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Original article

Psychosocial quality of life of elderly hemodialysis patients using visual analog scale: Comparison with healthy elderly in Japan

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A B S T R A C T

Background: The number of elderly hemodialysis (HD) patients is increasing in Japan, and the psychosocial impact of HD to the elderly remains unclear. The main purpose of this study was to evaluate quality of life (QOL) of elderly patients undergoing regular HD.
Methods: We examined the psychosocial status in elderly HD patients and compared it with that in healthy elderly individuals. The correlations between each item of QOL, laboratory data and comorbidities were explored. This study cohort consisted of 142 people (70 healthy elderly participants and 72 elderly HD patients). We assessed 10 items of QOL, i.e., health condition, appetite, sleep, mood, memory, family relationship, friendship, economical status, satisfaction in daily life, and happiness by visual analog scale (VAS).
Results: Overall, elderly HD patients had lower scores of VAS than healthy elderly participants, especially in sleep, mood, and happiness, but not in family relationship and friendship. Lower VAS scores for sleep were significantly correlated with the duration of HD therapy and the troubles in vascular access for HD. VAS scores for family relationship were also correlated with the duration of HD therapy.
Conclusion: The QOL of elderly HD patients was poorer than that in healthy elderly individuals, particularly in sleep, mood and happiness. Further study is needed to improve the QOL of elderly HD patients. This is of great importance, since the number of elderly HD patients is estimated to escalate in the future.

1. Introduction

With the advance of dialysis technology, the number of elderly dialysis patients is increasing in Japan. According to the statistical survey by the Japanese Society for Dialysis Therapy, the mean age of the whole dialysis population was increased from 61.2 years at the end of 2000 to 65.8 years in 2009. The mean age of patients who started dialysis was also increased from 63.8 years in 2000 to 67.3 years in 2009.[1]

At the end of 2000 and 2009, there were about 200,000 and 290,000 dialysis patients in Japan, respectively. It is considered that these dialysis patients might live with more mental stress, including anxiety for comorbidities, conflicts with their family and social restrictions, than healthy individuals. It has been reported that quality of life (QOL), mental health and physical health in hemodialysis (HD) patients were poorer than those in the general population.[2] Depression, a key factor of QOL items to evaluate patients with end-stage renal disease,[3] was an important predictor of patients' prognosis.[4] Therefore, more attention should be paid to QOL, psychological problems and medical conditions of dialysis

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patients. With regards to QOL, assessment of HD patients' self-evaluation for psychosocial status (subjective QOL) was of great importance. Although some reports studying psychosocial QOL of HD patients have been done, little was known regarding the QOL of elderly HD patients.

Many studies examining the QOL of HD patients were performed using Kidney Disease Quality of Life (KDQOL) or Short Form 36 (SF-36) for questionnaires; however, these questionnaires are time-consuming for the elderly. Generally speaking, Japanese people, especially the elderly, are not used to selecting a single answer and have some difficulties responding to such questions. Accordingly, a visual analog scale (VAS) was a better instrument to complete questionnaires in a short period of time, and a few studies examined QOL by VAS. The main aim of this study was to evaluate the psychosocial QOL of elderly HD patients and to compare it with that of healthy elderly participants using a VAS.

2. Methods

The study was performed in 2000 at Taigenkai Hospital and Kita-Eijinkai Hospital, located in Bisai and Amagasaki cities of Japan, respectively. Among HD patients followed in the dialysis unit at these two hospitals as outpatients, 231 were given questionnaires. Patients aged $\geq$ 65 years old were defined as "elderly", and those aged $<$ 65 years old were defined as "non-elderly". Based on this definition, our HD patients consisted of 83 elderly and 148 non-elderly patients. The control group was composed of 70 healthy elderly people in nearby welfare facilities (places where people spend their time for their health promotion and leisure). These healthy controls were defined as community-dwelling elderly. The study was approved by each constituted Ethics Committee of the institutions where the work was undertaken and conforms to the provisions of the Declaration of Helsinki. We obtained each participant's informed consent for the study. Participants were given a brief explanation of the questionnaire by the medical technician or by the attending physician and were asked to complete the questionnaire. Assistance was given for participants who were illiterate or had poor eyesight.

QOL assessment was performed by VAS. VAS is frequently used as a subjective scale of pain in the field of anesthesiology. The VAS questionnaire ended with a summing-up graph in the form of a 100 mm bar, graded with the subjectively worst condition on the left and the best on the right (Fig. 1). Patients were examined at the beginning of their first HD session of the week. Healthy elderly participants were examined during their regular meeting in the welfare facilities. Each participant was asked to mark, on the 100 mm bar, how his condition was. We defined the distance (mm) from the left to the marked position as the score of VAS (0–100), with high scores indicating a high QOL.[5] We assessed 10 items of QOL: (1) health condition; (2) appetite; (3) sleep; (4) mood; (5) memory; (6) family relationship; (7) friendship; (8) economical status; (9) satisfaction in daily life; and (10) happiness, as described by Matsubayashi et al[5] (Fig. 1). The VAS (10 items of QOL) has been validated for use in the Japanese population.[6] In elderly HD patients, demographic data including age, sex, and duration of HD therapy, laboratory data [which includes cardio-thoracic ratio (CTR), plasma level of blood urea nitrogen (BUN), hemoglobin (Hb) and albumin (Alb)], and comorbidities [which includes blood access trouble, ischemic heart disease (IHD), diabetes mellitus (DM), infectious diseases, bone fracture and cerebrovascular disease (CVD)] were simultaneously collected.

Data were analyzed using JMP v. 6.0.0 (SAS Institute Inc., Cary, NC, USA). With regards to characteristics, the means were analyzed using the t-test (age) and frequencies were analyzed using the Chi-square for independence test (sex). Medians of QOL scores were calculated and analyzed using the Mann-Whitney U test. In elderly HD patients, the correlation between scores of QOL and laboratory data/personal histories was analyzed using multivariate regression analysis. Statistical significance was considered to be $p < 0.05$.

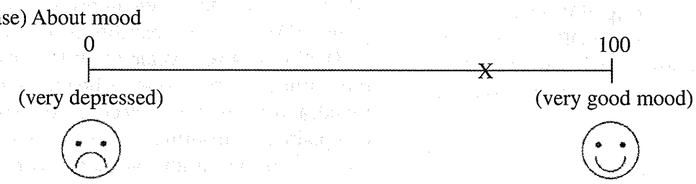
3. Results

Demographic characteristics are shown in Table 1. All of the 83 elderly patients were given questionnaires, and answers from 72 elderly patients (86.7%) were used for the analysis for completeness of questionnaire. By contrast, all the answers obtained from 70 healthy elderly participants (100%) were used for comparison.

The mean age of the elderly HD patients (71.8 years $\pm$ 5.6 years) was approximately 2 years less than that of the healthy elderly participants (74.0 years $\pm$ 6.7 years) ($p = 0.0317$); however, there

We would like to ask you some questions about your general daily life. On your present situation, mark a line segment with a cross " X " as showed below.

(case) About mood



(1) On which point is your health condition?
(2) How about your appetite?
(3) How is your sleep in the night?
(4) How is your daily mood?
(5) To what extent can you memorize something at present?
(6) Do you get along well with your mete, your family members, your sons or daughters, and your grandchildren?
(7) Are you satisfied with the relationships with your friends and relatives?
(8) Is your income enough now?
(9) Are you satisfied with your existing daily life?
(10) Taking every factor into consideration, what extent of happiness do you have?

Fig. 1. Questionnaire form for the study. We used this form translated into Japanese.

Table 1
Characteristics, laboratory data and comorbidities in HD patients

	Elderly patients ($n = 72$)
Age (y), mean ± SD	71.8 ± 5.6
Sex (M/F) (% male)	42/30 (58.3%)
Duration of hemodialysis (y), mean ±SD	6.9 ± 5.0
Chronic glomerulonephritis, n (%)	38 (24.5%)
Cardio-thoracic ratio (mmHg), mean ± SD	50.2 ± 4.9
Blood urea nitrogen (mmol/L), mean ± SD	26.0 ± 6.5
Hemoglobin (g/L), mean ± SD	87.8 ± 14.4
Albumin (g/dL), mean ± SD	38.5 ± 5.66
Blood access trouble	58.5%
Ischemic heart disease	28.6%
Diabetes mellitus	53.1%
Infectious diseases	18.4%
Bone fracture	17.1%
Cerebrovascular disease	13.3%

Data are expressed as means ± SD or incidence of each disease (%).

was no difference in gender between the groups (58.3% males in the elderly HD patients vs. 55.7% males in the healthy elderly participants, $p = 0.753$). VAS scores were significantly lower in the elderly HD patients than those in the healthy elderly participants in sleep (53.0 vs. 80.5, $p < 0.0001$), mood (62.0 vs. 82.0, $p < 0.0001$), and happiness (71.0 vs. 85.5, $p < 0.0001$), indicating impaired general QOL in the elderly HD patients, but not family relationships and friendship (Table 2).

In the elderly HD patients, there was a significant correlation between family relationships and gender (standard $\beta = 0.583$, $p = 0.0161$), duration of HD (standard $\beta = -0.528$, $p = 0.0237$) or CTR (standard $\beta = -0.471$, $p = 0.0364$), between friendship and gender (standard $\beta = 0.598$, $p = 0.0150$) or CTR (standard $\beta = -0.631$, $p = 0.0089$), between sleep and duration of HD (standard $\beta = -0.450$, $p = 0.0445$) or blood access trouble (standard $\beta = -0.856$, $p = 0.0018$), between memory and duration of HD (standard $\beta = -0.626$, $p = 0.0308$), and between economical status and gender (standard $\beta = 0.629$, $p = 0.0063$) or CTR (standard $\beta = -0.701$, $p = 0.0024$) (Table 3).

4. Discussion

In this study, we showed that elderly HD patients had lower psychosocial QOL than healthy elderly participants. We think that the response rate was high enough by using VAS in this study, despite the high age in our cohort. To compare QOL between the two groups, we analyzed the median of VAS scores using the Mann-Whitney U test, because VAS scores of some items were not normally distributed. QOL scores were significantly lower in the elderly HD patients than those in the healthy elderly participants, except in relation to family relationships and friendship. These data indicated impaired general QOL in elderly HD patients.

