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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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ABSTRACT

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 $p < 0.05$.

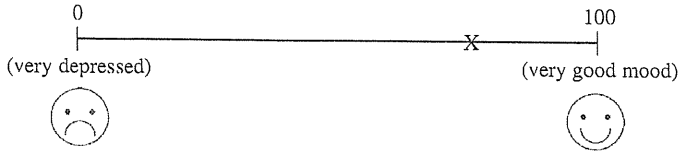
3. Results

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.

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.

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 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.

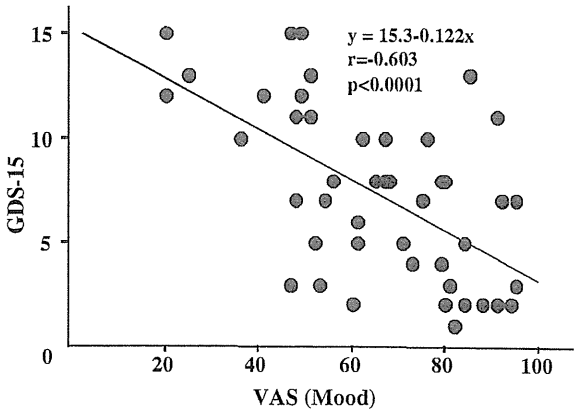


Fig. 3. Correlation between GDS-15 score and VAS in mood in elderly HD patients.

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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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.

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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.

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Differential effect of statins on diabetic nephropathy in db/db mice

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Abstract. Recent studies suggest a potential benefit of the lipid-lowering medication in the treatment of chronic kidney disease (CKD) such as diabetic nephropathy. Although statins have been widely used to lower serum cholesterol levels, the effect of these drugs on diabetic nephropathy has not been fully elucidated. In the present study, therefore, we addressed the role of different kinds of statins on diabetic nephropathy in db/db mice. Mice were fed with a standard diet with 0.005% (w/w) of pitavastatin, rosuvastatin, and pravastatin for 8 weeks starting from 8 weeks of age. The treatment with statins did not affect the food intake, body weight gain, adiposity, or blood pressure in db/db mice. Treatment with statins also had no effect on plasma lipid levels. In terms of the effect on albuminuria, pitavastatin and rosuvastatin reduced the urinary excretion of albumin by 60 and 40%, respectively, but not pravastatin, suggesting the effect of these two drugs on diabetic nephropathy. Furthermore, pitavastatin and rosuvastatin improved glomerular hypertrophy. All statins treatment improved insulin resistance. In addition, rosuvastatin and pravastatin treatment reduced oxidative stress measured by urinary 8-OHdG level, whereas the statins had no effect on the inflammatory response in the kidney of db/db mice. These results are not consistent with the renoprotective effect of statins. In conclusion, our data suggest that pitavastatin and rosuvastatin can improve diabetic nephropathy through the suppression of glomerular hypertrophy, independent of lipid-lowering or anti-oxidative effects.

Introduction

Diabetic nephropathy is one of the most common forms of chronic kidney disease (CKD) and the most frequent cause of mortality in patients with diabetes (1,2). The number of people affected by diabetic nephropathy or who need renal replacement is steadily increasing (3). Therefore, the establishment of therapeutic strategies for diabetic nephropathy is needed. Diabetic nephropathy results from complex interactions between genetic, metabolic, and hemodynamic factors, and can be characterized by mesangial expansion followed by glomerulosclerosis and a decline in renal function. The development of glomerulosclerosis in diabetes mellitus is always preceded by persistent albuminuria and glomerular hypertrophy (2). Therefore, these two manifestations could be promising therapeutic targets for the treatment of diabetic nephropathy.

3-Hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase inhibitors (statins) are widely used for diabetic patients to reduce their cardiovascular risk (4). Statins also have renoprotective actions and have been shown to reduce albuminuria in both experimental and clinical diabetic renal disease (5-8). Some of these benefits may be due to lipid lowering, since lipid levels are strongly associated with the development and progression of diabetic kidney disease (9,10). On the other hand, statins have a range of lipid-independent actions on cell proliferation, inflammation, and oxidative stress (11,12), which may impact the development and progression of renal damage in diabetes. These pleiotropic effects have been suggested to contribute to the renoprotective effect of statins. However, the precise mechanisms of the renoprotective effects are not fully understood. In addition, whether different statins have the same effect on diabetic nephropathy is not well known.

