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

Geriatr Gerontol Int 2012; **12:** *65–71*

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Comparison of the psychosocial quality of life in hemodialysis patients between the elderly and non-elderly using a visual analogue scale: The importance of appetite and depressive mood

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Aim: The number of hemodialysis (HD) patients is increasing along with their mean age in Japan. The assessment of their psychosocial status and quality of life (QOL) is therefore becoming more and more important along with laboratory data or comorbidities.

Methods: We examined the psychosocial status of 211 HD patients (72 elderly and 139 non-elderly) and compared the difference between elderly and non-elderly patients using a visual analogue scale (VAS). We then examined how QOL affected mortality rate in 3-year prospective follow up. We assessed 10 items of QOL: health condition, appetite, sleep, mood, memory, family relationships, friendship, economical status, life satisfaction in daily life, and happiness with qualified self-evaluating questionnaires along with laboratory data and comorbidities. Furthermore, we investigated the correlation between the scores of mood and geriatric depression scale (GDS)-15.

Results: There was no difference in VAS scores between elderly and non-elderly patients. Lower VAS scores for appetite and mood correlated with higher mortality in HD patients, especially in the non-elderly. VAS scores for mood correlated with GDS-15 in HD patients.

Conclusions: More attention should be paid to appetite and the diagnosis and therapy of depressive mood to improve the prognosis of HD patients, especially for the non-elderly. **Geriatr Gerontol Int 2012; 12: 65–71.**

Keyword: appetite, depressive mood, hemodialysis, quality of life, visual analogue scale.

Accepted for publication 21 June 2011.

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doi: 10.1111/j.1447-0594.2011.00731.x

Introduction

With the advance of dialysis technology, the number of dialysis patients along with the proportion of older patients is increasing in Japan. According to the annual statistical survey by the Japanese Society for Dialysis Therapy from the end of 2003 to 2009, the mean age of the whole dialysis population rose from 61.5 to 65.8 years old, much older than in 1985 (50.3 years old).

In the years 2003 and 2009, there were about 220 000 and 290 000 dialysis patients in Japan, respectively. It is likely that these dialysis patients live with more mental stress, including anxiety from comorbidities, conflict with their family and social restrictions.[1] It is reported that mental and physical health-related quality of life (QOL) in hemodialysis (HD) patients is lower than that in the general population,[2] and that depression is one of the most important predictors of patients' prognosis,[3] which is one of the main QOL factors used to evaluate patients with end-stage renal disease (ESRD).[4] Therefore, we should pay more attention to QOL and the psychological problems of dialysis patients in addition to medical factors. In terms of QOL, assessment of HD patients' self-evaluation for psychosocial status (subjective QOL) is very important. Although there are some reports on psychosocial QOL in HD patients, few studies have addressed the comparison between elderly and non-elderly patients.[5]

The aim of this study, therefore, was to evaluate psychosocial QOL of HD patients and to compare it between the elderly and non-elderly. Furthermore, we investigate how QOL affects the mortality of HD patients in a 3-year prospective follow up.

Patients and methods

This study was performed at Taigenkai Hospital and Kita-Eijinkai Hospital, located in Japan from 2000–2003. All HD outpatients in the dialysis units (231 patients) of these two hospitals were given questionnaires. Patients 65-years-old or older were defined as "elderly", those under 65-years-old as "non-elderly". On the basis of this definition, the HD population consisted of 83 elderly and 148 non-elderly patients. This study was approved by the Ethical Committee of Kita-Eijinkai Hospital and Taigenkai Hospital and conforms to the provisions of the Declaration of Helsinki. Written informed consent for the study was obtained from each patient. Participants were given a brief explanation of the questionnaire by a medical technician or the attending physician and were asked to complete the questionnaire.

QOL assessment of subjects was carried out using a visual analogue scale (VAS). VAS is frequently used as a subjective scale of pain in the field of anesthesiology. Each VAS questionnaire ended with a summing-up graph in the form of a 100 mm bar, graded with subjectively the worst condition on the left and best one on the right. The participant was asked to mark on the 100 mm bar how they evaluated their condition. We defined the distance (mm) from the left to the marked position as the score of VAS (0–100), with high scores indicating high QOL.[6] We assessed 10 QOL items: health condition; appetite; sleep; mood; memory; family relationships; friendship; economical status; life satisfaction in daily life; and happiness, as described by Matsubayashi *et al.*[6] The VAS (10 items of QOL) has been validated for use in the Japanese population.[7] Demographic data including age, gender, and duration of HD therapy, laboratory data, which included cardiothoracic ratio (CTR), plasma level of blood urea nitrogen (BUN), hemoglobin (Hb), albumin (Alb), and comorbidities including blood access trouble, ischemic heart disease, diabetes mellitus, infectious diseases, bone fracture, cerebrovascular disease were simultaneously collected. After patients rested in the supine position for at least 5 min, systolic blood pressure was measured twice by medical staff at the bedside and the average of those was calculated. Patients were examined at the beginning of their first HD session of the week, as is done in routine medical care.

We followed these patients for 3 years prospectively. The end point for patients was the trial end or death from any cause. At first, we examined the survival analysis in elderly and non-elderly HD patients. We then investigated how QOL affects the mortality of HD patients. At the end of the 3-year observation period we also screened for depression using the geriatric depression scale (GDS)-15 with a self-assessed questionnaire (0 [good] – 15 [very depressed])[8] and investigated the correlation between the scores of the GDS-15 and QOL item mood, which was also examined simultaneously.

Data were analyzed using JMP v. 6.0.0 (SAS Institute Inc., Cary, NC, USA). For patient age, duration of HD and laboratory data, means were analyzed using *t*-test. For patient gender and comorbidities, frequencies were analyzed using χ^2 for independence test. Medians of QOL scores were calculated and analyzed using Mann–Whitney *U*-test. According to the average score of each VAS from all patients, a survival rate curve was analyzed by Kaplan–Meier analysis followed by log–rank test. Correlation between each score of QOL and mortality rate was analyzed using multivariate Cox regression analysis corrected for age, gender, duration of HD therapy, laboratory data and comorbidities. Correlation between the scores of GDS-15 and mood was analyzed using univariate regression analysis. Statistical significance was considered to be a P value of <0.05.

Results

Questionnaires were given to 231 patients and the response rate was 100%. However, answers from 211

Table 1 Characteristics, laboratory data and comorbidities in hemodialysis (HD) patients

	Elderly patients ($n = 72$)	Non-elderly patients ($n = 139$)	P value
Age (years, means ± S.D.)	71.8 ± 5.6	52.4 ± 9.3	<0.0001
Sex (male)	58.3%	64.7%	0.3613
Duration of HD (years, means ± S.D.)	6.9 ± 5.0	8.5 ± 6.9	0.0696
SBP (mmHg, means ± S.D.)	155 ± 23	153 ± 22	0.6046
CTR (%, means ± S.D.)	50.2 ± 4.9	48.0 ± 5.0	0.0025
BUN (mmol/L, means ± S.D.)	26.0 ± 6.5	28.4 ± 5.8	0.0073
Hb (g/L, means ± S.D.)	87.8 ± 14.4	94.7 ± 15.6	0.0033
Alb (g/L, means ± S.D.)	38.5 ± 5.7	42.4 ± 4.9	<0.0001
Blood access trouble	58.5%	57.6%	0.9175
IHD	28.6%	25.7%	0.7410
DM	53.1%	42.7%	0.2567
Infectious diseases	18.4%	5.7%	0.0549
Bone fracture	17.1%	23.8%	0.4111
CVD	13.3%	17.4%	0.5614

Patient characters were compared between elderly and non-elderly. Data are expressed as means ± S.D. or incidence of each disease (%). Alb, albumin; BUN, blood urea nitrogen; CTR, cardiothoracic ratio; CVD, cerebrovascular disease; DM, diabetes mellitus; Hb, hemoglobin; IHD, ischemic heart disease; SBP, systolic blood pressure.

Table 2 Median of quality of life (QOL) scores in hemodialysis patients

Items of QOL	Elderly patients ($n = 72$)	Non-elderly patients ($n = 139$)	P value
Health condition	50	49	0.3047
Appetite	76.5	82	0.2415
Sleep	53	54	0.8906
Mood	62	60	0.6133
Memory	45	51	0.0948
Family relationships	91.5	89	0.1982
Friendship	88	80	0.3215
Economical status	70.5	51.5	0.0512
Satisfaction in daily life	68	57	0.0903
Happiness	71	67	0.4419

QOL scores were compared by Mann–Whitney U-test between elderly and non-elderly hemodialysis patients for each item of QOL. There was no significant difference between elderly and non-elderly hemodialysis patients.

patients (91.3%) were used for the analysis, because the rest were incomplete. Table 1 demonstrates patient characteristics, laboratory data, and comorbidities. The mean age of elderly and non-elderly HD patients was 71.8 ± 5.6 and 52.4 ± 9.3, respectively ($P < 0.0001$). There was no significant difference in the proportion of gender or the duration of HD between the two groups. For the 10 items of QOL, there was no significant difference in VAS scores between elderly and non-elderly HD patients (Table 2).