By contrast, we showed that there was no difference in psychosocial QOL in these 10 items between elderly and non-elderly HD patients.[7] Taking these results into account, our results indicate that older age by itself does not always impair QOL in HD patients. Age has been considered to be an important factor when dialysis therapy is indicated, which was not shown in this study. Therefore, as a recent report suggested,[8] age alone should not be a barrier to initiate the dialysis therapy.

A number of studies have been reported in terms of QOL in HD patients. Most of these studies were examined using KDQOL or SF-36 for questionnaires, and have reported that the QOL of HD patients was markedly impaired in comparison to that of the general population in both physical and mental components.[1] In Japan, a study using SF-36 reported that QOL sores of HD patients are lower than national standards in all eight dimensions, indicating impaired QOL in physical and psychosocial status.[9] However, it has been reported that QOL in both physical and mental components of older old HD patients (≥75 years old) was similar to that in the general population.[10] In our study, eight out of ten QOL items were significantly lower in the elderly HD patients than those in the healthy elderly participants, which was different from the study mentioned above. This could be related to the differences in the demographic characteristics, the age composition of HD patients, or the age with which the HD patients were classified.

Many studies concerning the QOL of HD or end stage renal disease (ESRD) patients have used KDQOL or SF-36, because these methods have high reliability and validity, and have been used internationally. With these methods, the participants need to answer no less than 36 questions, which is time-consuming and requires patience. Japanese people, especially the elderly, are not used to selecting a single answer and have some difficulties in responding to 36 questions. Therefore, we used VAS which could be completed in a short period of time, as the only requirement is to place a mark on the 100 mm bar.[11] Inter-rater reliability ($r = 0.74$, $p < 0.05$) and test-retest reliability ($r = 0.82$, $p < 0.05$) of VAS had been already confirmed.[5] For VAS, we assessed ten items of QOL, and the rate of available answers was as much as 92.8% (= 72+70/83+70) in the elderly, including HD patients and healthy participants. A previous study reported that VAS scores of health conditions in dialysis patients were 58 [0(worst)–100(best)].[12] As far as we know, our investigation is the first study to use VAS to assess psychosocial QOL in elderly HD patients.

Our study also revealed that the QOL of elderly HD patients was more impaired than that of healthy individuals, especially in sleep, mood, and happiness. A recent study reported that 45% of HD patients complained of insomnia compared with 4–29% in the general population.[13] In our study, 54.5% of HD patients (56.3% in elderly) had sleep disturbance, although most patients suffering from insomnia took hypnotics (data not shown). Sleep apnea syndrome (SAS), restless leg syndrome (RLS), and skin itching may also contribute to insomnia. The relationship between these comorbidities and sleep disturbance remains to be determined in elderly HD patients.

In terms of mood, several studies found a 10–35% prevalence of depression among ESRD patients.[14] The QOL item "mood" in this study, however, does not always mean depression. In order to examine the prevalence of "real" depression, on collecting the score of "mood" 3 years later, we simultaneously examined the prevalence of depression using the Geriatric Depression Scale (GDS)-15 (Fig. 2),[15] and the incidence was estimated at 53.8% (58.3% in elderly patients) by using a cut-off of 5/6 (data not shown). This may be due to ethnic differences or the method of depression screening. Patel

Table 2
QOL scores (median) of healthy elderly and elderly HD patients

Items of QOL	Healthy elderly ($n = 70$)	Elderly patients ($n = 72$)	p
Health condition	76.5	50	<0.0001
Appetite	88	76.5	0.031
Sleep	80.5	53	<0.0001
Mood	82	62	<0.0001
Memory	62.5	45	0.0005
Family relationship	90	91.5	0.5705
Friendship	90	88	0.1242
Economical status	86	70.5	0.0033
Satisfaction in daily life	92	68	0.0001
Happiness	85.5	71	<0.0001

QOL scores were compared by Mann-Whitney U test between healthy elderly and elderly HD patients in each item of QOL, respectively.

Table 3
Relationship between VAS scores of QOL and laboratory data/personal histories in elderly patients

	Health condition	Appetite	Sleep	Mood	Memory	Family relationship	Friendship	Economical status	Satisfaction in daily life	Happiness
R^2	0.542	0.426	0.704	0.506	0.518	0.694	0.687	0.745	0.503	0.314
Age (y)	0.049	−0.276	0.032	0.152	0.222	0.176	−0.081	0.205	0.346	0.198
Sex (female)	−0.154	0.293	−0.049	0.32	0.007	0.583*	0.598*	0.629*	0.443	0.331
Period of HD (y)	0.093	−0.320	−0.450*	−0.394	−0.626*	−0.528*	−0.341	−0.234	−0.498	−0.343
CTR (%)	0.126	−0.371	0.058	−0.153	−0.177	−0.471*	−0.631*	−0.701*	−0.433	−0.171
BUN (mmol/L)	−0.170	0.245	0.144	−0.199	0.098	−0.049	0.206	−0.080	0.140	−0.044
Hb (g/L)	0.236	−0.173	−0.072	−0.397	−0.167	0.037	0.338	−0.316	−0.212	0.081
Alb (g/L)	−0.295	−0.073	0.200	0.297	0.419	−0.103	−0.421	0.150	0.072	0.009
Blood access trouble	0.213	−0.389	−0.856*	−0.410	−0.024	−0.228	−0.406	−0.247	−0.321	−0.360
IHD	0.550	0.360	0.468	0.570	0.376	0.066	0.085	0.260	0.079	0.067
DM	−0.049	−0.026	−0.209	−0.088	−0.395	−0.154	−0.038	0.064	0.034	0.033
Infectious diseases	−0.451	0.314	0.234	0.077	0.091	0.203	0.159	0.046	0.328	−0.060
Bone fracture	0.271	−0.350	0.091	0.325	0.410	0.238	−0.095	0.077	0.094	0.178
CVD	−0.469	0.085	0.165	−0.007	−0.066	0.354	0.192	−0.248	−0.055	0.086

* $p < 0.05$.
Relationship between VAS scores of QOL and laboratory data/personal histories were analyzed using multivariate regression analysis, corrected with age, sex, and period of hemodialysis (HD) therapy, cardio-thoracic ratio (CTR), blood urea nitrogen (BUN), hemoglobin (Hb), albumin (Alb), blood access trouble, ischemic heart disease (IHD), diabetes mellitus (DM), infectious diseases, bone fracture and cerebrovascular disease (CVD).
Each number indicates the standard β of each independent variable.

et al reported that there was a higher risk of depression in male patients and patients with religious beliefs.[16] Meanwhile, various methods for depression screening have been used, for example, Beck's Depression Inventory (BDI),[17] and the Center for Epidemiological Studies Depression Screening Index (CES-D).[18] We used GDS-15 as it was a self-assessed questionnaire composed of 15 yes or no questions and required only a few minutes to complete and score.[19] In Japan, Schreiner et al. reported that the cut-off score of 6 for GDS-15 in Japanese individuals, had a sensitivity of 97.3% and a specificity of 95.9%, which was the same as that reported for western individuals.[20] In our study, few or no antidepressant agents were prescribed to patients with a depressive mood. Therefore,

We would like to ask you some questions about your feeling for the last month.
On each question, circle "yes" or "no", please.

(1) Are you basically satisfied with your life? (yes/no)

(2) Have you dropped many of your activities and interests? (yes/no)

(3) Do you feel that your life is empty? (yes/no)

(4) Do you often get bored? (yes/no)

(5) Are you in good spirits most of time? (yes/no)

(6) Are you afraid that something bad is going to happen to you? (yes/no)

(7) Do you feel happy most of the time? (yes/no)

(8) Do you often feel helpless? (yes/no)

(9) Do you prefer to stay at home, rather than going out and doing new things? (yes/no)

(10) Do you feel you have more problems with memory than most? (yes/no)

(11) Do you think it is wonderful to be alive now? (yes/no)

(12) Do you feel pretty worthless the way you are now? (yes/no)

(13) Do you feel full of energy? (yes/no)

(14) Do you feel that your situation is hopeless? (yes/no)

(15) Do you think that most people are better of than you are? (yes/no)

Fig. 2. Geriatric Depression Scale-15. We used this form translated into Japanese.

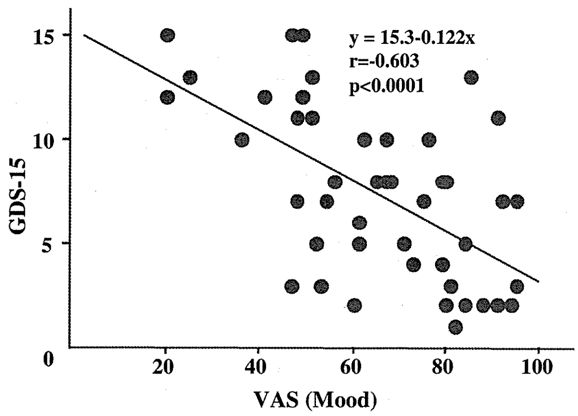


Fig. 3. Correlation between GDS-15 score and VAS in mood in elderly HD patients.

a prospective study to test the effect of antidepressants on QOL in elderly HD patients remains to be investigated.

As might be expected, the score of QOL item of mood "very depressed to very good mood" and that of GDS-15, were significantly correlated with each other by univariate regression analysis in elderly HD patients (Fig. 3). These data indicate that the VAS of "mood" can be used to support GDS scores for depression.

Concerning the relationship between QOL and laboratory data/ personal histories, it is noteworthy that better sleep was inversely correlated with the existence of blood access trouble, which indicated that the sleeping position (for example, resting one's head against one's arm) is one of the reasons of blood access obstruction. It is notable that female sex and the low values of CTR were correlated with better family relationships, friendship or economical status. These data might be due to the nature of female genes in comparison to those of males.

This study has some limitations. Although it is the first investigation to use VAS to assess psychosocial QOL in elderly HD patients, the sample size was small. In order to establish the validity and reliability of VAS in examining QOL, a study with a larger sample size should be performed.

In conclusion, elderly HD patients have a lower score of QOL than healthy elderly individuals. VAS could be a convenient tool to examine psychosocial QOL for the elderly.

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Effect of resistance training on physical performance and fear of falling in elderly with different levels of physical well-being

SIR—Several factors are involved in the maintenance of activities of daily living (ADL) in older adults. Skeletal muscle mass and strength are important factors for maintaining independence and quality of life in elderly. Several recent cross-sectional studies have shown the associations of muscle strength with physical fitness and disability [1, 2]. Loss of muscle mass (sarcopenia) is prevalent in older adults [3] and represents an impaired state of health with mobility disorders, increased risk of falls and fractures, impaired ability to perform ADL, disabilities and loss of independence [4–6].