In this study, we addressed the role of various statins, such as pitavastatin, rosuvastatin, and pravastatin on the development of diabetic nephropathy in db/db mice.

Materials and methods

Materials. Pravastatin and rosuvastatin were provided by Daiichi Sankyo Co., Ltd. and pitavastatin was provided by Kowa Pharmaceutical Co., Ltd.

Animal procedure and experimental design. Male db/db mice (n=24) and their lean control db/m (n=6) mice were obtained from Charles River at 6 weeks of age. The mice were fed with normal chow without additional supplementation (non-treated group) or with chow supplemented with 0.005% (w/w) pravastatin, pitavastatin or rosuvastatin for 8 weeks starting from 8

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Key words: statin, diabetic nephropathy, albuminuria, pleiotropic action

Table I. Characteristics of db/m and db/db mice treated with or without statins.

		db/db			
	db/m	Con	Pra	Pit	Ros
Body weight (g)	32.5±0.40	53.1±3.90	51.2±5.1	50.3±3.80	51.3±5.70
Liver weight (g)	1.15±0.29	2.99±0.41	2.78±0.54	2.55±0.36	3.19±0.85
eWAT weight (g)	0.37±0.05	3.23±0.25	3.08±0.59	3.01±0.41	3.10±0.62
Kidney weight (g)	0.31±0.07	0.50±0.02	0.51±0.06	0.42±0.01[a]	0.41±0.03[a]
Food intake (g/day)	3.82±0.33	7.45±2.43	7.15±0.72	7.70±1.65	7.04±1.58
SBP (mmHg)	NA	113.2±11.6	113.5±3.00	109.5±9.50	114.6±5.60

Con, control; Pra, pravastatin; Pit, pitavastatin; Ros, rosuvastatin; eWAT, epididymal white adipose tissue; SBP, systolic blood pressure. Results are expressed as mean ± SD (n=6 in each group). [a]P<0.05 vs. Con.

weeks of age. Animals had access to food and water *ad libitum* and were maintained on a 12-h light/dark cycle. All animal experiments were conducted according to the Guidelines for Animal Experiments at Kyoto University.

Analysis of metabolic parameter. Plasma glucose concentration was measured with a Glutest Ace (Sanwa Kagaku Kenkyusho Co., Ltd.). Plasma insulin concentration was measured with an insulin assay kit (Morinaga Institute of Biological Science). Plasma cholesterol and triglyceride levels were respectively measured with the Cholesterol E and Triglyceride E tests (Wako Pure Chemical Industries, Ltd.).

Measurement of urinary albumin and creatinine. Urinary albumin and creatinine were measured at 16 weeks of age from 24-h collection samples from mice housed in individual metabolic cages. During the urine collection, the mice were allowed free access to food and water. Albumin concentration in the urine was measured by Albuwell (Exocell). Urinary creatinine was measured with a Hitachi Mode 736 analyzer (Hitachi). The urinary albumin concentration was adjusted by the urinary creatinine concentration.

Measurement of urinary oxidative stress. Urinary 8-OHdG concentrations were measured at 16 weeks of age using a competitive enzyme-linked immunosorbent assay kit (8-OHdG Check, Japan Institute for the Control of Aging). Urinary 8-OHdG excretion was expressed as the total amount excreted in 24 h.

Quantitative real-time PCR. Total-RNA was extracted from frozen kidney tissue (50 mg) at 16 weeks of age using an RNeasy mini kit (Qiagen). The cDNA was synthesized from total-RNA using SuperScript III (Invitrogen). Real-time PCR was performed on an ABI PRISM 7900 using the SYBR-Green PCR Master Mix (Applied Biosystems). Primer sets were as follows: tumor necrosis factor (TNF)-α forward, 5'-CCCAGA CCCTCACACTCAGATC-3' and reverse, 5'-GCCACTCCAG CTGCTCCTC-3'; β-actin forward, 5'-TACCACAGGCATTG TGATGG-3' and reverse, 5'-TTTGATGTCACGCACGAT TT-3'. The mRNA levels were normalized relative to the amount of β-actin mRNA and expressed in arbitrary units.