In the 3-year prospective follow up, the number of deceased patients was 44 and the mortality rate was 21.8%. We also investigated the correlation between VAS scores in the QOL items and survival rate by univariate analysis according to the average score of each QOL. The Kaplan–Meier analysis according to the VAS score of each QOL item in elderly and non-elderly HD patients is shown in Table 3. We found that higher VAS scores of health condition, appetite, sleep, mood and satisfaction in daily life were associated with better survival in non-elderly patients, but not in elderly patients.

On the other hand, higher VAS scores in appetite, mood, friendship, and satisfaction in daily life were significantly associated with better survival in non-elderly HD patients according to multivariate Cox regression analysis adjusted for age, gender, and duration of HD therapy, clinical data including CTR, BUN, Hb, Alb

Table 3 Kaplan–Meier analysis by each item of quality of life (QOL) in hemodialysis patients in elderly and non-elderly

	Cut-off point	Elderly patients ($n = 72$) P value	Non-elderly patients ($n = 139$) P value
Health condition	50 <= vs 49 =>	0.4824	0.0138
Appetite	75 <= vs 74 =>	0.6832	0.0021
Sleep	59 <= vs 58 =>	0.8158	0.0059
Mood	62 <= vs 61 =>	0.8342	0.0047
Memory	53 <= vs 52 =>	0.7448	0.1317
Family relationships	78 <= vs 77 =>	0.4242	0.3575
Friendship	74 <= vs 73 =>	0.3438	0.5439
Economical status	54 <= vs 53 =>	0.5022	0.1990
Satisfaction in daily life	61 <= vs 60 =>	0.5047	0.0420
Happiness	66 <= vs 65 =>	0.7771	0.4040

Correlation between mortality and each item of QOL was analyzed by Kaplan–Meier analysis, followed by log–rank test. Cut off point (according to the average score of each QOL) is shown.

and comorbidities (appetite: relative risk [RR] = 0.931, $P = 0.0041$; mood RR = 0.938, $P = 0.0005$; friendship: RR = 0.949, $P = 0.0317$; satisfaction in daily life: RR = 0.967, $P = 0.0178$) (Table 4, right). Statistical significance was also found in family relationships (RR = 0.967; $P = 0.0009$) and friendship (RR 0.977; $P = 0.0180$) for all HD patients (Table 4, left), and appetite in elderly patients (RR = 1.048; $P = 0.0247$) (Table 4, center).

We then assessed the correlation between mood and GDS-15 in HD patients. There was an inverse correlation between VAS scores for mood and GDS-scores among all HD patients ($r = -0.585$, $P < 0.0001$), and when divided into elderly ($r = -0.603$, $P < 0.0001$) and non-elderly patients ($r = -0.610$, $P < 0.0001$).

Discussion

In this study we have shown that there is no difference between elderly and non-elderly HD patients in 10 psychosocial QOL items. However, better appetite, mood, and satisfaction in daily life were associated with better survival in non-elderly HD patients by Cox regression analysis and Kaplan-Meier analysis; no relationship was found between the scores of those QOL items and laboratory data/comorbidities (data not shown). These results indicate more attention should be paid to appetite, depressive mood, and satisfaction in daily life to improve the survival especially in non-elderly HD patients.

We found no significant difference in QOL between elderly and non-elderly HD patients. Few reports have addressed the relationship between age and QOL in HD patients. Tovbin *et al.* demonstrated that age is not associated with self-evaluated individualized QOL according to life domains including health, family, work/studies, economic situation and leisure.[5] Kutner *et al.* reported that prevalence of sleep disorders is not clearly associated with an increasing age of patients, and that elderly patients often report better psychosocial adjustment to dialysis than younger patients.[9] Leinau *et al.* reported that the prevalence of depression is not restricted to older participants (≥60 years 31%; ≤60 years; 22%).[10] These studies are consistent with our study showing no difference in QOL assessments between elderly and non-elderly HD patients.

Quite a number of studies have been reported in terms of QOL in HD patients. Most of the studies used the Kidney Disease Quality of Life (KDQOL) or Short Form 36 (SF-36) questionnaire and have reported that QOL of HD patients is markedly disturbed compared to that of the general population in both physical and mental components.[2] In Japan, a study using SF-36 reported that QOL sores of HD patients were lower than the national standard in all of eight scales, indicating disturbed physical and psychosocial QOL.[11] However, in the KDQOL and SF-36 questionnaires the participants need to answer as many as 36 questions, which might be time consuming and require them to be patient to some extent. Japanese people, especially the elderly, are not used to multiple choice questionnaires and may have some difficulties responding to 36 questions. Therefore, we used a VAS that can be completed quickly, because participants only have to put a mark on the 100 mm bar.[12] Inter-rater reliability ($r = 0.74$, $P < 0.05$) and test–retest reliability ($r = 0.82$, $P < 0.05$) of the VAS score has been already confirmed.[6] For the VAS examination we assessed 10 items of QOL, and the rate of available answers was as high as 91.3% in HD patients. Previous studies have reported that VAS scores of health conditions in dialysis patients were 58.[13] Although more tests might be needed to prove further

Table 4 Correlation between mortality and each visual assessment scale (VAS) score of quality of life (QOL) items in hemodialysis patients in total, elderly, and non-elderly patients

	Relative risk	Total patients ($n = 211$) 95% CI	P value	Relative risk	Elderly patients ($n = 72$) 95% CI	P value	Relative risk	Non-elderly patients ($n = 139$) 95% CI	P value
Health condition	0.983	(0.956–1.008)	0.1866	0.987	(0.932–1.048)	0.6430	0.982	(0.939–1.026)	0.4116
Appetite	1.004	(0.988–1.023)	0.6087	1.048	(1.006–1.103)	0.0247	0.931	(0.871–0.980)	0.0041
Sleep	0.993	(0.976–1.011)	0.4511	1.029	(0.973–1.093)	0.3112	0.975	(0.936–1.009)	0.1462
Mood	0.982	(0.963–1.000)	0.0516	1.013	(0.971–1.053)	0.5270	0.938	(0.895–0.973)	0.0005
Memory	0.986	(0.966–1.005)	0.1393	1.020	(0.965–1.071)	0.4506	0.974	(0.937–1.004)	0.0881
Family relationships	0.967	(0.948–0.986)	0.0009	1.006	(0.945–1.076)	0.8544	0.965	(0.918–1.006)	0.0979
Friendship	0.977	(0.958–0.996)	0.0180	0.994	(0.916–1.067)	0.8763	0.949	(0.898–0.996)	0.0317
Economical status	1.001	(0.985–1.016)	0.9219	0.993	(0.940–1.035)	0.7229	0.990	(0.964–1.014)	0.4187
Satisfaction in daily life	0.990	(0.974–1.005)	0.1762	1.015	(0.982–1.046)	0.3423	0.967	(0.936–0.994)	0.0178
Happiness	0.988	(0.967–1.008)	0.2371	1.013	(0.972–1.052)	0.5097	0.997	(0.950–1.042)	0.8848

Correlation between mortality and each item of VAS score of QOL was analyzed by multivariate Cox regression adjusted for age, gender, duration (years) of hemodialysis therapy, cardio-thoracic ratio (CTR), blood urea nitrogen (BUN), hemoglobin (Hb), albumin (Alb), and presence or absence of comorbidities including blood access trouble, ischemic heart disease (IHD), diabetes mellitus (DM), infectious diseases, bone fracture and cerebrovascular disease (CVD).

validation, our investigation is the first study to use VAS to assess psychosocial QOL in HD patients.

Anemia is considered to be an important factor for QOL and survival. As reported in western countries, there was a recent report from Japan that lower mortality risk was associated with higher Hb levels and that lower Hb levels were associated with lower QOL scores.[14] In contrast, the relationship between anemia and depression has been controversial.[10] In this study we did not find any correlation between the Hb level and VAS score of any QOL items using multivariate regression analysis. It has been reported that diminished appetite is associated with a higher mortality rate from a viewpoint of malnutrition–inflammation complex syndrome (MICS).[15] In this study, we analyzed data such as Alb (for nutritional status) and presence or absence of comorbidities such as infectious diseases (for inflammatory state). However, we did not find any relationship between comorbidities and Alb. These negative results might be ascribed to the small sample size in this study.

