disturbance, cognition, transfer, and urinary continence, which are risk factors of falls identified by previous studies. Most items were evaluated by nurses' subjective judgment. The advantage of this tool is that nurses can finish the assessment in a relatively short period of time at an early phase of hospitalization and repeat the assessment during hospitalization. However, it was not clear how accurate nurses can assess the cognitive function of elderly patients with this tool. To this end, we tried to investigate whether or not nurses can accurately judge cognitive impairment in elderly patients using this tool by comparing the data independently obtained by mini-mental state examination (MMSE)[13] performed by a trained clinical assistant.

The aim of this study was, therefore, to examine the relationship between the clinical judgment of nurses on cognitive function during fall risk assessment and independently MMSE scores in elderly inpatients.

2. Methods

2.1. Designs

The design of this study was a cross-sectional study.

2.2. Participants and data collection

In this study we collected data from medical records for 63 inpatients who received comprehensive geriatric assessment (CGA) during hospitalization at the Department of Geriatric Medicine of Kyoto University Hospital from January 2006 to June 2010. The data was collected from CGA of inpatients judged as frail by attending physicians. All inpatients received fall risk assessment as usual care.

Of 63 inpatients, one patient was excluded because CGA was performed after more than one month of clinical judgment and the other was due to missing information. The remaining 61 inpatients were analyzed for this study.

The approval for this study was obtained from Kyoto University Graduate School and Faculty of Medicine Ethics Committee (No. E1042, 2010). Patients were informed about our study at Kyoto University Hospital and the Department of Geriatric Medicine, Kyoto University website.

2.3. Measurements

Cognitive function was evaluated by four items in the fall risk assessment tool on admission, at least within 24 hours after admission by primary nurses, in which nurses clinically judged cognitive function of each patient. The nurses judged the presence or absence of disorientation, impaired judgment, lack of comprehension, and memory loss. The fall risk assessment tool including these items was applied to prevent falls for almost all patients in our hospital.

CGA was conducted less than 30 days of the initial hospital stay. The mean ± standard deviation of the period from admission to evaluation was 8.0 ± 6.0 days. The information was collected on socio-demographic data, living environment, health status and hospitalization data. We collected data to assess functional and cognitive status, and depressed mood by MMSE and geriatric depression scale (GDS), and so forth. MMSE was performed by a trained clinical assistant and the patients were divided into three groups according to MMSE scores. Patients with MMSE scores from 0 to 17 points were classified as moderate to severe impairment, those from 18 to 23 points as mild impairment, and those from 24 to 30 points as slight or no impairment.[14]

2.4. Statistical analysis

We described mean ± standard deviation or median, minimum and maximum for the continuous variable and numbers and percentages for the discrete variable. Liner regression models were constructed to examine the association of nurse's judgments on cognitive function with the MMSE scores. Additionally, at least one of the four abnormalities of judgment by nurses was compared in the two groups according to the MMSE scores using Chi-square test. The cutoff of these groups was 24.

The Statistical Package for Social Sciences, version 18.0 J (SPSS Japan Inc., Tokyo, Japan) was used for statistical analysis. All probability values were two-tailed with a significant level of $p < 0.05$.

3. Results

Table 1 shows the characteristics and main measurements of the patients. The mean age was 80.1 years and 55.7% of them were female. The median of their hospitalization length was 19 days. Of the 61 patients, 56 were discharged to home (91.8%). In terms of their cognitive function, 36% of the patients were judged to have memory loss, which was the highest among the four items. Twenty-six percent of the patients were judged to have impaired judgment, 21% lack of comprehension, and 13% disorientation. Furthermore, 43% of the patients were judged to have at least one of the four abnormalities. The median of MMSE scores was 26.

Table 2 shows the percentage of cognitive impairment judged by nurses in each group of patients classified according to their MMSE scores. Twenty-five percent of patients with moderate to severe impairment, 21% with mild impairment, and 9.3% with slight or no impairment were judged to be disoriented, respectively. Although no statistically significant association was found between disorientation and MMSE scores (p for trend = 0.053), the percentage of patients judged to have disorientation in the moderate to severe impairment group tended to be higher than those with slight or no impairment. In terms of impaired judgment, 75% of the patients with moderate to severe impairment, 36% with mild impairment, and 19% with slight or no impairment were judged to have impaired judgment, respectively. As a result, the percentage of patients judged to have impaired judgment was significantly higher in patients with lower MMSE scores (p for trend = 0.001). In lack of comprehension, 50% of the patients with moderate to severe impairment, 21% with mild impairment, and 19% with slight or no impairment were judged to have lack of comprehension,

