0	1.2	1.3	1.4	1.4
SPECT								
AD pattern (%)	60.6**		81.3		67.0*		81.3	

*$P < 0.05$ versus non-diabetes, ANCOVA adjusted for age and sex. **$P < 0.03$ versus diabetes glycated hemoglobin (HbA1c) >7.0% and non-diabetes, χ^2-test. AD, Alzheimer's disease; IC, intracranial space; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; WML, white matter regions.

diabetic patients with HbA1c ≥7.0% ($n = 46$) and non-diabetic patients with AD ($n = 144$) who showed an AD pattern.

Discussion

The present study clearly identified that diabetic older adults diagnosed as having AD with HbA1c <7% have differential clinical features and pathophysiology from those with HbA1c ≥7.0%. Patients with higher HbA1c have increased vascular complications of diabetes, insulin resistance, impaired ADL, and altered bone and muscle metabolism. Although cognitive function was similar between the two groups, BPSD such as lack of interest, overeating and excessive daytime sleeping apparently increased in patients with higher HbA1c, which might have contributed to difficulties in the management of diabetes with dementia. Although the frequencies of Apo E4 carriage and of posterior cerebral hypoperfusion on SPECT in poorly controlled diabetic subjects were similar to those in non-diabetic AD patients, the group of diabetic patients with lower HbA1c had a lower incidence of Apo E4 carriage and an AD pattern on SPECT, suggesting the involvement of non-AD pathophysiology in this group. It seems plausible that difficulties in the management of diabetes with AD are due not only to non-adherence to diabetes treatment, but also several symptoms and pathophysiological characteristics of dementia.

Patients with AD show a variety of problematic behaviors during the course of the disease. One of these behaviors, increased food intake has been described in 9–26% of AD cases.[35] The neuroanatomical basis for overeating in AD remains unclear, but hyperphagia is often accompanied by forgetfulness and hyperorality.[36] Overeating has been of less concern in non-diabetic AD, because weight loss and malnutrition are more important in the late stages of dementia. However, in the case of diabetic elderly patients, overeating can lead directly to hyperglycemia. Food intake is controlled by a complex regulatory network in the brain. The hypothalamus plays a particularly important role in regulating appetite and energy expenditure. It has been postulated that interactions between adiposity and the central neuropeptidergic cascade are impaired in obesity.[37] Poor glycemic control is associated with overeating, even in adolescents with type 2 diabetes,[38] suggesting that eating disorders in our diabetic participants could be related to not only dementia disease, but also diabetes. In addition, we found a correlation between HbA1c and urinary incontinence. Thus, an interactive relationship should be considered between hyperglycemia and some problematic symptoms of dementia.

In this connection, the present study showed a link between daytime sleep and overeating. Recent studies suggest that insufficient sleep can facilitate feeding behavior by changing circulating hormones involved in feeding, glucose metabolism and appetite.[39] Thus, whether a lifestyle intervention to reduce excessive daytime sleep could prevent overeating should be tested in diabetic patients with AD in the future.

In patients with HbA1c ≥7.0%, FRI increased and basic ADL decreased. FRI is a surrogate marker for falls, but also for frailty in older adults.[28] Interestingly, the serum level of 25-hydroxyvitamin D was significantly reduced in patients with higher HbA1c. A recent meta-analysis showed that the serum concentration of 25-hydroxyvitamin D is decreased in AD.[40] Hypovitaminosis D is also associated with insulin resistance, and 25-hydroxyvitamin D levels are inversely related to HbA1c in type 2 diabetic patients.[41,42] The present study found low concentrations of serum high-molecular-weight adiponectin in patients with HbA1c ≥7.0%, which strongly suggested elevated insulin resistance.[43] Insulin resistance and hypovitaminosis D play a major

© 2014 Japan Geriatrics Society