In terms of mood, a previous study found 10–35% prevalence of depression among ESRD patients.[16] In this study, we assessed depressive mood by measuring the VAS score for mood. However, the score did not necessarily mean that the patients had depression. Therefore, we used GDS-15 in the third year of the prospective follow up, because it is validated for Japanese subjects[17] and is a self-assessed questionnaire composed of 15 yes or no questions, requiring only a few minutes to complete and score.[18] As expected, the score of mood and that of GDS-15 was inversely correlated by univariate regression analysis in HD patients in both elderly and non-elderly patients. This indicates that the VAS of mood could be used as a relative score to assess depression to some extent. The correlation coefficient (r) was about –0.6, which means there is some discrepancy between mood and GDS. One reason that explains this discrepancy is that feelings such as anxiety might have been included in mood in our study.[19] The prevalence of depression (GDS scores 6 or more) was found to be 54.5% in our study. This relatively high prevalence of depression may be due to the screening method. In our study, little, if any, antidepressive agent was prescribed to patients with depressive mood. Therefore, a prospective study to test the effect of antidepressants on QOL in HD patients needs to be investigated.

It has been reported that the prevalence of depression is increasing with age in the general population.[20] However, according to a patient survey performed by the Ministry of Health, Labor and Welfare in Japan in 2005, patients with depression were distributed widely between the ages of 30 to 70. This could account for the lack of difference in mood between elderly and non-elderly HD patients.

To investigate whether poor QOL reflects a poor health condition, we assessed the relationship between health condition and QOL in elderly and non-elderly patients using regression analysis. In non-elderly patients there was a correlation between health condition and appetite, sleep and mood ($r = 0.28$; $P = 0.0008$, $r = 0.29$; $P = 0.0006$ and $r = 0.51$; $P < 0.0001$, respectively). However, the r value was relatively low ($r < 0.30$) except in relation to mood. In elderly patients, there was correlation between health condition and appetite, sleep and mood ($r = 0.41$; $P = 0.0004$, $r = 0.38$; $P = 0.0012$ and $r = 0.65$; $P < 0.0001$, respectively) and the r value was relatively high ($r > 0.30$). These results indicate that the QOL items appetite and sleep would be better markers of the health condition of elderly HD patients than non-elderly HD patients and that the QOL item mood would be a better marker of the health condition of both elderly and non-elderly HD patients. In contrast, we showed that better appetite and mood were associated with better survival in non-elderly HD patients. Furthermore, there was no relationship between the scores of these QOL items and laboratory data/comorbidities (data not shown). These data indicate the importance of QOL assessment in HD patients.

The relationship between depression and mortality rate is reported to be controversial.[21] Husebye *et al.* reported that psychosocial variables are prognostically important for the survival of dialysis patients over the age of 70, but depression is not associated with mortality rate.[22] Drayer *et al.* reported that depressed HD patients are younger and depression is associated with decreased QOL including sleep and increased mortality rate.[23] In terms of psychological factors, Kimmel *et al.* reported that there is an inverse relationship between the number of symptoms (pain, trouble with sleep, tiredness and shortness of breath) and QOL including psychological items and that no clinical parameter (duration of ESRD, serum Alb, Hb, Kt/V and Karnofsky Performance Status Scale) correlates with any measure of QOL.[24] Moreover, Leinau *et al.* demonstrated that non-ESRD-specific conditions such as fatigue, pain, and depression are as prevalent as ESRD-specific conditions (use of a catheter for access, Hb, intact parathyroid hormone, phosphorous, and Kt/V) and highlighted the importance of diagnosing and treating non-ESRD-specific conditions to improve the health and QOL of persons with ESRD.[11] As reported in these latter two literatures, QOL factors such as sleep disturbance, depression and so on should be paid as much attention as clinical parameters as suggested in the guidelines for ESRD.

We have highlighted the need for assessment of elderly HD patients using self-evaluation for psychosocial status (subjective QOL). In this study, however, a higher QOL score for appetite, sleep, mood and satisfaction in daily life was associated with better survival by both of univariate analysis (Kaplan–Meier analysis; Table 3) and multivariate analysis (Cox regression analysis; Table 4), in non-elderly HD patients only. These negative results in elderly patients might be ascribed to the small sample size. Actually, among the laboratory data that showed differences between elderly and non-elderly patients (Table 1), higher levels of Alb were associated with better survival in elderly patients, but there was no relationship between Alb and the scores of any QOL item (data not shown).

In conclusion, there was no difference in 10 psychosocial QOL items between elderly and non-elderly HD patients. Paying attention to appetite and depressive mood may lead to the improvement of the mortality rate of HD patients, especially for the non-elderly.

Acknowledgements

We thank Toshiko Hori (Kyoto University), Kazuko Nishiyama (Kita-Eijinkai Hospital) and Masanori Shibata (Taigenkai Hospital) for technical assistance and giving the questionnaire to participants.

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Archives of Gerontology and Geriatrics xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Chronic kidney disease (CKD) is an independent risk factor for long-term care insurance (LTCI) need certification among older Japanese adults: A two-year prospective cohort study

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ARTICLE INFO

Article history:
Received 15 January 2013
Accepted 16 March 2013
Available online xxx

Keywords:
CKD
Risk factor
LTCI
Older adults
Japanese

ABSTRACT

CKD is associated with impairments in health status, physical function, and frailty. The aim of the current prospective cohort study was to determine whether CKD predicted new LTCI need certification among community-dwelling older Japanese adults. This was a prospective cohort study. We analyzed the cohort data from a prospective study, The Japan Multicenter Aging Cohort for Care Prevention (J-MACC). We followed 8063 elderly adults for 2 years, and we analyzed the relationship between CKD and LTCI need. The outcome studied was new certification for LTCI service need during a 2-year period. We measured serum creatinine (the estimated glomerular filtration rate; eGFR), serum albumin, frailty checklist scores, and body mass index. During the 2-year follow-up, 536 subjects (6.6%) were newly certified as needing LTCI services. We stratified the cohort according to eGFR quartile and performed multivariate analyses using an eGFR value of 71.4–83.6 ml/min/1.73 m^2 as a reference. We found that subjects with eGFR values <60.0 ml/min/1.73 m^2 had a significantly elevated risk of LTCI service need (adjusted hazard ratio: 1.44 [95% CI 1.12–1.86]). Our results indicate that CKD is independently associated with new LTCI service need certification and is an important marker of frailty in older adults.

1. Introduction

Frailty in older adults is a serious problem in countries with aging populations, such as Japan. In general, frailty is defined as a vulnerable state that places older adults at high risk of adverse health outcomes, such as falls, hospitalization, and mortality (Wiswell et al., 2001).

Age is a major risk factor for CKD, which is a growing health problem in Japan. The prevalence of CKD in the adult Japanese population is estimated to be 13% (Imai et al., 2009). In addition, the number of patients with end-stage renal disease (ESRD) has increased by approximately 7% per year in Japan (Akiba et al., 2000). CKD is associated with impairments in health status and physical function, as well as frailty (Brogan, Haber, & Kutner, 2000; Kurella et al., 2004; Kurella, Yaffe, Shlipak, Wenger, & Chertow, 2005). CKD is also associated with oxidative stress, chronic inflammation, insulin resistance, vascular calcification, and osteoporosis (Ensrud et al., 2007; Landau et al., 2011; Shanahan, 2005). Furthermore, a decreased creatinine clearance <60 ml/min/1.73 m^2 has been shown to predict incident falls among community-dwelling older women (Gallagher, Rapuri, & Smith, 2007). Thus, CKD poses a considerable medical and public health challenge, particularly in the older population.

Japan implemented a LTCI system in April 2000 to help manage a rapidly aging population. Prior to 2000, long-term care services were provided under a tax-based social welfare system for seniors with limited economic resources and family support (Campbell & Ikegami, 2000). However, since the implementation of LTCI, the services of this program have been provided to elderly adults who are certified as requiring support or care according to their care needs and certification assessment (Tsutsui & Muramatsu, 2005).

The aim of the current prospective cohort study, therefore, was to determine whether CKD was a risk factor for LTCI need among community-dwelling older Japanese adults.