Table 1
Characteristics and main measurements of the inpatients

	All n = 61
Age; years	80.1 ± 6.0
Gender, female (%)	34 (55.7)
Length of stay in the hospital, days	19 [5, 56]
Place after discharge from the hospital	
Home	56 (91.8)
Other hospitals	3 (4.9)
Other departments	2 (3.3)
Cognitive function of judgment by nurses	
Disorientation	8 (13.1)
Impaired judgment	16 (26.2)
Lack of comprehension	13 (21.3)
Memory loss	22 (36.1)
At least one of the 4 abnormalities	26 (42.6)
Mini-Mental State Examination scores	26 [13, 30]

Number(%).
Mean ± standard deviation or median [minmum, maximum].

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Table 2
Relationship between nurses' clinical judgment and Mini-Mental State Examination scores

	Moderate to severe impairment n = 4	Mild impairment n = 14	Slight or no impairment n = 43	p for trend
Cognitive function of judgment by nurses				
Disorientation	1 (25.0)	3 (21.4)	4 (9.3)	0.053
Impaired judgment	3 (75.0)	5 (35.7)	8 (18.6)	0.001
Lack of comprehension	2 (50.0)	3 (21.4)	8 (18.6)	0.043
Memory loss	3 (75.0)	7 (50.0)	12 (27.9)	0.001
At least one of the 4 abnormalities	4 (100)	9 (64.3)	13 (30.2)	<0.001

Number (%).
All patients were divided into 3 groups according to MMSE scores.
0-17points: moderate to sever impairment
18-23points: mild impairment
24-30points: slight or no impairment
A liner trend test was used with the discrete value in each groups according to the MMSE scores in liner regression models.

respectively. The percentage of patients judged to have lack of comprehension was significantly higher in patients with lower MMSE scores (p for trend = 0.043). In memory loss, 75% of patients with moderate to severe impairment, 50% with mild impairment, and 28% with slight or no impairment were judged to have memory loss, respectively. The percentage of patients judged to have memory loss was significantly higher in patients with lower MMSE scores (p for trend = 0.001). Finally, all patients with moderate to severe impairment, 64% with mild impairment, and 30% with slight or no impairment were judged to have at least one of the four abnormalities, respectively. The percentage of patients judged to have at least one of the four abnormalities was significantly higher in patients with lower MMSE scores (p for trend <0.001).

In the 14 patients with mild impairment, nine were judged to have at least one of the four abnormalities and five were not. Although those five patients were not judged to have impaired cognition using the four items by nurses at admission, four were judged to have at least one of the four abnormalities at the second time of evaluation by nurses during hospitalization. The second evaluation by nurses was performed from 1 to 2 weeks after admission. Thus, most of the patients were judged to have at least one of the four abnormalities by nurses at the second assessment (data not shown). Therefore, we assume that it takes time for nurses to assess the cognitive function of inpatients.

Fig. 1 shows how many of the patients with mild to severe impairment or slight to no impairment can be judged to have at least one abnormality by nurses. The patients with mild to severe impairment determined by MMSE were more likely to be judged to have at least one of the four abnormalities than those with slight or no impairment (p = 0.002). However, nurses could not detect impaired cognition using the four items in one-third of the patients with mild to severe impairment determined by MMSE, while they judged to have some kind of cognitive impairment in one-third of the patients with slight to no impairment.

Fig. 2 shows the number of items judged to have abnormality in four items on cognitive function by nurses in each group of patients classified according to their MMSE scores. There was no relationship between the number of items judged to have abnormality and the level of cognitive function according to MMSE scores.

4. Discussion

In the present study, we demonstrated that the percentage of patients judged by nurses to have cognitive impairment were

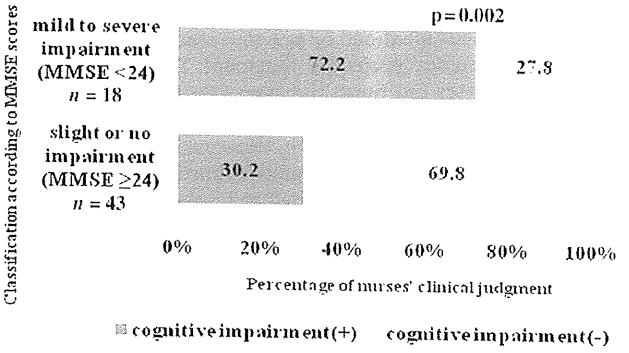

Fig. 1. The percentage of patients to be judged to have at least one abnormality by nurses in patients with mild to severe cognitive or slight to no impairment by MMSE. The difference was determined using Chi-square test.

higher in elderly patients with lower MMSE scores than those with higher MMSE scores. Despite using the four items to detect cognitive impairment, our study demonstrated that the assessment used by nurses was not completely successful to evaluate the cognitive function of elderly patients.