Fear of falling is common in older adults. The prevalence varies from 21 to 85%, is higher in women than in men, and increases with age [7]. The risk factors of fear of falling are shown to be physical frailty [8], perception of poor health [9], obesity, cognitive impairment, depression, poor balance [10] and history of at least one fall [7].

Resistance training is an effective intervention to improve the physical function in older adults by increasing strength and physical performance [11]. However, it is still controversial whether resistance training is effective for all levels of elderly people. For example, we reported that decreased muscle power is a reliable predictor of falls only in frail elderly [12].

We hypothesised, therefore, that there is a differential effect of resistance training on physical performance according to the level of physical well-being. The aim of this study was to compare the effects of resistance training on skeletal muscle mass, physical performance and fear of falling in robust and frail elderly.

Methods

Participants

Participants were recruited by an advertisement in a local press. We used the following criteria to screen participants in an initial interview: aged ≥65 years, community dwelling, has visited a primary care physician within the previous 3 years, score of ≥8 by Rapid Dementia Screening Test [13], able to walk independently, willing to participate in group exercise classes for at least 6 months, access to transportation and no regular exercise in the previous 12 months.

We also used the interview to exclude participants based on the following exclusion criteria: severe cardiac, pulmonary, or musculoskeletal disorders, pathologies associated with an increased risk of falls (i.e. Parkinson's disease or stroke) and use of psychotropic drugs. We obtained written informed consent from each participant in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1975.

Frailty definition

The frailty classification was based on a composite of previous work. The Timed Up and Go (TUG) is a simple test developed to screen basic mobility performance and has been shown to be significantly associated with ADL in frail older adults [14]. It has been reported that elderly with a TUG score greater than 13.5 s can have an increased risk of falling [15]. Frailty was defined as a TUG score >13.5 s. Based on key components of the screening examination (TUG score greater than 13.5 s), 159 elderly adults were classified as the frail group, whereas 178 elderly adults were classified as the robust group because they had a TUG score of ≤13.5 s.

Resistance training

All participants underwent resistance training sessions twice a week for 50 weeks. All participants performed the seated row, leg press, leg curl and leg extension exercises on resistance-training machines. Training loads were chosen using the 10-repetition maximum (10-RM, the maximal weight that can be lifted 10 times). Participants used the 10-RM for 3 sets of 10 repetitions for each machine exercise. Participants were required to adjust the training weight to ensure failure at the 10-RM. It took approximately 1 h to finish all sessions, with 15-min warm-up at the beginning and 10-min cool-down stretch at the end.

Bioelectrical impedance analysis measurement

A bioelectrical impedance data acquisition system (Physion MD; Physion Co. Ltd, Kyoto, Japan) was used to determine the bioelectrical impedance of the right upper and lower limbs [16]. This system applies a constant current of 800 mA at 50 kHz through the body. Participants lay supine with their arms and legs extended and relaxed during bioelectrical impedance measurement. Leg lean mass (LLM) per whole-body weight was used for the analysis.

Measurement of physical performance

All participants underwent five measurements upon entry into the study (pre-test), which included 10-m walk test, TUG test, single leg standing (SLS), functional reach (FR) and 5-chair stand. The order of performing these tests was random. For each performance task, the participants performed two trials, and an average score was calculated from these two trials. All baseline and pre-test measurements were completed prior to randomisation.

Measurement of fear of falling

Falls Efficacy Scale (FES) [17] is the most frequently used surrogate measure for fear of falling in older adults. The reliability and validity of FES have been previously reported [17]. FES was measured at baseline and at 12 months. FES is based on the operational definition of fear as 'low perceived self-confidence at avoiding falls during essential, relatively nonhazardous activities'. Briefly, participants were asked how concerned they were about the possibility of falling while performing 10 different activities on a 4-category scale from 1 (not at all concerned) to 4 (very concerned). If participants indicated that they did not perform or were unable to perform the activity, they were encouraged to respond hypothetically. FES emphasises mainly indoor, home-based activities.

Required sample size

We designed the effect size of the current study to be 0.4. With a significance level of 0.05, a power of 80%, and a moderate effect size (0.4), a minimum of 100 participants were needed in both the intervention and control groups. Accounting for a potential 20% attrition rate, a total of 240 participants were recruited for this study, which was deemed large enough to detect statistically significant differences.

Statistical analysis

We analysed the effects of resistance training on all outcome measures using a mixed 2 (group: robust and frail groups) × 2 (time: pre-intervention, post-intervention) ANOVA. A 0.05 type 1 error rate was chosen *a priori* to indicate statistical significance. A *post hoc* paired *t*-test for within-group comparisons was performed to compare each dependent variable. The Bonferroni procedure was used to adjust the type 1 error rate of each analysis to 0.025 (0.05/2) as an indication of statistical significance to guarantee an overall type 1 error rate of 0.05. Data were entered and analysed using the Statistical Package for Social Science (Windows version 18.0).

Results

We screened 412 elderly and enrolled 337 (81.8%) who met the inclusion criteria for the trial and agreed to participate (Figure 1A). Most of the elderly who did not meet the inclusion criteria ($n = 66$) were excluded because they had exercised regularly for 6 months prior to the screening. Nine people who might have been eligible for the study declined after telephone screening. Of the 337 individuals who were enrolled in this study, 307 (91.1%) completed the 12-month

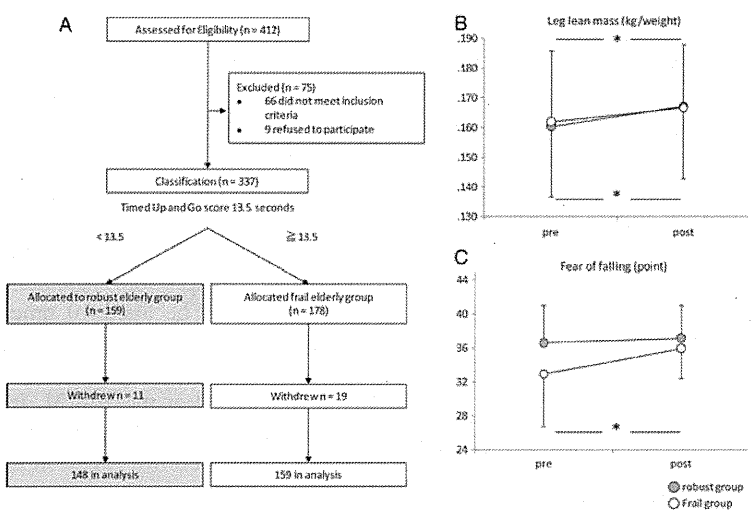

Figure 1. (A) Flow chart showing the disposition of participants throughout the trial. (B) LLM after resistance training in the robust and frail groups was significantly increased from baseline ($P < 0.05$). (C) The frail group had significantly greater improvements in fear of falling ($P < 0.025$).

intervention along with the second interview and the tests at the end of the study. Among them 148 in the robust group (93%) and 159 in the frail group (89%) completed the study.

All 100 scheduled intervention sessions were completed. The median relative adherence was 92% (25–75th percentile, 85–95%) for the robust group and 92% (85–95%) for the frail group. No health problems, such as cardiovascular and musculoskeletal complications, occurred during the training sessions or testing. Minor problems were observed in both groups such as aching muscles after the first training session and fatigue. All the problems were managed easily by adjustment of the intervention and were improved during subsequent interventions.

Effect of the resistance training on outcome measures

LLM after resistance training in the robust and frail groups was significantly increased from the baseline ($P < 0.05$) (Table 1, Figure 1B). Pre- and post-intervention group statistics and group × time interactions are summarised in Table 1. A statistically significant group × time interaction was observed for TUG, FR and fear of falling ($P < 0.05$) (Figure 1C). Bonferroni-corrected paired-sample *t*-tests demonstrated a significant effect of the resistance training on TUG, FR and fear of falling in the frail group ($P < 0.025$).

Discussion

In this study, we showed that LLM was improved by the resistance training programme in both groups. However, the effect on physical function was limited to frail elderly defined by TUG. The role of muscle strength on physical function is supported by numerous cross-sectional studies that have shown a strong association between low muscle strength and decreased mobility in elderly [18]. On the

Table 1. Functional fitness items by group at pre- and post-intervention

	Robust group ($n = 148$)		E/S	*P*-value[a]	Frail group ($n = 159$)		E/S	*P*-value[a]	*P*-value[b]	*F*-value 1. Time effect 2. Group × Time
	Mean	SD			mean	SD				
Age, years	75.4	7.7			76.1	8.3			0.440	
Height, cm	157.7	10.1			156.7	9.1			0.266	
Weight, kg	58.2	11.1			56.8	10.9			0.280	
Gender, female *n* (%)	74 (50.0%)				82 (51.5%)				0.436	
Fall incidence, *n* (%)	48 (32.4%)				77 (48.4%)				0.003	
Leg lean mass, kg/weight										
Pre	0.160	0.024	0.39	<0.001	0.162	0.024	0.27	0.002	0.448	32.1**
Post	0.167	0.024			0.167	0.021				1.1
Percent change, %	0.05	0.09			0.04	0.11				
Walking time, s										
Pre	10.0	1.9	0.11	0.294	16.1	3.8	0.16	0.130	0.017	1.1
Post	10.2	2.1			15.5	4.1				3.6
Percent change, %	0.3	15.5			−7.7	27.5				
Timed up and go test, sec										
Pre	9.9	1.8	0.09	0.374	17.4	3.0	0.32	0.004	0.002	6.1*
Post	10.1	2.5			16.1	3.9				10.5**
Percent change, %	0.9	18.1			−14.5	37.6				
One leg standing, s										
Pre	9.8	11.8	0.06	0.567	1.7	1.9	0.16	0.160	0.987	0.1
post	9.2	13.9			2.6	5.4				1.4
Percent change, %	−47.3	173.4			46.8	248.3				
Functional reach, cm										
Pre	23.5	5.9	0.01	0.948	18.0	5.6	0.46	<0.001	0.029	7.5**
Post	23.4	5.9			20.9	6.8				8.0**
Percent change, %	−7.2	46.4			23.6	48.1				
Five chair stand, s										
Pre	11.2	3.2	0.07	0.498	16.8	5.2	0.17	0.144	0.004	1.6
Post	11.5	4.7			15.1	8.6				3.1
Percent change, %	5.0	31.3			−29.9	72.8				
Fear of falling, points										
Pre	36.6	4.4	0.18	0.081	32.9	6.2	0.51	<0.001	<0.001	26.2**
Post	37.1	3.9			35.9	3.5				15.4**
Percent change, %	1.5	7.3			12.9	23.3				

E/S, effect size.