2. Methods

2.1. Subjects

We analyzed the cohort data from a prospective study entitled J-MACC. This cohort study investigated the factors associated with LTCI need in community-dwelling Japanese

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http://dx.doi.org/10.1016/j.archger.2013.03.009

adults aged 65 years or older. We recruited community-dwelling older adults who were independent in terms of the activities of daily living (ADL) in 2009. The exclusion criteria were older adults who were already ADL-dependent and were eligible to receive benefits from LTCI services. The subjects were followed prospectively for 2 years. During the follow-up period, 226 subjects died or moved; thus, we analyzed 8063 elderly adults. This study was conducted in accordance with the guidelines of the Declaration of Helsinki, and the study protocol was reviewed and approved by the Ethics Committee of the Kyoto University Graduate School of Medicine.

2.2. Serum creatinine and albumin

The serum creatinine and albumin levels of the subjects were measured. The estimated glomerular filtration rate (eGFR) was calculated using a formula reported by Matsuo et al. (2009): eGFR ($mL/min/1.73\ m^2$) = $194 \times Scr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female). This equation originated from the MDRD study group (Coresh, Astor, Greene, Eknoyan, & Levey, 2003) arranged for Japanese individuals, and it is recommended by the Japanese Society of Nephrology. The study cohort was divided into 4 groups according to serum albumin and eGFR quartiles.

2.3. Frailty checklist

The frailty checklist included simple yes/no questions concerning lifestyle (questions 1–5), motor abilities (questions 6–10), nutrition (questions 11–12), oral functions (questions 13–15), seclusion (questions 16–17), forgetfulness (questions 18–20), and emotions (questions 21–25) (Table 1). The total score on the frailty checklist is useful for predicting the risk of being newly certified as needing LTCI services (Coresh et al., 2003). Furthermore, physical exercise is an effective means of improving the total score on the frailty checklist (Imai et al., 2007).

2.4. Body mass index

The patients' height and weight were measured to calculate their body mass index (BMI).

2.5. Outcome measure

The outcome measure was new LTCI service need certification over a 2-year period. The selection process for classifying dependent older adults first involves a questionnaire that evaluates the person's current mental and physical condition (74 items), which is analyzed using a computerized algorithm. A long-term care approval board reaches a final decision based on the algorithm-aided analysis of the questionnaire, a doctor's recommendation, and a home visit report. Individuals who become certified as dependent older adults are subdivided into seven levels (support levels 1 and 2 and care levels 1–5), depending on their conditions. They are provided home and community-based or institutional services according to their care needs. Individuals who are not eligible for long-term care or support care may utilize preventive care services.

2.6. Statistical analysis

The baseline characteristics of the subjects who were certified or non-certified as needing LTCI services were compared. Differences in the demographic variables between the 2 groups were analyzed using Student's *t*-test or a chi-square test. In addition, differences in the demographic variables among the 4 groups stratified by eGFR quartile were examined using an analysis of variance (ANOVA) and a post hoc test. Kaplan-Meier survival curves were calculated for the group newly determined to need LTCI services and were stratified by eGFR quartile. Cox proportional hazards models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) of the relationships between

Table 1
The frailty checklist used in Japan.

Domain	Question	Items	Yes	No
Lifestyle	1	Do you ride the bus or train alone?	0	1
	2	Do you buy household goods for everyday use?	0	1
	3	Do you withdraw and deposit savings?	0	1
	4	Do you visit your friends' homes?	0	1
	5	Do you give advice to family and friends?	0	1
Motor abilities	6	Can you climb stairs without holding onto a handrail or the wall?	0	1
	7	Can get up from a chair without grabbing something?	0	1
	8	Are you able to keep walking for about 15 min?	0	1
	9	Have you fallen in the past year?	1	0
	10	Are you very worried about falling?	1	0
Nutrition	11	Have you ever lost more than 2–3 kg of weight in a 6-month period?	1	0
	12	BMI is less than 18.5.	1	0
Oral function	13	I cannot eat hard foods as well as 6 months ago.	1	0
	14	Have you ever choked on tea or soups?	1	0
	15	Are you concerned with being thirsty?	1	0
Seclusion	16	Do you leave your home at least once a week?	0	1
	17	Compared to last year, has the number of times you go out decreased?	1	0
Forgetfulness	18	Are you told that you are forgetful or you always tell me the same thing?	1	0
	19	Do you look up phone numbers and make phone calls yourself?	0	1
	20	Do you sometimes forget the date and month?	1	0
Emotions	21	(In the past 2 weeks) I do not feel fulfillment in my daily life.	1	0
	22	(In the past 2 weeks) The activities I used to enjoy are no longer enjoyable.	1	0
	23	(In the past 2 weeks) The activities I used to carry out with ease have become troublesome.	1	0
	24	(In the past 2 weeks) I do not think I am a useful person.	1	0
	25	(In the past 2 weeks) I feel tired for no reason.	1	0

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Table 2
Baseline characteristics of the study subjects in both groups.

	Certified for LTCI requirement ($n=536$)			Non-certified for LTCI requirement ($n=7527$)			
	Mean	SD	Min–max	Mean	SD	Min–max	*P*-Value
Age (years)	80.8	7.4	66–100	76.7	6.5	65–102	<0.001
Gender (female)	332 (61.9%)	4405 (58.5%)	0.043				
BMI (kg/m^2)	22.4	3.5	13.8–35.8	22.8	3.2	12.7–39.8	0.073
Frailty checklist (points)	6.5	4.9	0–23	4.3	4.0	0–24	<0.001
Serum albumin (g/dl)	4.2	0.3	3.2–5.0	4.3	0.3	2.6–5.4	<0.001
eGFR (ml/min/1.73 m^2)	68.5	20.7	22.2–121.3	71.4	17.2	20.3–123.8	<0.001

eGFR quartile and the time to new LTCI service need certification in univariate and multivariate analyses. Multivariate analyses were performed for each covariate and were adjusted for gender, BMI, frailty checklist score, and serum albumin level, factors that are known to be associated with frailty (Levey et al., 2006; Tomata et al., 2011; Yamada, Arai, Sonoda, & Aoyama, 2012). Survival time was defined as the time between enrollment (the date of the baseline measurements) and either the new LTCI service need certification or the end of the follow-up period (March 31, 2011). The data were analyzed using PASW (Windows version 18.0, SPSS, Inc., Chicago, IL). A P value <0.05 was considered statistically significant for all the analyses.

3. Results

During the 2-year follow-up, 536 subjects (6.6%) became newly certified as needing LTCI services (Table 2). Those who were certified for LTCI need were significantly older (80.8 ± 7.4 vs. 76.7 ± 6.5, $P < 0.001$) and had higher frailty checklist scores (6.5 ± 4.9 vs. 4.3 ± 4.0, $P < 0.001$), lower serum albumin levels (4.2 ± 0.3 vs. 4.3 ± 0.3, $P < 0.001$), and lower eGFR values (68.5 ± 20.7 vs. 71.4 ± 17.2, $P < 0.001$) than those who were not certified. More women than men became certified in this cohort (female: 61.6% vs. 58.5%, $P = 0.043$). However, the BMIs were not different between the two groups ($P = 0.073$) (Table 2). We also examined whether eGFR was associated with BMI, frailty checklist score, or serum albumin level. We found that the subjects with eGFR < 60.0 ml/min/1.73 m^2 were significantly older and had lower BMIs, higher frailty checklist scores, and lower serum albumin levels ($P < 0.05$) (Table 3).

Next, we examined the relationship between each variable and new LTCI need certification. The subjects with BMIs <20.5 exhibited a significantly elevated risk of LTCI service need according to multivariate analyses using a BMI of 22.7–24.7 as the reference (adjusted hazard ratio: 1.41 [95% CI 1.11–1.78]) (Table 4). The mean BMI was 22.7 ± 3.3, with a range from 12.7 to 39.8; 1975 participants (24.5%) had BMIs <20.5. The subjects with frailty checklist scores >6 had a significantly elevated risk of LTCI service need according to multivariate analyses using frailty checklist scores <2 as the reference (adjusted hazard ratio: 2.24 [95% CI 1.73–2.90]) (Table 4). The mean frailty checklist score was 4.5 ± 4.1, with a range from 0 to 24; 2042 participants (25.3%) had frailty checklist scores >6. Participants with serum albumin levels <4.1 g/dl tended to exhibit an elevated risk of LTCI service need according to multivariate analyses using a serum albumin level >4.4 g/dl as the reference (adjusted hazard ratio: 1.25 [95% CI 0.97–1.62]). However, the univariate analysis indicated that subjects with serum albumin levels <4.1 g/dl had an elevated risk of LTCI service need (Table 4). The mean serum albumin level was 4.2 ± 0.3 g/dl, with a range from 2.6 to 5.4; 1722 participants (21.3%) had serum albumin levels <4.1 g/dl.