According to our data, nurses could not detect impaired cognition with the four items in one-third of the patients with mild impairment determined by MMSE. This percentage was unexpectedly high. We assume that it is difficult for nurses to accurately assess patient's cognitive function at admission; however, nurses could detect impaired cognition in patients with mild impairment at the second assessment, which was done 1 to 2 weeks after admission. Thus, it is conceivable that nurses may not have obtained sufficient information for the assessment at admission. However, most falls in hospital occur within a week.[15] In addition, demented patients have a markedly increased fall and fracture risk, almost two times more in comparison with nondemented elderly.[16–18] Furthermore, diminished motor control is related to cognitive status in older adults. Thus, changes in cognitive function may contribute to an increased fall risk. Accordingly, it is necessary

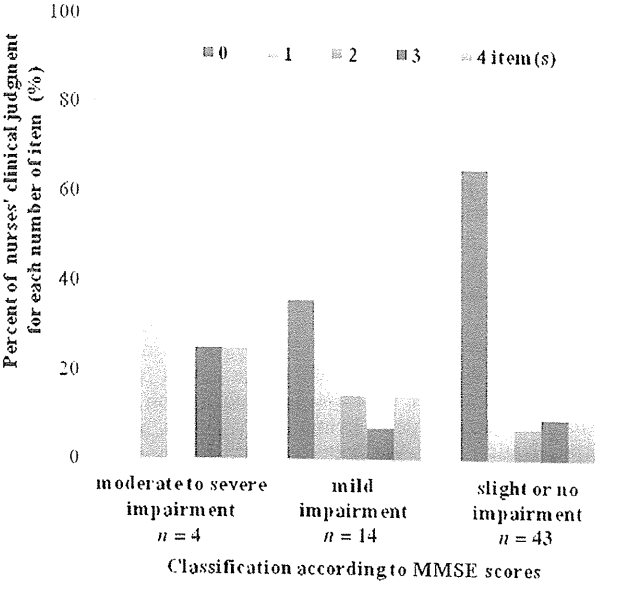

Fig. 2. The number of items judged to have abnormality in four items on cognitive function by nurses in each group of patients classified according to their MMSE scores.

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for nurses to assess even mild cognitive impairment as well as severe impairment at an early stage of admission.[19] According to these results, it is conceivable to think that we should develop a better fall assessment tool to detect mild cognitive impairment and educate nurses to assess patients with cognitive impairment more accurately. However, generally speaking, screening of cognitive function by nurses should be aimed for higher sensitivity than higher specificity.

Although all patients with moderate to severe impairment were judged to have at least one of the four abnormalities, they were not completely judged to have each abnormality. It is suggested that a comprehensive evaluation using all of the four items of cognitive impairment is better to evaluate than using each item at admission. The percentage of patients judged by nurses to have memory loss was the highest among the four items. In contrast, the percentage of patients judged by nurses to have disorientation was the lowest. Nurses obtain information of patients during nursing care including active daily life assistance. It is extremely difficult to confirm whether a patient recognizes date, a day of the week, and a place during active daily life assistance. However, it is easy to assess whether or not a patient forgets recent episodes, to repeat the same questions and talks, and forgets where he or she puts something. The most likely explanation is that the judgment of disorientation is more difficult to assess than memory loss. Therefore, the judgment of disorientation might be unnecessary in this tool.

Many studies have shown the development of effective several assessment tools to identify fall risk in the elderly at high risk in institutionalized settings.[11,12] Many hospitals have implemented routine screening to assess fall risk for a patient, followed up with a more focused assessment of those deemed to be at high risk.[11,12] In addition, previous study showed that nurses' clinical judgments could predict falls of a patient as well as fall risk assessment tool.[20–22] However, these studies did not indicate how nurses made successful predictions. They only implicated that the intuition by nurses can predict falls. Because of this, we thought it necessary to show the validity of nurses' clinical judgment by performing MMSE in frail geriatric patients.