[a]As calculated by comparing pre- and post-intervention.

[b]As calculated by group comparison.

*$P < 0.05$.

**$P < 0.01$.

other hand, muscle strength does not depend solely on muscle mass, and the relationship between strength and mass is not linear [19]. Rantanen *et al.* reported that the relationship between muscle strength and physical disability in older adults is non-linear [20]. The discrepancy between these results may stem from the heterogeneity of subjects. In this study, we stratified subjects into robust and fail elderly groups. In frail elderly, the 50-week resistance training programme was effective for the improvement of LLM and physical performance. In contrast, there was no correlation between the change in LLM and physical performance in robust elderly undergoing the resistance training programme. These results suggested that our resistance training programme is not effective for the improvement of physical performance in robust elderly. Furthermore, resistance training improved muscle strength, but did not improve physical performance in the relatively healthy elderly [21]. On the other hand, in frail elderly, improvements in leg power, independent of strength, appear to make an important contribution to clinically meaningful improvements in physical performance [22].

Resistance training improved balance function, such as FR in frail elderly. Improved balance function with resistance training is hypothesised to occur by reduced motor-unit discharge variability [23]. However, SLS was not improved. These results suggested that balance improvement after power training may be explained, in part, by adaptations in force control. However, resistance training *per se* is not effective for balance function. For the improvement of balance function, it is useful to add not only the resistance training but also balance training, such as Tai Chi Chuan [24].

In addition to improving physical performance, the resistance training programme was effective for decreasing fear of falling, but only in the frail group. It is considered important to reduce fear of falling by targeting downstream factors such as physical functioning [25] or predictors of those factors [26]. Thus, our study has an important implication for the reduction in fear of falling in frail elderly.

There are several limitations to this study that warrant mention. First, although we used only TUG to define frailty, TUG may not be enough to define frailty. For example, the short physical performance battery evaluates balance, gait, strength and endurance by examining an individual's ability [27]. It has been recently recommended by an international working group to use a functional outcome measure in clinical trials in frail older adults [28]. Second, we did not measure muscle force. The relationship between LLM and muscle strength is still unclear and needs to be addressed in future studies. Third, no follow-up was conducted. Evidence regarding the long-term effect of exercise on fall prevention is limited, and, therefore, this issue also needs to be addressed. Finally, a control group was lacking. The participants in both groups may have had higher motivation and interest in health issues than the general elderly population.

This is the first study to demonstrate that the effects of a resistance training programme on physical performance differed according to the level of physical well-being. Future work should determine whether tailor-made interventions can effectively improve physical function in both robust and frail elderly.

Key points

- The current trial compared the effects of resistance training between robust and frail elderly on skeletal muscle mass, physical performance and fear of falling.
- Skeletal muscle mass after resistance training was significantly increased from the baseline in both groups.
- The resistance training programme was more effective for the improvement of physical performance and fear of falling in frail elderly than in robust elderly.

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Conflicts of interest

None declared.

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Transient ischaemic attack, vascular risk factors and cognitive impairment: a case–controlled study

SIR—Cognitive impairment, especially difficulties with temporal orientation and verbal recall, is associated with the increasing number and severity of vascular risk factors (VRFs) such as hypertension and diabetes [1–3] which can result in an associated impairment of the cerebral microcirculation causing white matter volume changes linked to large artery stiffness [4, 5]. These cognitive deficits can be detected by using simple standard screening tools [6] such as the Mini Mental State Examination [7], Montreal Cognitive Assessment (MoCA) [8] and the DemTec [9], and have been shown to be related to the development of both subclinical (mild) or established vascular disorders [7–12].

However, our understanding of the relation between transient ischaemic attacks (TIAs) and cognitive status is incomplete. We hypothesised that subjects with newly diagnosed TIA would have evidence of an associated mild cognitive impairment; this being a manifestation of the same pathological process underlying the pathogenesis of the vascular event being initiated and accelerated by VRFs. The aims of the current study were, therefore, (i) to examine whether patients with first ever TIA and no history of stroke have evidence of cognitive impairment and, if so, whether the extent of the impairment was greater than expected compared with an age-, sex-matched control populations without VRFs and (ii) to determine which VRFs are associated with cognitive impairment.

Methodology

We conducted a case–controlled study between August and November 2008 in a University Hospital in UK (catchment population 750,000). Cases were defined as those patients with first ever TIA aged ≥45 years, assessed in a

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DUAL-TASK WALK IS A RELIABLE PREDICTOR OF FALLS IN ROBUST ELDERLY ADULTS

To the Editor: Falls are relatively common in elderly people, with approximately 30% of individuals aged 65 and older falling at least once a year and approximately half experiencing repeated falls.[1] In daily-life situations, locomotion occurs under complicated circumstances with cognitive attention focused on a particular task, such as watching traffic or reading street signs, rather than performing the specific motor task of walking. A seminal study demonstrating that the characteristic "stops walking when talking" could serve as a predictor of falls introduced a novel method for fall prediction based on dual-task (DT) performance.[2] Recently, a number of studies have evaluated DT walking in elderly people, but one found that reliable conclusions based on DT results for fall prediction cannot be made because of the lack of standardization in DT paradigms.[3] The aim of the current study was therefore to examine prospectively whether two kinds of DT walking (cognitive task (CT) and manual task (MT)) could predict the risk of falls in a community-dwelling elderly population according to physical function.

The study population consisted of 1,038 community-dwelling elderly Japanese people aged 65 and older (401 men, 637 women, mean age 77 ± 8) in 2009. Six items of physical function were assessed: single-task (ST) 10-m walking time, DT (CT and MT) 10-m walking time, Timed Up and Go (TUG) Test,[4] functional reach, and five-chair stand test (Table 1). In CT walking, participants walked 15 m at the most comfortable speed while counting numbers aloud in reverse order starting at 100. In MT walking, participants walked 15 m at the most comfortable speed while carrying a ball (7 cm in diameter, 150 g in weight) on a tray (17 cm in diameter, 50 g in weight). The DT cost (CT and MT) was then calculated as follows:

$$\text{DT cost}[\%] = 100 \times (\text{DT walking time} - \text{ST walking time}) / ((\text{ST walking time} + \text{DT walking time})/2)$$

Information on the incidence of falls during the following year was collected from participants in a monthly

Table 1. Characteristics of 1,038 Individuals Aged 65 to 97 According to Quartiles of Timed Up and Go Test Results (Seconds)

	Mean ± Standard Deviation							
	Fastest (≤ 8.3) (n = 230)		Faster (8.4–11.0) (n = 258)		Slower (11.1–14.9) (n = 264)		Slowest (≥ 15) (n = 286)	
Characteristic	Faller, 46 (20.0%)	Nonfaller,	Faller, 47 (18.2%)	Nonfaller	Faller, 90 (34.1%)	Nonfaller	Faller, 126 (44.1%)	Nonfaller
Age	77.9 ± 7.9	78.4 ± 6.6	77.4 ± 7.3	78.2 ± 8.0	77.5 ± 8.1	78.2 ± 8.8	77.6 ± 9.3	77.3 ± 8.3
Height, cm	154.4 ± 8.4	153.3 ± 6.8	156.5 ± 9.5	154.7 ± 9.4	157.6 ± 8.3	156.3 ± 11.1	153.6 ± 10.2	154.2 ± 9.6
Body, kg	55.6 ± 11.0	53.6 ± 8.3	50.1 ± 22.9	48.9 ± 16.8	51.7 ± 14.7	53.3 ± 9.3	50.4 ± 17.1	49.7 ± 26.1
Locomotive function, seconds*	9.6 ± 2.0	9.2 ± 2.0	10.5 ± 1.9	10.5 ± 2.5	11.4 ± 2.7	11.2 ± 3.6	17.5 ± 7.1	16.8 ± 7.3
Balance function, cm†	27.1 ± 5.5	25.0 ± 5.4	24.3 ± 7.2	22.6 ± 6.4	21.4 ± 7.9	21.6 ± 7.6	16.6 ± 7.0	18.6 ± 7.0
Muscle power, seconds‡	7.7 ± 1.7	7.5 ± 1.9	9.7 ± 2.8	9.9 ± 2.4	12.8 ± 4.7	11.4 ± 3.5§	17.4 ± 9.8	14.9 ± 5.9§
Cognitive task costs, %	18.7 ± 29.7	16.4 ± 25.5	21.8 ± 23.6	10.6 ± 19.1§	20.2 ± 17.2	20.1 ± 22.2	20.8 ± 20.9	23.1 ± 23.6
Manual task costs, %	8.5 ± 15.8	0.2 ± 11.0§	2.2 ± 14.0	5.8 ± 14.7	12.8 ± 14.0	14.5 ± 16.5	14.5 ± 19.7	16.3 ± 20.7

*Time to complete single-task 10-m walk.
†Distance of functional reach.
‡Time to complete five-chair stand.
§Independent variable that remained in the final step of the regression model.

telephone interview. A fall was defined as any event that led to unplanned, unexpected contact with a supporting surface during walking.

For analysis, the TUG test results were divided into quartiles (fastest, faster, slower, and slowest). A multivariate analysis using logistic regression with a stepwise-forward method was performed to investigate which of the five measures of physical function (ST walking time, CT cost, MT cost, functional reach, and five-chair stand test) was independently associated with falls.

In the fastest group (n = 230), the regression analysis indicated that the MT cost (odds ratio (OR) = 1.068, 95% confidence interval (CI) = 1.04–1.10, $P<.001$) was an independent predictor of falling that remained in the final step of the regression model. In the faster group (n = 258), the regression analysis indicated that the CT cost (OR = 1.03, 95% CI = 1.01–1.04, $P<.001$) was an independent predictor of falling. In the slower (n = 264) and slowest groups (n = 286), the five-chair stand test (slower group OR = 1.11, 95% CI = 1.03–1.19, $P<.001$; slowest group OR = 1.05, CI = 1.01–1.09, $P=.045$) was found to be an independent predictor of falling.