Fig. 1 shows the Kaplan-Meier survival curves according to new LTCI service need certification, with the subjects stratified into 4 groups according to eGFR quartile. Individuals with eGFR values <60.0 ml/min/1.73 m^2 had a significantly elevated risk of LTCI service need according to multivariate analyses using an eGFR value of 71.4–83.6 ml/min/1.73 m^2 as the reference (adjusted hazard ratio: 1.44 [95% CI 1.12–1.86]) (Table 4). The mean eGFR was 71.2 ± 17.4 ml/min/1.73 m^2, with a range from 20.3 to 123.8 ml/min/1.73 m^2; 1963 participants (24.3%) had eGFR values <60 ml/min/1.73 m^2.

4. Discussion

In this study, we found that approximately 25% of adults aged 65 years or over had eGFR values <60 ml/min/1.73 m^2, which indicates that CKD is common among older Japanese adults. The multivariate analyses demonstrated eGFR values <60.0 ml/min/1.73 m^2 were independently associated with new certifications for LTCI service need. Thus, our data indicate that CKD is a critical marker of frailty in older adults.

According to the multivariate analyses, lower BMIs (less than 20.5), and higher frailty checklist scores (more than 6) were associated with certification for LTCI service need. These results are consistent with those of previous studies (Levey et al., 2006; Tomata et al., 2011; Yamada et al., 2012), which revealed that the subjects with the lowest BMIs had an elevated risk of requiring care and that frailty checklist scores were strongly associated with new LTCI service need certifications (Levey et al., 2006). Thus, it is important to assess nutrition, cognitive function, mood, and ADL for care prevention, and the frailty checklist includes these items.

In terms of nutrition, however, our study failed to demonstrate that serum albumin levels were significantly associated with new LTCI service need certification after adjusting for other frailty-related factors, although the univariate analysis demonstrated that

Table 3
Demographic differences according to eGFR quartile.

	eGFR (ml/min/1.73 m^2)									
	Q1: <60.0		Q2: 60.0–71.3		Q3: 71.4–83.6		Q4: >83.6		*P*-value	Post hoc
Gender (female)	1122 (57.2%)		1153 (54.2%)		1066 (54.2%)		1429 (71.2%)		<0.001	Q2,3 < Q1 < Q4
BMI (kg/m^2)	23.1	3.3	22.7	3.2	22.9	3.1	22.4	3.4	<0.001	Q1 > Q4 > Q2,3
Frailty checklist (points)	5.2	4.6	4.0	3.9	3.2	3.6	3.9	3.8	<0.001	Q1 > Q2 > Q4 > Q3
Serum albumin (g/dl)	4.11	0.27	4.16	0.26	4.21	0.25	4.21	0.26	<0.001	Q1 < Q2 < Q3,4

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Table 4
Predictors of new LTCI service need certification during a 2-year follow-up period.

		Certified for LTCI requirement		Non-certified for LTCI requirement		Univariate analysis			Multivariate analysis		
						HR	95%CI	P-value	HR	95%CI	P-value
Gender	Female	332	7.0%	4405	93.0%	ref			ref		
	Male	204	6.1%	3122	93.9%	0.88	0.76–1.03	0.11	0.98	0.83–1.17	0.86
BMI	Q1: <20.5	179	9.1%	1796	90.9%	1.53	1.21–1.92	<0.01	1.41	1.11–1.79	<0.01
	Q2: 20.5–22.6	120	5.9%	1915	94.1%	1.00	0.78–1.29	1.00	1.01	0.78–1.30	0.92
	Q3: 22.7–24.7	121	6.0%	1892	94.0%	ref			ref	-	
	Q4: >24.7	140	6.9%	1900	93.1%	1.13	0.88–1.44	0.35	1.09	0.85–1.39	0.51
Frailty checklist	Q1: <2	91	4.1%	2106	95.9%	ref			ref		
	Q2: 2–3	105	5.5%	1802	94.5%	1.36	1.03–1.80	0.03	1.30	1.30–1.73	0.13
	Q3: 4–6	117	6.1%	1800	93.9%	1.51	1.15–1.99	<0.01	1.41	1.06–1.86	0.01
	Q4: >6	247	12.1%	1795	87.9%	3.04	2.38–3.87	<0.01	2.63	2.05–3.39	<0.01
Serum albumin	Q1: <4.1	167	9.7%	1555	90.3%	1.75	1.36–2.24	<0.01	1.36	1.05–1.75	0.02
	Q2: 4.1–4.2	150	6.7%	2076	93.3%	1.19	0.92–1.53	0.18	1.04	0.81–1.35	0.75
	Q3: 4.3–4.4	140	6.0%	2200	94.0%	1.09	0.84–1.40	0.52	1.01	0.78–1.31	0.93
	Q4: >4.4	101	5.6%	1694	94.4%	ref			ref		
eGFR	Q1: <60.0	191	9.7%	1772	90.3%	1.99	1.55–2.54	<0.01	1.63	1.26–2.09	<0.01
	Q2: 60.0–71.3	142	6.7%	1983	93.3%	1.37	1.06–1.77	0.02	1.25	0.96–1.62	0.10
	Q3: 71.4–83.6	97	4.9%	1871	95.1%	ref			ref		
	Q4: >83.6	128	6.4%	1879	93.6%	1.29	0.99–1.68	0.06	1.17	0.89–1.53	0.26

The multivariate analysis was adjusted for gender, BMI, frailty checklist score, and serum albumin level.

a significantly larger number of subjects in the first quartile were certified as needing LTCI. Furthermore, previous studies have indicated that lower serum albumin levels are associated with future functional decline in older adults (Kalyani et al., 2012; Kane, Shamliyan, Talley, & Pacala, 2012). We assume that this result was caused by our study lacking sufficient power to demonstrate a contribution of low serum albumin to new LTCI service need certifications and by the small number of subjects with malnutrition in this cohort. Nonetheless, CKD was found to be significantly associated with new LTCI service need certification. Therefore, it should be noted that CKD may independently predict new LTCI service need certification in older adults.

We found that the subjects with the highest eGFR values (4th quartile) tended to have a higher risk of new LTCI service need certification, lower BMIs, and higher checklist scores than those in the 3rd quartile, although this difference was not statistically significant. Because eGFR is calculated using serum creatinine levels, a higher eGFR may indicate lower muscle mass, especially in older adults. Therefore, it should be noted that older adults with elevated eGFR values may be frail. Further research is required to address the role of eGFR in frailty.

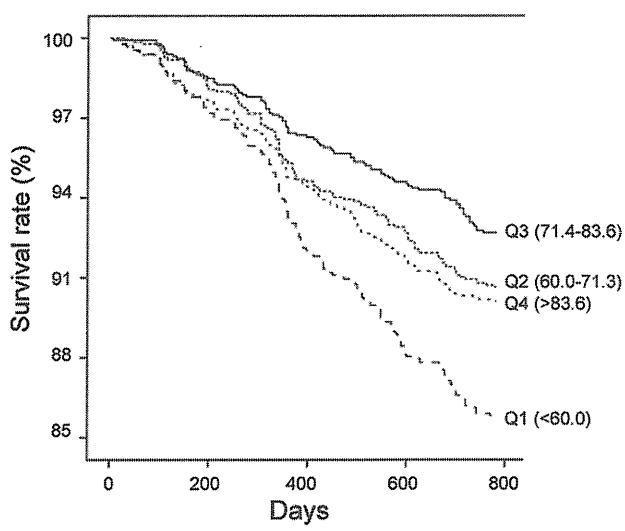

Fig. 1. Kaplan-Meier survival curves for new LTCI service need are shown for 4 groups according to eGFR quartile.

Malnutrition is known to be associated with frailty. Several studies have suggested that vitamin D deficiencies are common among patients with CKD (Reuben et al., 2002; Zuliani et al., 2001). Both vitamin D2 and D3 are first converted to 25-hydroxyvitamin D by hepatic vitamin D-25-hydroxylase and are then converted to the active form, 1,25-hydroxyvitamin D, by renal 1α-hydroxylase (Zuliani et al., 2001). Reduced activation of vitamin D has been associated with the development of hypertension, left ventricular hypertrophy, heart failure, and vascular calcification (Holick, 2007). In addition, vitamin D deficiency has been associated with sarcopenia, falls, fractures, and dementia (Bischoff-Ferrari, 2012; Chonchol, Kendrick, & Targher, 2011; Cozzolino & Ronco, 2011). Therefore, we hypothesized that CKD was a risk factor for new LTCI service need certification.