Several potential limitations should be considered when interpreting these results. First, the two measurements used in this study, four items of cognitive impairment in the fall risk assessment tool and MMSE, were not evaluated at the same time so information bias could occur. However, we excluded the data in which CGA was performed after more than one month of clinical judgment. Clinical judgment by nurses was also performed at admission, and all of the patients were judged by nurses before MMSE. The nurses were not informed of the patients' MMSE scores. Thus, the evaluation of MMSE did not affect nurses' clinical judgment. Second, we did not investigate the experience of nurses which might have affected the results. Third, the education level in the patients was also a confounding factor in this study. Information about the education levels of the patients was not obtained, because the literacy rate is extremely high in Japan and the education levels of Japanese patients is quite similar. Therefore, we assumed that the effect of educational levels would be minimal. Finally, the patients were limited those who admitted only to the Department of Geriatric Medicine in one university hospital and selected for CGA. It could be difficult to generalize these results.

In conclusion our data indicated that a comprehensive evaluation using all of the four items on cognitive impairment more effective in detecting cognitive impairment in elderly than using individual items. However, one-third of cognitively impaired elderly patients based on the result of MMSE were not accurately assessed by nurses despite using the four items on cognition, while the presence of disorientation assessed by nurses was not able to predict cognitive impairment based on the results of MMSE. Therefore, disorientation in this tool should be deleted in the future. Furthermore, it is important to repeat nurses' assessment on cognition after 1 or 2 weeks of admission because cognition levels might change after the acute phase. It is important to educate nurses to assess patients with cognitive impairment more accurately.

Acknowledgments

We thank Drs. Tsuboyama and Nagao in Kyoto University, who allowed us to analyze the fall risk assessment tool. We also thank Priscila Yukari Sewo Sampaio for the critical reading of our manuscript.

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Original Article

Ezetimibe Ameliorates Early Diabetic Nephropathy in db/db Mice

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Lipid-lowering medications have been suggested to have a potential benefit in the treatment of chronic kidney disease (CKD) such as diabetic nephropathy. Although ezetimibe has been widely used to lower serum cholesterol levels, the effect of this drug on diabetic nephropathy remains unclear. In the present study, therefore, we examined the protective effect of ezetimibe on diabetic nephropathy in db/db mice. Db/db mice were fed a standard diet with 0.01% (w/w) of ezetimibe for 8 weeks from 8 weeks of age. Treatment with ezetimibe did not affect food intake, body weight gain, adiposity, or blood pressure in db/db mice. Ezetimibe also had no effect on glucose metabolism such as fasting plasma glucose and insulin; however, it markedly reduced plasma lipid levels and hepatic lipid contents and reduced the urinary excretion of albumin by 50% in db/db mice, suggesting the effect of ezetimibe on diabetic nephropathy. Furthermore, ezetimibe improved glomerular hypertrophy. Although ezetimibe had no effect on oxidative stress measured by urinary 8-OHdG in db/db mice, the plasma adiponectin level was normalized, and the expression of adiponectin receptor 1 in the kidney was increased by ezetimibe treatment. In conclusion, our data suggest that ezetimibe can improve early diabetic nephropathy through its hypolipidemic effect, and the amelioration of adiponectin resistance may also be responsible for the renoprotective effect of ezetimibe as its underlying mechanism.

J Atheroscler Thromb, 2012; 19:000-000.

Key words; Ezetimibe, Diabetic nephropathy, Albuminuria, Adiponectin

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]. Furthermore, CKD such as diabetic nephropathy is strongly associated with the development of cardiovascular disease[4, 5]; therefore, the establishment of therapeutic strategies for diabetic nephropathy is awaited. Diabetic nephropathy results from complex interactions among 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 preceded by persistent albuminuria and glomerular hypertrophy[2]; therefore, these two manifestations are promising therapeutic targets for the treatment of diabetic nephropathy.