Measurement of glomerular size. The mice were euthanized at 16 weeks of age. The kidneys were rapidly fixed in 10% formaldehyde, and embedded in paraffin. Paraffin sections were cut at 3 μm. For measurement of the glomerular size, paraffin sections were stained with hematoxylin and eosin. The size of the glomerular surface area was measured using the Image-Pro Plus software version 3.0.1 (Media Cybernetics, Inc.).

Statistical analysis. Data are expressed as the mean ± SD. Multiple comparisons among the groups were conducted by one-way analysis of variance with Fisher's PLSD test for post hoc analysis. P-values of <0.05 were considered significant.

Results

Effect of statin treatment on body weight, adiposity and systolic blood pressure. In db/db mice fed with a standard diet for 8 weeks starting at 8 weeks of age, body weight, epididymal white adipose tissue (eWAT) weight, liver weight were increased compared to those of db/m mice. Treatment with statins had no effect on body weight, food intake, liver weight and eWAT weight in db/db mice (Table I). In addition, there was no difference in systolic blood pressure between statin-treated and non-treated db/db mice.

Effect of statin treatment on renal function in db/db mice. Because albuminuria reflects renal function (13), we measured the urinary excretion of albumin in normal chow-fed db/db mice at 16 weeks of age. Urinary excretion of albumin was markedly increased in db/db mice compared with db/m mice (Fig. 1). Pitavastatin, rosuvastatin, but not pravastatin improved albuminuria in db/db mice. Kidney weights in pitavastatin- and rosuvastatin-treated db/db mice were reduced compared with non-treated db/db mice (Table I). These data suggest that pitavastatin and rosuvastatin treatment improves renal function in db/db mice.

Effect of statin treatment on plasma lipid level in db/db mice. To clarify the mechanism by which statins ameliorated renal function, we first examined the effect of statin treatment on lipid metabolism in db/db mice. Plasma triglyceride and total cholesterol level were increased in non-treated db/db mice compared with db/m mice (Fig. 2A and B). On the other hand,

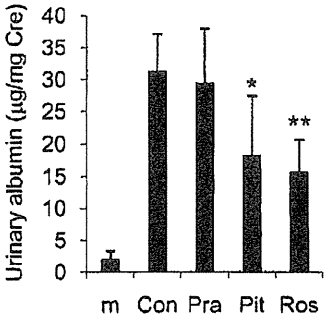

Figure 1. Effect of statins on renal function in db/db mice. The graph shows the urinary excretion of albumin in db/m mice (m), non-treated (Con), pravastatin-treated (Pra), pitavastatin-treated (Pit) and rosuvastatin-treated (Ros) db/db mice. Results are expressed as mean ± SD. *P<0.05, **P<0.01 vs. non-treated db/db mice (n=6 in each group).

statin treatment had no effect on plasma lipid levels in db/db mice (Fig. 2A and B), suggesting that the renoprotective effect of statins is independent of their lipid-lowering action.

Effect of statin treatment on insulin resistance in db/db mice. It has been reported that the development of insulin resistance contributes to renal dysfunction (14). Therefore, we next examined the effect of statin treatment on glucose metabolism in db/db mice. Blood glucose level, plasma insulin level, and HOMA-IR were markedly increased in db/db mice compared with db/m mice, indicating an increase in insulin resistance (Fig. 2C-E). Although statin treatment had no effect on plasma glucose, all statins reduced plasma insulin levels, resulting in a decrease in HOMA-IR (Fig. 2C-E). The data suggest that statin treatment improves insulin resistance.

Because hypoadiponectinemia is associated with the development of insulin resistance and kidney disease (15), we examined the effect of statin treatment on plasma adiponectin levels in db/db mice. In non-treated db/db mice, plasma adiponectin levels were decreased compared with db/m mice. Meanwhile, statin treatment had no effect on plasma adiponectin level in db/db mice (Fig. 2F).