In conclusion, this study demonstrated that DT cost is an independent and prospective predictor of falls in elderly adults with higher functional capacity (faster and fastest groups), although DT cost did not predict falls in elderly adults with lower functional capacity (slower and slowest groups). Thus, the finding that DT walking is a reliable predictor of falls is limited to the robust elderly population.

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TAURINE DIURETIC AND RENAL-REVITALIZING EFFECTS IN NONAGENARIANS

To the Editor: Congestive heart failure (CHF) is the most ominous cause of edema in older adults living in extended-care nursing homes. Despite no obvious CHF, edema resistant even to diuretic doses that cause hypotension, especially in fragile nonagenarians, often develops, and an alternative was sought.

Long-term oral taurine (OT 3 g/d) ameliorates CHF,[1] so it was desired to determine whether OT (1.0 g three times per day) relieves edema without causing hypotension in nonagenarians. Forty-nine residents of an extended-care nursing home (20 taking antihypertensive therapy) who developed edema (score ≥ 2, Appendix A) despite hospital-prescribed diuretics or excessive hypotension precluding effective diuretic usage were enrolled from March 1, 2007, to March 31, 2010.

The remarkable effects of OT on edema were apparent within the first month of treatment (Figure 1A); decreases in body weight occurred with some delay. Required doses of diuretics decreased after institution of OT in the majority of residents. Serum albumin levels increased in 32 hypoalbuminemic residents (Figure 1B).

Significant increases were observed in estimated glomerular filtration rate (eGFR) expressed as a percentage of baseline values from 6 months to 2.25 years of treatment in residents with chronic kidney disease (CKD) Stage 3 or greater (Figure 1C, lower panel); the effects of OT were distinctly greater in residents with CKD Stage 3 or greater than in those with CKD Stage 2 or less (two-way analysis of variance $P<.001$), with differences reaching significance in the third year (Figure 1C upper panel; Bonferroni***). The hyperuricemia (≥ 8.6 mg/dL) observed in eight residents became normal in 6 to 9 months (Figure 1D).

Factors other than CHF play a significant pathogenic role in edema in older extended-care nursing home residents

→

Figure 1. (A) Effects of taurine are strongest on edema, significantly decreasing body weight. (B) Taurine increases albumin levels in patients with <3.8 g/dL at baseline. (C) Effects of taurine on renal function: Lower panel: taurine significantly increases estimated glomerular filtration rate (eGFR) in patients with chronic kidney disease (CKD) Stage 3 or greater when normalized to baseline values by the sixth month of treatment, and continues to improve significantly for up to 2.25 years. Upper panel: greater improvement of eGFR in residents with CKD Stage 3 or greater compared that in those with CKD Stage 2 of less (two-way analysis of variance $P<.001$) reaches significance after 3 years of treatment (Bonferroni***). (D) Taurine decreases hyperuricemia greater than 8.6 mg/dL to normal levels in 3 to 6 months. ANOVA = analysis of variance; SEM = standard error of the mean.

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Original article

Prevalence of the metabolic syndrome in elderly and middle-aged Japanese

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ABSTRACT

Background/Purpose: Diagnosis and management of the metabolic syndrome (MetS) are beneficial for successful aging. In spite of several criteria for MetS, there is little information on cardiometabolic risk clustering in elderly Japanese. The purpose of this study was, therefore, to determine the relationship between age-associated changes in obesity and metabolic components in the Japanese.
Methods: We analyzed data from the nationwide survey conducted in 2000. Using Adult Treatment Panel III (ATP III) and Japanese diagnostic criteria for MetS, we analyzed 2366 people aged from 40 to 79 years (men, 1425 and women, 941) from the total participants.
Results: The prevalence of MetS was almost three fold higher by modified ATP III, International Diabetes Federation, and Japanese criteria, in elderly women than in middle-aged women, whereas no difference was found between middle-aged and elderly men by the three criteria. A marked increase in the prevalence of MetS was found by modified ATP III and International Diabetes Federation criteria compared with that by the Japanese criteria in women. Among the risk factors, the prevalence of central obesity and dyslipidemia increased only in women and that of high fasting glucose and high blood pressure increased in both genders with aging. Among the MetS subjects who fulfilled the modified ATP III criteria, more clustering of risk was observed in elderly than in middle-aged subjects, especially in women. Blood pressure increased and triglyceride decreased in both genders, and non-high-density-lipoprotein cholesterol decreased in elderly men. The prevalence of dyslipidemia decreased in elderly men.
Conclusion: Aging is an important factor that affects the metabolic abnormality, and aging of the population would lead to increase in the prevalence of MetS. Therefore, the development of better approaches to the prevention and management of MetS is necessary for successful aging in our society.

1. Introduction

In the developed countries, life expectancy has shown a continuous increase in the last decades, especially in Japan, along with an increase in age-associated diseases and disabilities.

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Because of the westernization of our lifestyle, this aging population will endure more chronic medical conditions, such as cardiovascular disease, dyslipidemia, diabetes mellitus, chronic kidney disease, and the metabolic syndrome (MetS). MetS is a constellation of multiple risk factors, such as central obesity, dyslipidemia, elevated glucose, and elevated blood pressure, in which insulin resistance is the main underlying disorder.[1] Because the degree of insulin resistance increases with age, elderly are at a higher risk to develop cardiometabolic disorders.[2] At the same time, elderly with MetS are supposed to have a higher risk of cardiovascular disease.[3] In elderly, the diagnosis of MetS is also related to a more pronounced cognitive decline and, thus, disability.[4] Therefore, the identification and treatment of patients with MetS would be an important approach to reduce morbidity and impairment in elderly.

In 2000, we conducted lipid survey in various districts in Japan.[5] In this survey, we found that the level of triglyceride increased in middle-aged men along with the increased body mass index (BMI) compared with the data in 1990.[6] However, the BMI did not change in the elderly population in spite of a small increase in triglyceride levels. Although MetS is a risk factor for cardiovascular disease in middle-aged and elderly people and, therefore, a public health problem, it is still unknown whether the same diagnostic criteria can be applied to both groups.

In the last few years, several expert groups have attempted to set forth simple diagnostic criteria to be used in clinical practice to identify patients with MetS. The committee of International Diabetes Federation (IDF) adopted waist circumference as the surrogate marker for central obesity as an essential component of this syndrome,[7] whereas the National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria required no single factor for diagnosis, but instead, required the presence of at least three out of five components for the diagnosis.[1] In Japan, the committee has established the diagnostic criteria under the same principle as the IDF criteria, except the cutoff for high glucose as 110 mg/dL instead of 100 mg/dL.[8] The cutoff of waist circumference for central obesity was adopted as 85 cm or greater in men and 90 cm or greater in women in Japanese criteria, although the Asian cutoff of waist circumference is 90 cm or greater in men and 80 cm or greater in women. Recently, several groups have shown that the Asian cutoff for the waist circumference is better than that of the Japanese.[9–12] Furthermore, Hata et al.[13] have shown that MetS defined by the Japanese criteria, with the modification of a waist circumference of 90 cm or greater in men and 80 cm or greater in women, is a better predictor of each ischemic stroke subtype in the Japanese population. Therefore, modification of the Japanese criteria for MetS might be necessary in the future.

The purpose of this study was to examine the prevalence of MetS in the Japanese elderly population and to compare the prevalence of MetS and comorbidities with those in the middle-aged population. We also compared the prevalence of MetS by modified ATP III, IDF, and Japanese diagnostic criteria.

2. Methods

2.1. Designs and data collection

The Research Group on Serum Lipid Level Survey 2000 in Japan asked the members of 36 institutes from various areas around Japan to join this survey. The project was designed to produce representative data of serum lipid levels in the civilian Japanese population. The subjects were people receiving annual health examinations in general community, companies, and schools, and not those visiting hospitals. Among the total number of 12,839 participants, we measured the waist circumferences of 3264 people aged 20–79 years (men, 1917 and women, 1357). In this study, we examined the prevalence of MetS in subjects aged 40–79 years (men, 1425 and women, 941) and compared the prevalence of MetS along with each metabolic abnormality according to the Japanese and ATP III criteria. The Ethics Committee in Kyoto University School of Medicine approved this study. Oral informed consent was obtained from all the participants.

2.2. Laboratory methods

All serum and plasma samples were obtained in the fasting state. All lipid and other analyses were conducted on venous blood samples within 1 week of collection at Bio Medical Laboratories (BML) (Saitama, Japan). Serum cholesterol and triglyceride levels were measured by enzymatic assay. High-density-lipoprotein (HDL) and low-density-lipoprotein cholesterols were measured enzymatically by a kit from Daiichi Kagaku Co. Ltd. (Tokyo, Japan). The results of lipid analyses in the four surveys were indirectly standardized according to the criteria of the Centers for Disease Control and Prevention (CDC) Lipid Standardization Program.[14] Thus, the cholesterol levels in these five surveys appear to be comparable. Plasma glucose was determined enzymatically, and hemoglobin A1c (HbA1c) was determined by a kit from Kyowa Medex Co. Ltd. (Tokyo, Japan). Serum insulin was determined by immunoradiometric assay (Abbott Diagnostics Division, Abbot Park, IL). Waist circumference at the umbilical level was measured in the late exhalation phase in standing position.

2.3. Definition of MetS

According to the definition released by ATP III, published in 2008, we analyzed the prevalence of MetS. We modified the criteria by using the Asian cutoff of waist circumference (90 cm for men and 80 cm for women). Other differences are fasting glucose greater than or equal to 100 mg/dL and HDL cholesterol less than 50 mg/dL in women. MetS of modified ATP III criteria was defined as the presence of at least three abnormalities among central obesity, hypertriglyceridemia, low HDL cholesterolemia, high blood pressure, and fasting high glucose. We also analyzed using the Japanese diagnostic criteria of the MetS in 2005, defining MetS as the presence of two or more abnormalities in the presence of central obesity (waist circumference: 85 cm or more in men and 90 cm or more in women). Three abnormalities are as follows: (1) triglycerides greater than or equal to 150 mg/dL and/or HDL cholesterol less than 40 mg/dL or under treatment for this type of dyslipidemia; (2) systolic blood pressure greater than or equal to 130 mmHg and/or diastolic blood pressure greater than or equal to 85 mmHg, or under treatment for high blood pressure; (3) fasting glucose greater than or equal to 110 mg/dL or under treatment for diabetes (Table 1). Furthermore, we used modified IDF criteria for comparison. People treated with lipid-lowering drugs who had normal triglyceride and HDL cholesterol in this study were excluded, because we could not obtain data whether they were treated for hypercholesterolemia or hypertriglyceridemia.