Two limitations of this study warrant mention. First, we did not collect information about the subjects' comorbidities. Therefore, the effects of comorbidities on the risk of new certifications for LTCI service need remain unclear. Second, the study participants may have had a greater motivation and interest in health issues than the non-participants. Therefore, it is possible that the non-participants had a higher prevalence of CKD and frailty.

In conclusion, this is the first study to demonstrate that CKD is independently associated with new certifications for LTCI service need. In addition, a relatively high percentage of the subjects had moderate to severe CKD (eGFR <60 ml/min/1.73 m^2). Intervention studies are needed to explore whether treating CKD may delay or prevent new certifications for LTCI service need among older adults.

Conflicts of interest

None of the authors have conflicts of interest or financial disclosures.

Acknowledgments

The authors acknowledge Ms. Tomoko Kodama and Mr. Seiji Moriguchi for their contributions to the data collection. This study

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was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

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Please cite this article in press as: Yamada, M., et al., Chronic kidney disease (CKD) is an independent risk factor for long-term care insurance (LTCI) need certification among older Japanese adults: A two-year prospective cohort study. Arch. Gerontol. Geriatr. (2013), http://dx.doi.org/10.1016/j.archger.2013.03.009

Geriatrics Gerontology INTERNATIONAL Medline Indexed

Geriatr Gerontol Int 2013; **13:** *437–442*

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Global brain atrophy is associated with physical performance and the risk of falls in older adults with cognitive impairment

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Aim: Falls are common in patients with cognitive disorder. The purpose of this study was to determine whether global brain atrophy is associated with cognitive function, physical performance and fall incidents in older adults with mild cognitive disorder.

Methods: A total of 31 older adults with mild cognitive disorders (mean age 78.9 ± 7.3 years) were studied, and 10 of them had experienced falls and the others had not in the past 1 year. Cognitive function and physical performance were measured in these patients. Global brain atrophy was determined by the Voxel-Based Specific Regional Analysis System for Alzheimer's Disease software.

Results: Fallers showed significantly worse scores than the non-fallers in the Global Brain Atrophy Index, Clock Drawing Test (CDT), Verbal Fluency Test (animal), maximum walking time and Timed Up & Go (TUG) Test. The Global Brain Atrophy Index was correlated with the Verbal Fluency Test (animal; $r = -0.522$), the Verbal Fluency Test with letter (ka; $r = -0.337$), CDT ($r = -0.547$), TUG ($r = 0.276$) and Five Chair Stands Test ($r = 0.303$) by age-adjusted correlation analyses. Stepwise regression analysis showed that the Global Brain Atrophy Index ($\beta = 1.265$, 95% CI 1.022–1.567) was a significant and independent determinant of falls ($R^2 = 0.356$, $P = 0.003$).

Conclusion: Global brain atrophy might be indicated as one of the risk factors for falls in older adults with mild cognitive disorders. **Geriatr Gerontol Int 2013; 13: 437–442.**

Keywords: falls, global brain atrophy, mild cognitive disorder.

Introduction

Falls are a significant cause of injuries, loss of confidence, increased morbidity and mortality in older adults.[1,2] One-third of community-dwelling older adults aged 65 years and older, and up to 50% of those aged 80 years and older experience falls each year.[3,4] It has been noted that older adults with cognitive impairment are more likely to suffer falls.[5] In fact, the fall rate in patients with Alzheimer's disease (AD) was reported to be nearly twofold higher than age-matched controls.[6] Furthermore, older adults with cognitive disorders have impaired balance and gait,[7] as well as impaired executive functions.[8]

Although patients with cognitive disorders have a higher risk of falls, few studies have been reported on the relationship between morphological changes of the brain and fall incidents. White matter lesions, frequently found in magnetic resonance imaging (MRI) of the aging brain,[9] are attributed to cerebral microangiopathic changes.[10] White matter lesions in older adults are also associated with gait and balance impairment,[11,12] cognitive impairment[13] and frequent falling.[14] A previous study suggested that periventricular white matter lesions might be related to falls in patients with a mild to moderate cognitive disorder.[15] Furthermore, white matter lesions can predict the incident of hip fracture in persons younger than 80 years-of-age.[16]

Previous reports showed that measures of cognitive performance in old age, such as scores on tests of intelligence, information processing speed and memory, are predicted by global and local brain atrophy.[17] However, there have been no studies to address the relationship between global brain atrophy and fall incidents. Therefore, the purpose of the present study was to determine whether global brain atrophy is associated with cognitive function, physical performance and fall incidents in older adults with mild cognitive disorders.

Accepted for publication 2 July 2012.

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doi: 10.1111/j.1447-0594.2012.00927.x

Methods

Participants

Patients with a cognitive disorder who were referred to the memory clinic of the Department of Geriatric Medicine in Kyoto University Hospital, Kyoto, Japan, were enrolled in the present study. All patients underwent brain MRI, as well as a battery of laboratory tests. The diagnosis of AD and mild cognitive impairment (MCI) was made according to the following criteria: AD, Diagnostic and Statistical Manual of Mental Disorders, 4th edition and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association;[18,19] and MCI, Petersen's criteria.[20] In the present study, we did not set the upper limit of the Mini-Mental State Examination (MMSE) for the diagnosis of MCI. Of the 31 patients with a cognitive disorder, 20 were classified as mild AD and 11 were classified as MCI by the criteria. Those with MMSE scores below 19 were excluded from the present study.[21] Other exclusion criteria used in the present study were vascular dementia, dementia with Lewy bodies, lacunar infarcts, Fazekas grade 3 periventricular hyperintensity (PVH)/deep white-matter hyperintensity (DWMH),[22] severe cardiac, pulmonary or musculoskeletal disorders, and the presence of comorbidities associated with greater risk of falls, such as Parkinson's disease and stroke.

Written informed consent was obtained from each participant or his/her family members for the trial in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1975.

MRI

MRI scans were carried out with a 1.5-T superconductive MRI unit (Magnetom Symphony; Siemens Medical, Erlanger, Germany). Whole-brain volumetric imaging with 3-D gradient refocused echo sequence (magnetization prepared rapid gradient echo, or MPRAGE) was carried out for voxel-based morphometry analysis using the following parameters: field of view (FOV) 22 × 22 cm, matrix 256 × 256, 120 contiguous 1.25-mm thick sagittal slices, TR/TE/TI 1700/3.93/800 ms and FA 15°.

Voxel-based morphometry

The voxel-based analysis system in the present study has been validated.[23] Currently, their software is distributed in Japan under the name, Voxel-Based Specific Regional Analysis System for Alzheimer's Disease (VSRAD). VSRAD automatically calculated the following analysis results, which reflect the severity of gray matter loss in the global brain by comparing the original normal database template. The severity of global brain gray matter loss was estimated with the Global Brain Atrophy Index, which was calculated as a percentage rate of voxels with a *Z*-score >2 compared with the whole brain.

Fall experience

Fall events in the past 1 year were recorded based on an interview with the family members. A fall was defined as "an event that results in a person coming to rest inadvertently on the ground or other lower level regardless of whether an injury was sustained, and not as a result of a major intrinsic event or overwhelming hazard".[5] The date, number, characteristics (e.g. while rising from a lying or sitting position, while turning in the opposite direction, while tripping over an obstacle) and consequences (e.g. bruise, fracture) of the falls were recorded using a standardized questionnaire.

Cognitive function measures

Cognitive functions were assessed by MMSE, Clock Drawing Test (CDT), Trail Making Test part A (TMT-A), Verbal Fluency Test (animal) and Verbal Fluency Test with letter (ka). MMSE is a short screening test to assess cognitive impairment, which consists of five areas: orientation, registration, attention and calculation, and recall language. The CDT is a sensitive test for executive function and early cognitive impairment. The participant was asked to draw a clock with all the numbers on it and to set the time to 10 min past 11. We used a 10-point scoring system by Rouleau *et al.*[24] The TMT-A assesses working memory capacity. Patients need to connect the numbers in order, beginning with 1 and ending with 25, as fast as possible. Word fluency is a sensitive test to detect early changes in cognitive function. In the Verbal Fluency Task (animal), patients were instructed to name as many animals as possible within 1 min. In the Verbal Fluency Task, the subject was asked to say as many words as possible beginning with the letters "ka" in 1 min.[25]

Physical performance measures

The participants were subjected to five physical function tests that are widely used to identify frail elderly. For each performance task, the participants performed two trials, and the better performance of two trials was used as scores in the analysis. The physical performance assessment, such as 10-m walking time,[26] Timed Up & Go (TUG) Test,[27] Functional Reach (FR),[28] One-Leg Stand (OLS) test[29] and Five Chair Stands (5CS) Test,[30] was carried out as previously described.