Effect of statin treatment on the renal inflammation in db/db mice. Accumulating evidence now indicates that inflammatory mechanisms play a significant role in the development and progression of diabetic nephropathy. Especially, TNF-α is a pleiotropic inflammatory cytokine and has been shown to cause enhanced albumin permeability (16). Therefore, we next examined the effect of statin treatment on inflammation in the kidney of db/db mice. The expression of TNF-α mRNA was increased in the kidney of db/db mice compared with that of db/m mice, whereas statin treatment had no effect on its expression in db/db mice (Fig. 3A). These data suggest that statins had no effect on the inflammatory response in the kidneys of db/db mice.

Effect of statin treatment on the oxidative stress in db/db mice. To examine the effect of statin treatment on oxidative stress, we measured urinary 8-OHdG concentrations in db/db mice. Urinary 8-OHdG levels in non-treated db/db mice were significantly higher than those in db/m mice. Pravastatin and rosuvastatin reduced urinary 8-OHdG levels in db/db mice, whereas pitavastatin had no effect on oxidative stress despite detecting the amelioration of albuminuria (Fig. 3B).

Effect of statin treatment on glomerular hypertrophy in db/db mice. Glomerular hypertrophy is a hallmark in diabetic

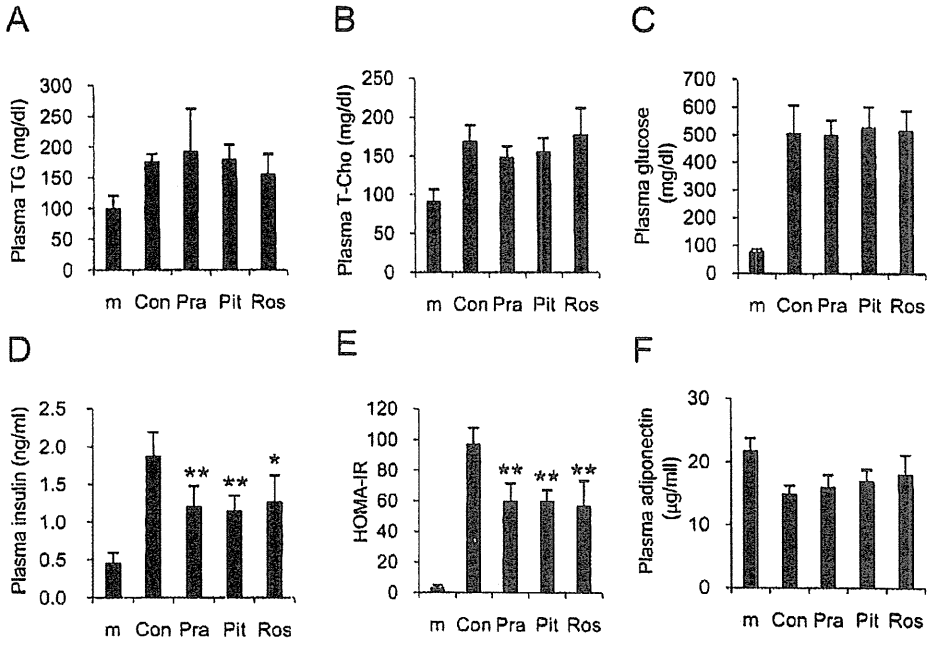

Figure 2. Effect of statins on lipid and glucose metabolism in db/db mice. (A) Plasma triglyceride (TG), (B) total cholesterol (T-Cho), (C) glucose, (D) insulin, (E) HOMA-IR and (F) adiponectin levels in db/m mice (m), non-treated (Con), pravastatin-treated (Pra), pitavastatin-treated (Pit) and rosuvastatin-treated (Ros) db/db mice. Results are expressed as mean ± SD. *P<0.05, **P<0.01 vs. non-treated db/db mice (n=6 in each group).