2.4. Data analysis

The results were expressed as mean value ± standard deviation. Differences in means were evaluated by unpaired t test, Mann–Whitney test, or analysis of variance, when appropriate. The categorical variables were compared by chi-square test. The analysis was performed by the Statistical Package for Social Sciences (ver. 11.5; SPSS Japan Inc., Tokyo, Japan). A p value of 0.05 or less was considered to indicate a statistically significant difference.

Table 1
Comparison among Japanese, modified IDF, and modified ATP III criteria for metabolic syndrome

Definition of metabolic syndrome	Japanese (1) + any 2 or more of (2)–(4)	Modified ATP III for Asians 3 or more of (1)–(5)	Modified IDF for Asians (1) + any 2 or more of (2)–(5)
Components			
Central obesity (waist circumference)	(1) ≥85 cm (men), ≥90 cm (women)	(1) ≥90 cm (men), ≥80 cm (women)	(1) ≥90 cm (men), ≥80 cm (women)
High blood pressure	(2) ≥130/85 mmHg and/or antihypertensive medication	(2) ≥130/85 mmHg and/or antihypertensive medication	(2) ≥130/85 mmHg and/or antihypertensive medication
Fasting high glucose	(3) ≥110 mg/dL and/or antidiabetic medication	(3) ≥100 mg/dL and/or antidiabetic medication	(3) ≥100 mg/dL and/or antidiabetic medication
Dyslipidemia	(4) Triglyceride ≥150 mg/dL and/or HDL-C <40 mg/dL	(4) Triglyceride ≥150 mg/dL	(4) Triglyceride ≥150 mg/dL
		(5) HDL-C <40 mg/dL (men), <50 mg/dL (women)	(5) HDL-C <40 mg/dL (men), <50 mg/dL (women)

IDF = International Diabetes Federation; ATP III = Adult Treatment Panel III; HDL-C = high-density-lipoprotein cholesterol.

3. Results

Table 2 shows the prevalence of MetS in Japanese middle-aged and elderly men and women according to the Japanese and modified ATP III and IDF criteria. According to the Japanese criteria, the prevalence of MetS was higher in both elderly men and women (13.3% *vs.* 18.9% in men and 1.5% *vs.* 4.8% in women). In women, the prevalence of MetS was almost three fold higher in the elderly than that in the middle-aged group ($p < 0.01$ by chi-square test). When we apply the modified ATP III and IDF criteria, the prevalence of MetS was also increased in women of each group ($p < 0.01$ in ATP III and IDF criteria by chi-square test), and the three fold increase in MetS in elderly women was consistent among the three criteria. The increase of MetS prevalence in women by modified ATP III and IDF criteria compared with that by the Japanese criteria was also statistically significant ($p < 0.01$). Intriguingly, when we used modified IDF criteria, the prevalence of MetS in middle-aged and elderly men was similar to that using the Japanese criteria. However, the prevalence of MetS in women by modified IDF criteria was similar to that by modified ATP III criteria.

To assess the effect of aging on each metabolic component, we compared the prevalence of central obesity, dyslipidemia, high blood pressure, high fasting glucose, and MetS in each age group according to the Japanese and modified ATP III criteria. In men, the prevalence of MetS was similar in each age group; yet, more people satisfied the modified ATP III criteria than the Japanese criteria (Table 3). In women, the prevalence of MetS was about 5% in the elderly, and almost no subjects were diagnosed with MetS less than 65 years old by the Japanese criteria. According to the modified ATP III criteria, the prevalence of MetS in women also increased in their 60s and was almost the same as that of men older than 65 years. We found a big difference in the prevalence of central obesity diagnosed by Japanese and Asian criteria for waist circumference in both genders. Thus, it is critical which cutoff is used to diagnose MetS.

The prevalence of central obesity in men was almost constant according to the Japanese or Asian criteria of waist circumference, although the prevalence seemed to be decreased in their 70s. The prevalence of central obesity in women increased toward menopause and remained almost the same after their 50s. However, when we used the Asian criteria, the prevalence of central obesity in women further increased in their 70s. The prevalence of dyslipidemia was almost constant in men among each age group and increased toward menopause in women. However, the prevalence reached a plateau after 55 years of age. As expected, the prevalence of dyslipidemia was higher in women according to the ATP III criteria than that by the Japanese criteria. The prevalence of high blood pressure increased with age both in men and in women. Intriguingly, the prevalence of high blood pressure did not show further increase after 60 years of age in both genders. The prevalence of high fasting glucose increased after 50 years of age in men and after 65 years of age in women. Thus, the prevalence of MetS and related components are associated with age, especially with menopause in women. We also compared the number of the MetS traits by dividing the cohort into three groups: from 40 to 49 years (young middle age); from 50 to 64 years (old middle age); and from 65 to 79 years (elderly). As shown in Figure 1, the prevalence of the subjects with indicated numbers of MetS components according to the modified ATP III criteria is quite similar in men of all age groups. However, in older women, the number of MetS components increased, which is consistent with the data in Table 2.

Next, we compared the demographic characteristics of men and women diagnosed with MetS by the modified ATP III criteria. As shown in Table 4, age and total, HDL, and low-density-lipoprotein cholesterol were higher, and waist circumference, triglyceride, diastolic blood pressure, remnant-like particle (RLP) cholesterol, and fasting glucose were lower in women than in men.

We then compared the demographic characteristics of elderly and middle-aged men and women with MetS by modified ATP III criteria. As shown in Table 5, systolic blood pressure was higher in older-middle-aged and elderly than in younger-middle-aged group, and diastolic blood pressure was higher in older middle-aged group in both genders. HDL cholesterol was lower in younger-middle-aged men and non-HDL cholesterol was lower in elderly men. Triglyceride was lower in elderly men and women. Insulin levels decreased according to age in men. There were no statistical differences in the other components.

Table 2
Prevalence of metabolic syndrome in middle-aged and elderly Japanese

%	Male (1425)		*p*	Female (941)		*p*
	40–64 yr (1266)	65–79 yr (159)		40–64 yr (732)	65–79 yr (209)	
Japanese criteria	13.3	18.9	NS	1.5	4.8	<0.01
Modified Adult Treatment Panel III	19.0	21.4	NS	9.0	26.8	<0.01
Modified International Diabetes Federation	14.0	14.8	NS	8.2	23.9	<0.01

The numbers in parentheses indicate the number of subjects in each group. *p* Value, 40–64 yr *vs.* 65–79 yr.
NS = not significant.

Table 3
Prevalence of metabolic syndrome and metabolic components according to the Japanese and modified ATP III criteria in each age group in the Japanese population (%)

Criteria and metabolic components	Sex															
	Male (age group, yr), %								Female (age group, yr), %							
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79
n	291	289	359	191	136	67	62	30	171	123	185	108	145	93	75	41
Japanese criteria																
Central obesity	49.1	56.4	54.0	57.1	55.1	61.2	48.4	43.3	5.3	11.4	16.8	16.7	11.7	16.1	14.7	17.1
Hypertriglyceridemia	33.7	43.6	31.2	28.8	33.1	25.4	25.8	13.3	6.4	7.3	15.1	22.2	20.7	20.4	18.7	14.6
Low HDL cholesterolemia	11.3	14.2	12.3	13.1	12.5	9.0	9.7	13.3	1.8	4.1	2.2	2.8	2.8	6.5	2.7	4.9
Dyslipidemia	36.4	46.0	34.5	33.5	36.0	31.3	30.6	20.0	7.6	8.9	15.1	22.2	22.1	21.5	20.0	19.5
High blood pressure	16.2	20.8	28.7	27.2	49.3	41.8	43.5	40.0	8.8	8.9	17.8	19.4	49.7	49.5	40.0	43.9
High fasting glucose	11.3	15.6	19.5	23.6	22.8	22.4	25.8	16.7	1.8	4.9	3.8	10.2	9.7	15.1	16.0	14.6
Metabolic syndrome	9.6	15.2	14.2	12.0	16.2	22.4	17.7	13.3	0.0	0.8	2.2	3.7	1.4	5.4	4.0	4.9
Modified ATP III criteria																
Central obesity	23.7	34.6	30.1	26.7	30.9	38.8	22.6	23.3	18.7	32.5	31.4	47.2	36.6	48.4	60.0	63.4
Hypertriglyceridemia	33.7	43.6	31.2	28.8	33.1	25.4	25.8	13.3	6.4	7.3	15.1	22.2	20.7	20.4	18.7	14.6
Low HDL cholesterolemia	11.3	14.2	12.3	13.1	12.5	9.0	9.7	13.3	8.2	15.4	15.7	12.0	17.9	23.7	24.0	19.5
Dyslipidemia	36.4	46.0	34.5	33.5	36.0	31.3	30.6	20.0	12.9	17.9	22.7	26.9	29.7	33.3	32.0	31.7
High blood pressure	16.2	20.8	28.7	27.2	49.3	41.8	43.5	40.0	8.8	8.9	17.8	19.4	49.7	49.5	40.0	43.9
High fasting glucose	34.7	38.4	43.2	44.0	39.7	41.8	40.3	36.7	8.8	15.4	14.6	18.5	24.8	29.0	33.3	26.8
Metabolic syndrome	14.1	22.8	19.2	16.2	25.0	22.4	19.4	23.3	1.8	5.7	9.2	13.9	16.6	26.9	30.7	19.5

ATP III = Adult Treatment Panel III; HDL = high-density lipoprotein.