Physical activity measures

In physical activity, a valid, accurate and reliable pedometer, Yamax Power walker EX-510 (Yamasa, Tokyo, Japan) was used to measure free-living step counts.[31] Participants were instructed to wear the pedometer in their pocket on the side of the dominant leg for 14 consecutive days except when bathing, sleeping and carrying out water-based activities. This pedometer has a 30-day data storage capacity. We calculated the averages of their daily step counts for 2 weeks.

Statistical analysis

The *t*-test and χ^2-test were used to compare the results of measurements between faller and non-faller groups. The relationship between the global brain atrophy and the other measurements was investigated with the Spearman's correlation coefficient. The partial correlation coefficient between the global brain atrophy and the other measurements were adjusted for age. Multivariate logistic regression analysis using a stepwise method was carried out to investigate whether age, sex, body mass index (BMI), Global Brain Atrophy Index, word fluency animals, CDT, maximum walking time and TUG were independently associated with the fall incident. Data were analyzed using the Statistical Package for Social Science, Windows version 20.0 (SPSS, Chicago, IL, USA).

Results

There were no significant differences in age (fallers 78.2 ± 7.1 years, non-fallers 77.7 ± 5.4 years, $P = 0.53$), percentage of female (fallers 80.0%, non-fallers 71.4%, $P = 0.48$), height (fallers 150.7 ± 11.9 cm, non-fallers 153.2 ± 7.9 cm, $P = 0.37$), weight (fallers 52.9 ± 12.4 kg, non-fallers 50.5 ± 7.8 kg, $P = 0.74$) or BMI (fallers 23.2 ± 3.7, non-fallers 21.5 ± 2.8, $P = 0.39$) between the two groups (Table 1).

The fallers had significantly worse scores than the non-fallers in the Global Brain Atrophy Index (fallers 13.9 ± 8.3, non-fallers 6.8 ± 3.8, $P = 0.01$), CDT (fallers 8.2 ± 1.1, non-fallers 9.3 ± 0.8, $P = 0.01$), Verbal Fluency Test (animal; fallers 6.2 ± 2.7, non-fallers 9.5 ± 3.9, $P = 0.02$), maximum walking time (fallers 10.4 ± 4.4, non-fallers 7.5 ± 1.7, effect size 0.64, $P = 0.03$) and TUG (fallers 13.5 ± 7.0, non-fallers 8.9 ± 1.9, $P = 0.01$). However, the other measurements were not significantly different between the two groups ($P > 0.05$; Table 1, Fig. 1).

Table 1 Comparison of demographic characteristics and measurements between the groups

	Faller $n = 10$		Non-faller $n = 21$		E/S	*P*-value
	Mean	SD	Mean	SD		
Characteristics						
Age	78.2	7.1	77.7	5.4	0.08	0.53
BMI	23.2	3.7	21.5	2.8	0.45	0.39
Sex (female), n (%)	8 (80.0%)		15 (71.4%)			0.48
Disease (MCI), n (%)	5 (50.0%)		6 (28.5%)			0.32
Brain volume						
Global brain atrophy, %	13.9	8.3	6.8	3.8	0.86	0.01
Cognitive function						
Mini-Mental State Examination, points	24.7	3.8	23.7	2.5	0.27	0.59
Word Fluency Test (animals), number	6.2	2.7	9.5	3.9	0.84	0.02
Letter Fluency Test (ka), number	6.0	2.4	6.0	2.6	0.00	0.88
Clock Drawing Test, points	8.2	1.1	9.3	0.8	0.92	0.01
Trail Making Test Part-A, sec	78.7	43.2	72.3	16.1	0.15	0.53
Physical function						
Comfortable walking time, sec	12.1	4.0	10.1	2.5	0.53	0.07
Maximum walking time, sec	10.4	4.4	7.5	1.7	0.64	0.03
Timed Up & Go Test, sec	13.5	7.0	8.9	1.9	0.65	0.01
Functional Reach, cm	18.8	8.5	22.2	6.4	0.41	0.36
One-Leg Standing time, sec	6.5	11.3	16.7	18.8	0.91	0.06
Five Chair Stands, sec	11.9	2.8	10.5	3.2	0.48	0.18
Activity						
Physical activity, steps	3167.9	2213.1	4499.8	2934.4	0.45	0.21

MCI, mild cognitive impairment.

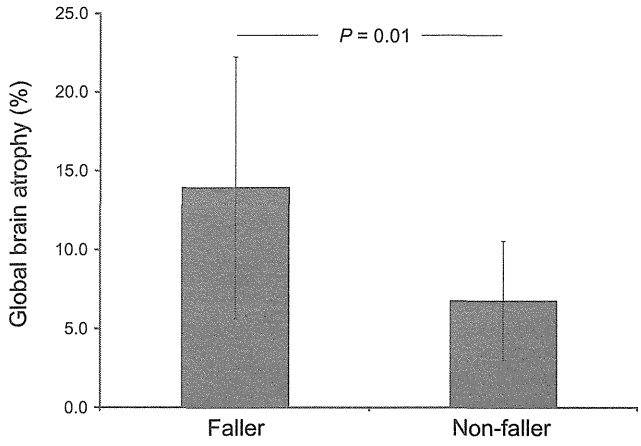

Figure 1 Comparison of Global Brain Atrophy Index (%) between the groups. The fallers ($n = 10$) had significantly worse scores than the non-fallers ($n = 21$) in the Global Brain Atrophy Index.

To determine the association of global brain atrophy with their demography, cognitive function, physical performance and physical activity, we determined Pearson's correlation coefficients. Table 2 shows that the Global Grain Atrophy Index was correlated with age ($r = 0.435$, $P < 0.05$), Verbal Fluency Test (animal; $r = -0.641$, $P < 0.05$), Verbal Fluency Test with letter (ka; $r = -0.320$, $P < 0.05$), CDT ($r = -0.338$, $P < 0.05$), comfortable walking time ($r = 0.555$, $P < 0.05$), maximum walking time ($r = 0.543$, $P < 0.05$), TUG ($r = 0.630$, $P < 0.05$), OLS ($r = -0.581$, $P < 0.05$), 5CS ($r = 0.437$, $P < 0.05$) and physical activity ($r = -0.389$, $P < 0.05$; Table 2).

To age-adjust the association of Global Brain Atrophy Index with their demography, cognitive function, physical performance and physical activity, we analyzed partial correlation coefficients. Table 2 shows that global brain atrophy was correlated with BMI ($r = 0.308$), Verbal Fluency Test (animal; $r = -0.522$, $P < 0.05$), Verbal Fluency Test with letter (ka; $r = -0.337$, $P < 0.05$), CDT ($r = -0.547$, $P < 0.05$), TUG ($r = 0.276$, $P < 0.05$) and 5CS ($r = 0.303$, $P < 0.05$; Table 2).

Stepwise regression analysis showed that the Global Brain Atrophy Index ($\beta = 1.265$, 95% CI 1.022–1.567) was a significant and independent determinant of falls ($R^2 = 0.356$, $P = 0.003$; Table 3).

Table 2 Correlation coefficients for global brain atrophy and other measurements

	Global brain atrophy	Global brain atrophy (adjusted for age)
Characteristics		
Age	0.435	
Cognitive function		
Mini-Mental State Examination	0.019	−0.147
Word Fluency Test (animals)	−0.641	−0.522
Letter fluency Test (ka)	−0.320	−0.337
Clock Drawing Test	−0.338	−0.547
Trail Making Test Part-A	0.067	0.053
Geriatric Depression Scale	0.210	0.181
Physical function		
Comfortable walking time	0.555	0.205
Maximum walking time	0.543	0.221
Timed Up & Go Test	0.630	0.276
Functional reach	−0.121	−0.009
One-Leg Standing time	−0.581	−0.204
Five Chair Stands	0.473	0.303
Activity		
Physical activity	−0.389	−0.169

Table 3 Logistic regression analysis

Independent variables	Adjusted R^2 value = 0.356 Standard regression value	95% CI
Age	–	–
Sex	–	–
BMI	–	–
Brain atrophy index	1.265	1.022–1.567
Word Fluency (animals)	–	–
Clock Drawing Test	–	–
Maximum walking time	–	–
Timed Up & Go Test	–	–

BMI, body mass index.