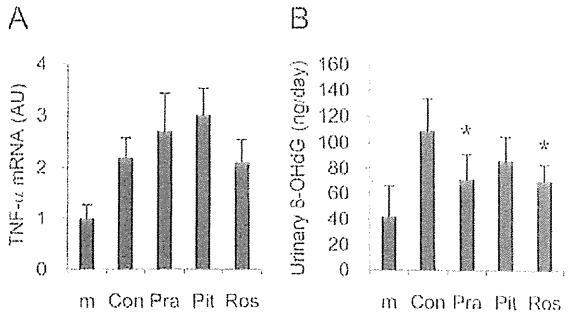

Figure 3. Effect of statins on renal inflammation and oxidative stress in db/db mice. (A) Expression of TNF-α mRNA in whole kidney and (B) urinary 8-OHdG levels in db/m mice (m), non-treated (Con), pravastatin-treated (Pra), pitavastatin-treated (Pit) and rosuvastatin-treated (Ros) db/db mice. Results are expressed as mean ± SD. P<0.05 vs. non-treated db/db mice (n=6 in each group).

nephropathy along with albuminuria. Therefore, we assessed the glomerular hypertrophy in db/db mice and the effect of statins by measuring the glomerular surface area. Mean glomerular surface area size in db/db mice was increased compared with db/m mice. Pitavastatin and rosuvastatin treatment, but not pravastatin treatment, suppressed the glomerular hypertrophy as well as urinary excretion of albumin in db/db mice (Fig. 4).

Discussion

In the present study, we showed that pitavastatin and rosuvastatin treatment improved albuminuria and suppressed glomerular hypertrophy, independent of its lipid-lowering and anti-oxidative effect in db/db mice.

In CKD patients, there is an increase in total cholesterol and LDL levels (17). The level of cholesterol is directly correlated with the degree of albuminuria (18), suggesting that hyperlipidemia is associated with the development of CKD such as diabetic nephropathy. In fact, lipid-lowering therapy by statin has been successful to the amelioration of renal function in patients with diabetic nephropathy (19,20). However, the present study and other animal studies showed that statin treatment significantly improved renal function without affecting the plasma lipid profile (5,8,21). Therefore, the renoprotective effect of statins may be mainly caused by its pleiotropic action rather than their lipid-lowering action.

Insulin resistance is associated with the development of renal dysfunction in type 2 diabetes. It has been shown that insulin resistance correlates with the onset of microalbuminuria in patients with type 2 diabetes as well as in nondiabetic subjects (14). Several studies showed that amelioration of insulin resistance resulted in a restoration of renal function (22-24). Statin also has an ability to ameliorate insulin resistance. Takagi *et al* (25) reported that pravastatin treatment improved insulin resistance through the increase in plasma adiponectin levels in db/db mice. In the present study, we also observed that all statin treatment improved insulin resistance detected by the reduction of HOMA-IR, while adiponectin was not altered by statin treatment in db/db mice. However, this amelioration was not consistent with the renoprotective effects of statins in db/db mice.

Oxidative stress and inflammation are also far more prevalent in CKD patients than in normal subjects (26). In the present study, we also observed the elevation of oxidative stress and inflammation in the kidneys of db/db mice compared with that of lean control mice. Renal disease is associated with a graded increase in oxidative stress markers even in early CKD (27). This oxidative stress can accelerate renal injury progression. In addition, inflammatory markers such as C reactive protein and cytokines increase with renal function deterioration suggesting that CKD is a low-grade inflammatory process (28). Therefore, the agents which have anti-oxidative and anti-inflammatory action have been attracted as a therapeutic strategy for renal dysfunction (29). Anti-oxidative and anti-inflammatory actions are also major pleiotropic effects of statins (12). Several reports have shown that these actions of statins contribute to their renoprotective effects (5,30,31). In the present study, we also observed that pravastatin and rosuvastatin suppressed oxidative stress in db/db mice as well as these reports, whereas we could not detect the anti-inflammatory effect of statins in the kidneys of db/db mice. Pitavastatin had no effect on oxidative stress, despite the presence of the restored renal function in db/db mice. This result suggests that the anti-oxidant action of statins is not primarily responsible for their renoprotective effect.