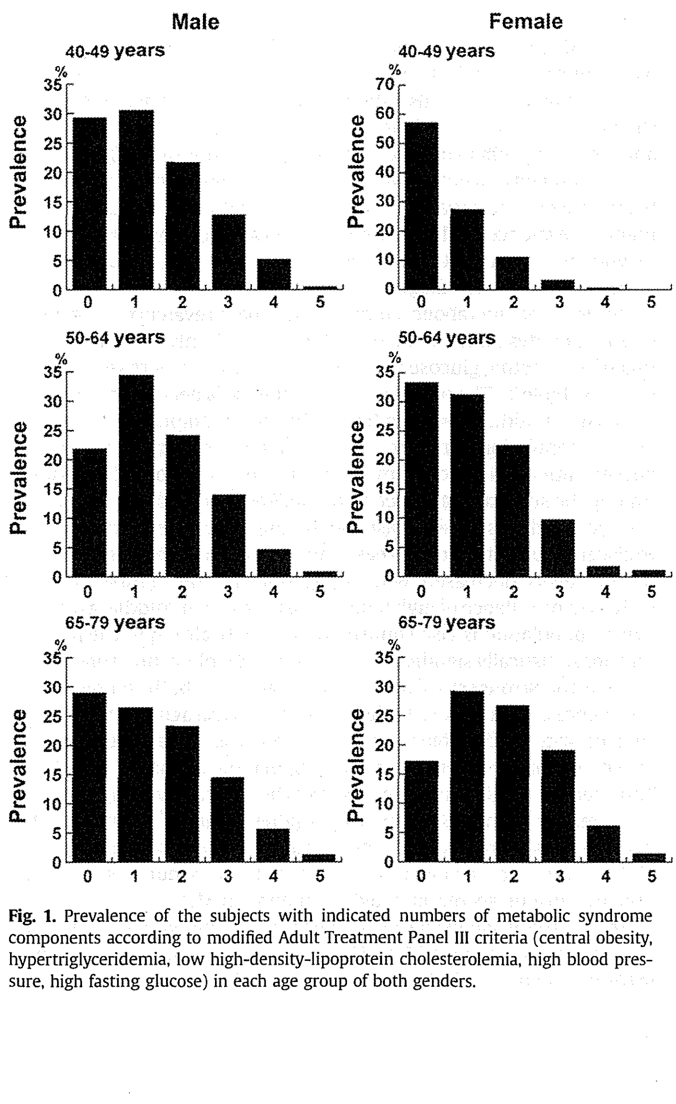

Fig. 1. Prevalence of the subjects with indicated numbers of metabolic syndrome components according to modified Adult Treatment Panel III criteria (central obesity, hypertriglyceridemia, low high-density-lipoprotein cholesterolemia, high blood pressure, high fasting glucose) in each age group of both genders.

Finally, we compared the prevalence of central obesity and other components among the people who satisfied the modified ATP III criteria according to their age in both genders. As shown in Table 6, the prevalence of hypertriglyceridemia and dyslipidemia in men was lower in the elderly, whereas the prevalence of high blood pressure increased in older-middle-aged and elderly men. In women, there was a tendency that the prevalence of hypertriglyceridemia was lower in elderly and that of high blood pressure increased according to age.

4. Discussion

In this study, we compared the prevalence of MetS in the Japanese middle-aged and elderly population by the Japanese and

Table 4
Demographic characteristics of men and women with metabolic syndrome

	Male ($n = 467$)		Female ($n = 201$)		*p*
	Mean	SD	Mean	SD	
Age, yr	53.4	8.8	61.9	9.4	<0.01
Body mass index	25.9	3.0	26.3	2.9	0.27
Waist circumference, cm	92.1	6.7	86.2	8.0	<0.01
Systolic blood pressure, mmHg	136	18	135	18	0.69
Diastolic blood pressure, mmHg	84	12.6	81	9.9	0.02
T-Cho, mg/dL	214	35.4	224	33.6	0.01
TG, mg/dL	197	155, 268	159	115, 194	<0.01
HDL-C, mg/dL	45.7	12.2	51.7	11.0	<0.01
Low-density-lipoprotein cholesterol, mg/dL	126	34.0	140	30.0	<0.01
Non-HDL-C, mg/dL	168	35.8	173	32.5	0.24
RLP-C, mg/dL	6.6	4.2, 10.7	4.3	3.2, 8.5	0.02
HbA1c, %	5.3	0.77	5.4	0.82	0.15
FBS, mg/dL	108	26	100	18.4	0.01
Insulin, μU/mL	8.3	4.7	8.0	4.4	0.52

TG and RLP-C are expressed as median (interquartile range). The difference was analyzed by unpaired *t* test except for TG and RLP-C. Mann–Whitney test was used for TG and RLP-C.
SD = standard deviation; HDL-C = high-density-lipoprotein cholesterol; T-cho = total cholesterol; TG = triglyceride; RLP-C = remnant-like particle cholesterol; HbA1c= hemoglobin A1c; FBS = fasting blood sugar.

Table 5
Demographic data of subjects with metabolic syndrome in each age group

	Sex	40–49 yr (M, 195; F, 27)		50–64 yr (M, 223; F, 102)		65–79 yr (M, 49; F, 72)		p
		Mean	SD	Mean	SD	Mean	SD	
Body mass index	M	26.1	3.0	25.9	3.1	25.5	2.5	0.55
	F	26.7	2.1	26.3	3.1	26.1	2.7	0.78
Waist circumference, cm	M	92.2	7.0	91.9	6.8	92.2	5.8	0.96
	F	87.9	8.7	85.6	9.1	86.3	6.7	0.65
Systolic blood pressure, mmHg	M	130	17.6	138	18.1	143	17.7	<0.01
	F	125	18.0	140	19.4	132	14.6	0.01
Diastolic blood pressure, mmHg	M	82	13.1	86	12.5	82	9.4	0.02
	F	80	11.2	84	10.9	79	7.8	0.04
T-Cho, mg/dL	M	219	34.9	212	35.6	203	33.6	0.06
	F	213	28.8	230	33.2	220	34.3	0.13
TG, mg/dL	M	272	154	234	242	171	71	0.03
	F	169	79.7	189	89.6	144	57.1	0.01
HDL-C, mg/dL	M	43.1	8.3	47.2	13.7	47.9	14.9	0.02
	F	48.3	9.6	52.9	11.5	51.4	10.7	0.38
Low-density-lipoprotein cholesterol, mg/dL	M	128	34.8	126	34.2	121	31.6	0.62
	F	131	26.2	142	28.9	140	31.1	0.51
Non-HDL-C, mg/dL	M	176	34.8	165	36.4	155	32.3	0.01
	F	165	33.5	178	31.0	169	33.6	0.26
HbA1c, %	M	5.1	0.7	5.4	0.9	5.4	0.6	0.14
	F	5.3	0.7	5.3	1.0	5.5	0.7	0.63
FBS, mg/dL	M	112	24.3	113	25.2	108	21.5	0.58
	F	100	13.6	106	22.5	106	19.7	0.61
Insulin, mU/mL	M	9.4	5.9	7.8	3.8	7.2	3.4	0.01
	F	7.9	2.0	8.1	3.6	8.0	5.6	0.98

p Value was analyzed by analysis of variance.
M = male; F = female; HDL-C = high-density-lipoprotein cholesterol; T-cho = total cholesterol; TG = triglyceride; RLP-C = remnant-like particle cholesterol; HbA1c= hemoglobin A1c; FBS = fasting blood sugar.

modified ATP III and IDF criteria. We showed that the prevalence of MetS was almost three fold higher by all the three criteria in elderly women than in middle-aged women, whereas there was almost no difference between middle-aged and elderly men. Consistent with our findings that the prevalence of MetS increased in elderly women compared with that in middle-aged population, other studies have also shown that the prevalence of MetS increases with increasing age.[15] Ford et al.[15] reported that the prevalence of MetS in subjects older than 60 years is approximately 40% in the Third Report of the National Cholesterol Education Program Expert Panel, in which they used the cutoff of 110 mg/dL for high fasting glucose and their criteria of waist circumference for central obesity. The prevalence of MetS in middle-aged population is approximately 25% in both genders, which is different from the result in our cohort. In Japan, Ishizaka et al.[16] and Aizawa et al.[17] have shown that the prevalence of MetS in men is approximately 20% in both middle-aged and elderly populations, whereas that in women is approximately 5% and 10% in middle-aged and elderly populations, respectively, although they used the original ATP III criteria and BMI instead of waist circumference. Tanaka et al.[18] also showed that the prevalence of MetS in Okinawa, a group of islands located in southwest of Japan, is approximately 30% in middle-aged and elderly men and 10% and 20% in middle-aged and elderly women, respectively, when they use ATP III criteria with the Japanese cutoff of waist circumference. Thus, the higher prevalence of MetS in middle-aged and elderly men than that in women is consistent in Japanese cohorts, although the prevalence is different with each diagnostic criterion.

Table 6
Prevalence of each metabolic abnormality in each age group in the subjects with metabolic syndrome

	Sex	Age group (yr) 40–49	50–64	65–79	p
Central obesity	M	74.5	72.1	82.4	0.47
	F	92.3	82.8	89.3	0.48
Hypertriglyceridemia	M	92.5	72.9	58.8	<0.01
	F	61.5	69	48.2	0.08
Low HDL cholesterolemia	M	39.6	34.3	32.4	0.61
	F	69.2	46.6	55.4	0.29
Dyslipidemia	M	94.3	77.9	73.5	<0.01
	F	76.9	79.3	71.4	0.62
High blood pressure	M	50.9	70.0	85.3	<0.01
	F	46.2	67.2	76.8	0.09
High fasting glucose	M	79.3	82.1	79.4	0.75
	F	46.2	65.5	64.3	0.41

The difference was analyzed by chi-square test.
M = male; F = female.

Among the metabolic components, the prevalence of central obesity and dyslipidemia increased with aging only in women, and that of high fasting glucose and high blood pressure increased in both genders (Table 3). The prevalence of dyslipidemia decreased in elderly men. Thus, middle-aged men tend to be more dyslipidemic, whereas elderly population tends to have a higher prevalence of central obesity, impaired glucose metabolism, and high blood pressure. Among the subjects diagnosed with MetS by modified ATP III criteria, systolic blood pressure increased with aging in both genders, whereas triglyceride and insulin decreased with aging in both genders, and insulin levels decreased with aging only in men (Table 5). The increased prevalence of high blood pressure in older middle-aged and elderly population is also confirmed in Table 6, although the p value was not statistically significant in women. Thus, blood pressure seems to have the strongest association with aging in both genders. The prevalence of central obesity did not increase with aging in the female subjects with MetS (Tables 5 and 6), whereas the prevalence of central obesity increased in female general population, as shown in Table 3. Thus, central obesity in women seems to be affected by aging, which is consistent with the results of other studies in Japan.[16,18] In men, the insulin levels decreased in the elderly in spite of the fact that FBS and HbA1c were not changed among the three groups, suggesting impaired insulin secretion in elderly men with MetS.