Discussions

The present study showed that the fall incident might relate to global brain atrophy in older adults with mild cognitive disorders. The fallers also showed a significantly higher Global Brain Atrophy Index, and lower physical and cognitive performance scores than the non-fallers. Age-adjusted correlation analyses showed that the Global Brain Atrophy Index was weakly correlated with several cognitive and motor performances. Furthermore, stepwise regression analysis showed that the Global Brain Atrophy Index was a significant

and independent determinant of the fall incident. Taken together, these findings led us to conclude that measuring global brain atrophy is potentially important to predict falls in patients with mild cognitive disorders.

The mechanisms by which global brain atrophy associates with fall incident and poor physical performance are not well understood. It is possible that global brain atrophy is related to poor neural connectivity. However, we assume that global brain atrophy is mostly attributed to the volume loss in the frontal lobe, because Rosano *et al.* suggested that a smaller prefrontal region was associated with slower gait speed.[32] In contrast, it has been shown that atrophy of dorsolateral prefrontal regions is associated with poorer executive function.[33] Previous imaging research has also shown that brain atrophy is associated with impaired physical and executive functions.[17,34] As expected, physical and executive functions have been associated with an increased fall risk in older adults.[35,36] These reports and the present study suggested that the function of the frontal lobe is associated with the risk of falls, and brain atrophy index can be a biomarker to predict falls.

There are several limitations in the present study. First, the limited sample size might introduce some error of inference, reduce the power of the analysis and limit generalization. Second, global brain atrophy might not be able to predict falls in more robust older adults, as the present study was based on the participants having experienced falls in the previous year. Further study is required to confirm our finding in patients who do not have an experience of falls. Finally, detailed information on falls was lacking. Therefore, the relationship between the decline of frontal lobe function and fall incidents requires further investigation. Thus, the results of the present study should be interpreted with caution.

In conclusion, this is the first study to show that global brain atrophy is associated with fall incident, motor and cognitive performance in older adults with mild cognitive disorders. From the present results, global atrophy might be indicted as one of risk factors for falls in older adults with mild cognitive disorders. Further investigation, such as a prospective study, is required to confirm the present study.

Acknowledgments

This work was supported by the Grants-in-aid for Scientific Research from the Japan Society for the Promotion of Science, from the Ministry of Education, Culture, Sports, Science, and Technology.

Disclosure statement

None of the authors have conflicts of interest or financial disclosures.

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The Journal of Frailty & Aging©
Volume 1, Number 2, 2012

NUTRITIONAL SUPPLEMENTATION DURING RESISTANCE TRAINING IMPROVED SKELETAL MUSCLE MASS IN COMMUNITY-DWELLING FRAIL OLDER ADULTS

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Abstract: *Objective:* Sarcopenia, the age-related loss of skeletal muscle mass, is highly prevalent in older adults. The aim of this study was to investigate the effects of the combination of resistance training and multinutrients supplementation (including vitamin D and protein) on muscle mass and physical performance in frail older adults. *Methods:* This trial was conducted in Japanese frail older adults (n=77), which underwent a standardized protocol of a 3-month physical exercise intervention. The sample population was divided into two groups, according to the adoption (S/Ex: n = 38) or not (Ex: n = 39) of the additional multinutrient supplementation. The outcome measures of interest for the present analyses were the skeletal muscle mass index (SMI) and several physical performance tests. *Results:* Participants in S/Ex group had significant improvements for the outcome measures, including SMI and maximum walking time ($P<0.05$), compared to those in Ex group. The prevalence of sarcopenia decreased from 65.7% to 42.9% in S/Ex group, while that in Ex group remained unchanged (68.6% to 68.6%) (relative risk = 1.60, 95% CI: 1.03-2.49). *Conclusion:* The results of this study suggest that the combination of resistance training and multinutritional supplementation may be more effective at improving muscle mass and walking speed than an intervention only based on resistance training.

Key words: Sarcopenia, vitamin D, protein, resistance training, muscle mass, older adults.

Introduction

Sarcopenia, the age-related loss of skeletal muscle mass, is highly prevalent in older adults (1). Multiple operational definitions have been proposed for this condition in literature. In the present study, we defined sarcopenia as coexistence of low muscle loss and slow walking speed according to consensus statement released by the Society of Sarcopenia, Cahexia and Wasting Disorders (SSCWD) (2). Sarcopenia is associated with the risk of falls and fractures, physical disability, mobility disorders, and mortality (3-5). The possible causes of sarcopenia are numerous and include increasing age, muscle disuse, endocrine dysfunction, neurodegenerative diseases, and malnutrition (6). In particular, given the strong relationship existing between nutritional status and skeletal muscle, it has been hypothesized that the combination of exercise and nutritional supplementation may be particularly important for adequately targeting sarcopenia (7).

In fact, resistance and/or aerobic exercise are important for the prevention and management of sarcopenia. A recent meta-analysis showed that the resistance training is effective at improving strength (8) and eliciting muscle mass gains in older adults (9). In a previous study, we demonstrated that leg muscle mass and physical performances are improved by a 1-year resistance training protocol in frail older adults (10). In addition, our 6-month pedometer-based walking program showed to effectively increase physical activity, improve physical performance, and augment leg muscle mass in sedentary older adults (11).

On the other hand, nutritional supplementation is similarly important to counteract the detrimental age-related effects on skeletal muscle. In particular, a proper protein intake is important at older age. Dietary protein intake is relevant for the maintenance of muscle mass and strength in community-dwelling older adults (12-13). Protein supplementation has been shown to enhance the muscle strengthening effect of resistance exercise (14-15). Similarly, amino-acids supplementation (crucial for protein synthesis (16)) has shown beneficial effects on muscle mass (17).

Recently, vitamin D has attracted a growing interest of researchers and clinicians in the field of geriatrics. The deficiency of such hormone is quite common in older adults. Several studies suggested that a low 25-hydroxyvitamin D (25(OH) D) concentration is associated with lower muscle strength, reduced physical performance, and increased disability (12, 18-19). Bischoff-Ferrari and colleagues showed that a high daily dose of supplemental vitamin D reduced the risk of falling; however, a low dose of supplemental vitamin D in older adults with vitamin D sufficiency may not reduce the fall risk (20).

The Society for Sarcopenia, Cahexia, and Wasting Disease recently recommended the combination of exercise with protein and/or vitamin D supplementation for reducing the age-related skeletal muscle decline (7). Evidence is still limited with only

Received April 12, 2012
Accepted for publication May 3, 2012

few trials having tested the effectiveness of nutritional supplementation in sarcopenia (21-23). The aim of the present study is to investigate the effects of the combination of resistance training with a multinutrient supplementation (including vitamin D and proteins) on muscle mass and physical performance in frail older adults with low muscle mass. We hypothesized that muscle mass and physical performance might better benefy from the combined intervention compared to when only resistance training is adopted.

Methods

Participants

Participants were recruited by an advertisement in the local press and public ads. We recruited 96 community-dwelling older adults from two communities with similar environment in Kyoto city. Participants of one community were allocated to a resistance training intervention (Ex); subjects from the other community received the same resistance training intervention and the additional nutritional supplementation (S/Ex).

The following inclusion criteria were verified during the initial interview:
- Frailty status as certified by the long-term care insurance service;
- Presence of low muscle mass (defined as appendicular muscle mass divided by squared height lower than 6.87 kg/m2 in men, and lower than 5.46 kg/m2 in women [24])
- Age of 65 years and older;
- Living in the community;
- No severe cognitive impairment (defined as a Rapid Dementia Screening Test score higher than 4) [25];
- Ability to independently walk (even with a cane);
- No regular supplementation of vitamin D and protein during the previous 12 months.

The exclusion criteria adopted in the present study were:
- Severe cardiac, pulmonary, or musculoskeletal disorders;
- Presence of comorbidities associated with an increased risk of falls, such as Parkinson's disease or stroke;
- Use of psychotropic drugs.

Written informed consent was obtained from each subject in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1975.

Of the total 96 screened community-dwelling older adults, 19 were excluded. The remaining 77 older adults with low muscle mass were divided into the 2 groups: nutritional supplementation during resistance training (S/Ex: n = 38) group and resistance training alone (Ex: n = 39) group (Figure 1).

Interventions

Multinutrient supplementation

A multinutrient supplementation, particularly aimed at increasing vitamin D and protein intakes, was provided 3 times a week for 3 months to participants in the S/Ex group. A detailed description of the adopted product (Resource PemPal Active®; 12.5 μg of vitamin D, 10.0 g of protein with branched chain amino acids; 200kcal, 41% carbohydrate, 37% fat, 20%

Figure 1
Flow chart describing the study design