In the present study, we observed a correlation between the renoprotective effects of statins and their suppressive effect

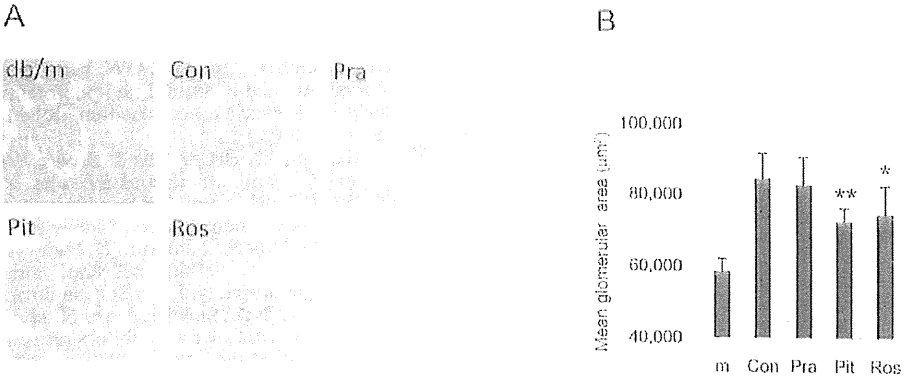

Figure 4. Effects of statins on the glomerular hypertrophy in db/db mice. (A) H&E staining of glomeruli (magnification, x200) and (B) mean glomerular surface area of db/m mice (m), non-treated (Con), pravastatin-treated (Pra), pitavastatin-treated (Pit) and rosuvastatin-treated (Ros) db/db mice. The mean area of fifty glomeruli per mouse was analyzed. Results are expressed as mean ± SD. P<0.05, P<0.01 vs. non-treated db/db mice (n=6 in each group).

of glomerular hypertrophy in db/db mice. The glomerular morphological changes in diabetic nephropathy are characterized primarily by mesangial expansion and glomerular based membrane (GBM) thickening. It has been reported that the dysregulated cell cycle by the increased inhibitor of cyclin dependent kinase (such as p21 and p27) contributes to these morphological changes and renal dysfunction (32,33). Pleiotropic effects of statins on the cell cycle are well known (12). Furthermore, Danesh *et al* (34) reported that statin treatment normalized the cell cycle through the suppression of p21 expression in high glucose-stimulated mesangial cells. In the present study, pleiotropic effects of statin on the cell cycle thus might improve glomerular hypertrophy and albuminuria. However, further study is required to clarify the effect of statins in glomerular hypertrophy and renal dysfunction.

In conclusion, we have shown the effects of various statins on diabetic nephropathy in db/db mice. Our study suggests that its renoprotective effect is mainly dependent on suppressing the glomerular hypertrophy, independent of its lipid-lowering or anti-oxidative effects, and there may be differences in the renoprotective ability between various statins.

Acknowledgements

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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

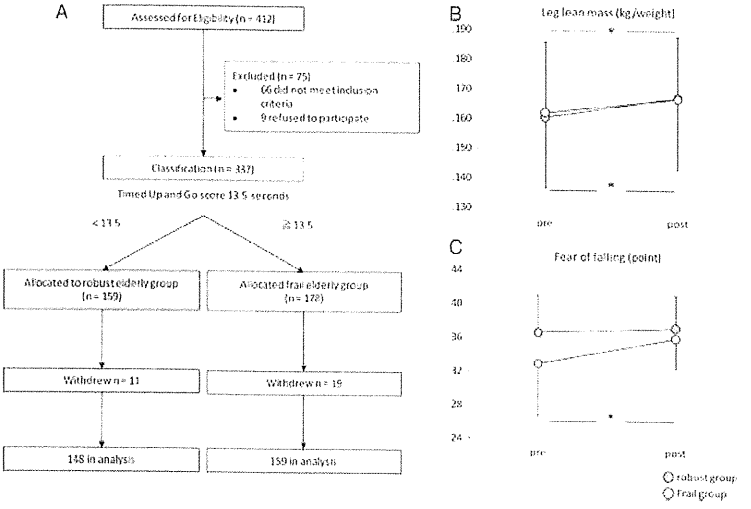

Figure 1. (A) Flow chart showing the disposition of participants throughout the trial. (B) LLM after resistance training in the robust and frail groups was significantly increased from baseline ($P < 0.05$). (C) The frail group had significantly greater improvements in fear of falling ($P < 0.025$).