In this study, we used the Japanese and modified ATP III and IDF definitions to determine MetS. However, there was a large difference in the prevalence of MetS among the three definitions. This difference is because of the fact that the Japanese definition requires the central obesity for its diagnosis as in the modified IDF criteria and has more stringent criteria for high fasting glucose for both genders and for HDL cholesterol for women. As shown in this study, the prevalence of MetS in elderly women by the Japanese criteria was very low. This is the reason why we used various analyses using modified ATP III criteria in this cohort. However, the Japanese guideline for MetS was established to identify patients with central obesity, who can reduce the risks by weight loss, whereas the ATP III criteria try to identify patients with multiple risk factors. Therefore, the Japanese criteria should be used to identify obese patients who can have a benefit by weight loss in middle-aged and elderly populations. However, in terms of risk prediction, there have been several reports discussing the cutoff levels of MetS components. Hata et al.[13] have shown significant associations between MetS defined by various criteria and the risk of ischemic stroke in the Hisayama study. In the study, they found that MetS was an independent risk factor for ischemic stroke when they used the modified Japanese criteria with Asian definition of central obesity. Another study from the same group showed that the optimal cutoff level of waist circumference to predict cardiovascular disease was 90 cm in men and 80 cm in women,[19] as we used in modified ATP III definition in this study. Sone et al.[11] also proposed to use the Asian cutoff for waist circumference to define central obesity from the data of Japan Diabetes Complication Study. In terms of the appropriate cutoff level of HDL cholesterol for the definition of MetS in Japanese women, not so many analyses have been done. In our study, the prevalence of low HDL cholesterolemia with the cutoff of 40 mg/dL was less than 5% and was approximately 20% with the cutoff of 50 mg/dL in elderly women. We previously showed that central obesity was significantly associated with low HDL cholesterolemia only when we used the cutoff of 50 mg/dL for women.[5] Therefore, further study is necessary to determine the appropriate cutoff level of HDL cholesterol in women.

In summary, we have shown the prevalence of MetS in Japanese elderly and middle-aged population using Japanese and modified ATP III and IDF criteria, and found the effect of aging on the prevalence only in women with either criterion. We also showed the effect of aging on each metabolic component in this cohort. Thus, aging is an important factor that affects the metabolic abnormality, and aging of the population would lead to the increase in the prevalence of MetS. Therefore, the development of better approaches to the prevention and management of MetS is necessary for successful aging in our society.

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REVIEW ARTICLE

Cognitive dysfunction: An emerging concept of a new diabetic complication in the elderly

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The incidence of type 2 diabetes mellitus (T2DM) has risen, and this trend is likely to continue. Recent advances suggest that T2DM is a risk factor for cognitive decline. We are now encountering novel complications of T2DM, namely cognitive dysfunction and dementia. Although the treatment strategy for diabetic patients with neurocognitive dysfunction has received a great deal of attention, the appropriate level of glycemic control for the prevention of the development and/or progression of cognitive decline in elderly diabetic patients remains to be elucidated. Another issue in diabetic treatment in patients with cognitive dysfunction is the selection of medicines. The best choice and combination of antidiabetic medications for the preservation of cognition should also be studied. Ample studies suggest that exercise helps to preserve cognitive function, although existing evidence does not necessarily indicate its effectiveness exclusively in diabetic patients. Exercise is a helpful non-pharmacological therapy. Considering the progressive aging of the worldwide population, more research to investigate the best way to manage this population is important. **Geriatr Gerontol Int 2013; 13: 28–34.**

Keywords: Alzheimer's disease type dementia, hypoglycemia, insulin resistance, neurocognitive assessment, vascular dementia.

Introduction

The incidence of type 2 diabetes mellitus(T2DM) has risen, and this trend is expected to continue.[1] Recent remarkable advances in pharmacological therapy in T2DM have resulted in a wide variety of treatments. Many large clinical trials have been carried out, and a variety of interventions are now available to prevent and treat the classic microvascular and macrovascular complications that occur with DM, so that people are living longer with the condition.[2] Recent studies suggested that T2DM is a risk factor for cognitive dysfunction and dementia in the elderly. With the increase in the number of elderly individuals with DM, the number of diabetic patients with cognitive dysfunction has been increasing. We are now encountering novel complications of T2DM that are not targeted by the current management strategies. As one of these new targets, cognitive impairment and dementia in patients with T2DM has generated a great deal of interest, and diabetic treatment in this population that takes brain protection into consideration should be provided.

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Cognitive impact of T2DM

Large epidemiological studies have shown the cognitive impacts of T2DM. In the Rotterdam Study,[3] T2DM patients showed an increased risk of developing dementia. The study also showed that patients treated with insulin were at a 4.3-fold higher relative risk for dementia. The Hisayama Study showed that the incidence of all-cause dementia, Alzheimer's disease (AD) and vascular dementia were significantly higher in patients with diabetes than in those with normal glucose tolerance[4] The same study showed that systemic insulin resistance was associated with the pathogenic process of AD, neuritic plaques formation.[5] The Religious Orders Study, which observed some 800 nuns and priests longitudinally for 9 years, showed that diabetic people had a 65% increased risk of developing AD.[6] The Honolulu Asia Aging Study, a cohort of Japanese Americans in Hawaii, showed that the diabetic population had a 1.8-fold higher risk of developing AD and a 2.3-fold risk of vascular dementia.[7,8]

Prospective trials also suggested that T2DM caused cognitive function to deteriorate in the elderly.

A diagnosis of diabetes increased the odds of cognitive decline 1.2-fold to 1.7-fold (95% CI 1.3–2.3) in several neurocognitive assessments.[9] A recent systematic review of large prospective trials reported that T2DM increased the risk of AD by a factor of 1.59 (range 1.15–2.7).[10] Another systematic review reported that T2DM has a risk of vascular dementia of 2.0–4.2.[9,11]

The advances in the research in this field strongly suggest that T2DM is a risk factor for cognitive dysfunction or dementia.[12,13]

Assessment of diabetes-associated cognitive dysfunction

To screen patients with cognitive impairment, several neuropsychological assessment tools might be applied. The Mini-Mental State Examination (MMSE) is an assessment scale for global cognition including orientation, memory, calculation, verbal ability and constructional disability.[14] A full score is 30, and a cut-off point of 23 out of 24 is usually used for the screening of dementia. The MMSE subset analysis identified impaired attention and calculation as specific characteristics of DM patients,[15] whereas patients with AD had lower scores in temporal orientation and recall.[16]

As a part of a large cohort study of older DM patients (Japanese Research of Cholesterol and Diabetes Mellitus, UMIN000000516 Japan CDM), we carried out MMSE on diabetic patients aged older than 65 years in a diabetic outpatient clinic (52 males, 61 females; mean age 74.7 ± 4.6 years). Of these patients, 75 were aged less than 75 years (younger-old mean age 69.9 ± 4.7 years) and 38 patients were aged older than 75 years (older-old mean age 80.7 ± 4.4). In the younger-old group, 76.0% of patients (57/75) had a MMSE score of more than 24 (mean score 25.3 ± 4.7), and in the older-old group, 52.6% (20/38) had a MMSE score of more than 24 (mean score 24.2 ± 4.6). This small assessment showed that many diabetic patients had lower cognitive scores indicative of dementia, especially in the older-old.

Diabetes affects a wide range of cognitive domains.[17] Among the domains affected by T2DM, cognitive speed might provide early detection of diabetes-related cognitive decline[18,19] The digit symbol substitution test (DSST) is a test of cognitive speed that can be carried out relatively easily. It consists of a number (e.g. nine) of digit-symbol pairs (followed by a list of digits). Under each digit, the patient is asked to write down the corresponding symbol as quickly as possible. The number of correct symbols written within the allowed time (e.g. 90 or 120 s) is measured.

In clinical settings, the diagnosis of dementia is generally made based on the Diagnostic and Statistical Manual of Mental Disorders III revised criteria in patients with or without DM.[20] The disturbance in memory impairment with at least one of the following is required for the diagnosis of dementia: abstract thinking, judgement, higher cortical function and personality changes interferes with work or social activities. The leading cause of dementia in diabetic patients is AD, as is those without DM. DM patients often have cerebrovascular disease, and clinical-pathological studies support the notion that vascular lesions aggravate the deleterious effects of AD pathology by reducing the threshold for cognitive impairment.[21]

Pathogenesis of diabetes-associated cognitive dysfunction

The precise mechanisms underlying T2DM-related cognitive dysfunction or the development of dementia, especially AD-type dementia, remain to be elucidated; however, several hypothetical mechanisms have been proposed (Fig. 1). To develop pharmacological and non-pharmacological strategies for treating the diabetic elderly with cognitive impairment, elucidating the pathogenesis of this complication might be essential.

High glucose concentration, a major pathological characteristic of diabetes, might have toxic effects on neurons in the brain through osmotic insults and oxidative stress, and the maintenance of chronic high glucose also leads to the enhanced formation of advanced glycation end-products (AGE).[22] AGE couple with free radicals and create oxidative damage, which in turn leads to neuronal injury,[23] and they also reactivate microglia, the resident innate immune cells in the brain. A wealth of evidence shows that activated microglia can become deleterious and damage neurons.[24]

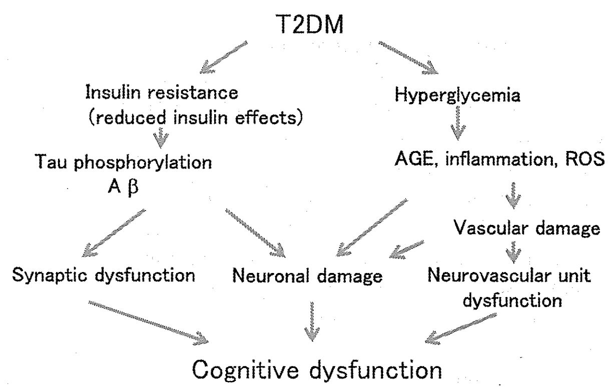

Figure 1 Pathogenesis of type 2 diabetes mellitus (T2DM)-associated cognitive dysfunction. Cognitive dysfunction in T2DM is induced by multiple pathways. Insulin resistance might be associated with Alzheimer's disease pathology, and hyperglycemia induces advanced glycation end-products (AGE) formation, inflammation and reactive oxygen species (ROS) production, which might lead to neuronal damage and neurovascular dysfunction.