Hypercholesterolemia has been suggested to be associated with the development of diabetic nephropathy[6]. In fact, lipid-lowering therapy using 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase inhibitors (statins) has been successful for the amelioration of diabetic nephropathy[7, 8]. Ezetimibe, another lipid-lowering drug that selectively inhibits cholesterol absorption by inhibiting Niemann-Pick

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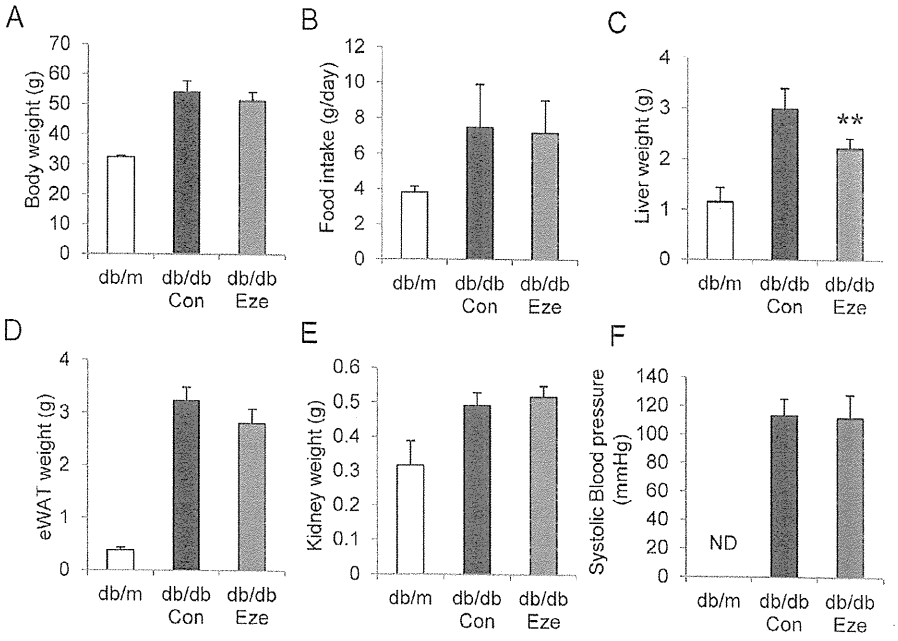


Fig. 1. Effect of ezetimibe on body weight, adiposity, and blood pressure in db/db mice at 16 weeks of age. The graphs show body weight (A), food intake (B), liver weight (C), epididymal white adipose tissue (eWAT) weight (D), kidney weight (E), systolic blood pressure (F) in db/m mice and non-treated (Con) or ezetimibe-treated (Eze) db/db mice. Results are expressed as the mean ± S.D. $^{**}p < 0.01$ vs. non-treated db/db mice ($n = 6$ in each group). ND: not determined.

C1-Like 1 (NPC1L1) protein, is also used for the treatment of dyslipidemia[9, 10]. In addition to its effect on hyperlipidemia, ezetimibe has been reported to ameliorate renal dysfunction such as non-diabetic nephropathy[11] and nephropathy after transplantation[12]; however, the effects of ezetimibe on diabetic nephropathy remain undetermined. In the present study, therefore, we examined the renoprotective effects of ezetimibe on diabetic nephropathy in db/db mice.

Methods

Animal Procedure and Experimental Design

Male db/db mice ($n = 12$) and their lean control db/+m ($n = 6$) mice were obtained from Charles River Laboratories Japan, Inc. (Yokohama, Japan) at 6 weeks of age. Db/db mice were fed with normal chow without additional supplementation (non-treated group, $n = 6$) or with chow supplementation with 0.01% (w/w) ezetimibe ($n = 6$) for 8 weeks from 8 weeks of age. Animals were provided with the diet and water ad libitum and were maintained on a 12-hour light/dark cycle. All animal experiments were conducted according to the Guidelines for Animal Experiments at Kyoto University.

Analysis of Metabolic Parameters

Blood samples were collected after fasting the mice for 16 h. Fasted plasma glucose concentration was measured with Glutest Ace (Sanwa Kagaku Kenkyusho Co, Ltd, Nagoya, Japan). Fasted plasma insulin concentration was measured with an insulin assay kit (Morinaga Institute of Biological Science, Yokohama, Japan). Serum total cholesterol (T-Cho), triglyceride (TG) and cholesterol contents of each lipoprotein fraction were analyzed by Skylight Biotech, Inc. (Tokyo, Japan). Serum adiponectin was measured with a Mouse/Rat Adiponectin ELISA kit (Otsuka Pharmaceuticals, Tokushima, Japan). Serum total protein, creatinine, and BUN were analyzed by SRL, Inc. (Tokyo, Japan).

Measurement of Hepatic Lipid Content

Hepatic triglyceride and cholesterol contents were measured with Triglyceride E and Cholesterol E test (Wako Pure Chemical Industries Ltd., Osaka, Japan) as previously described[13]. Tissue triglyceride

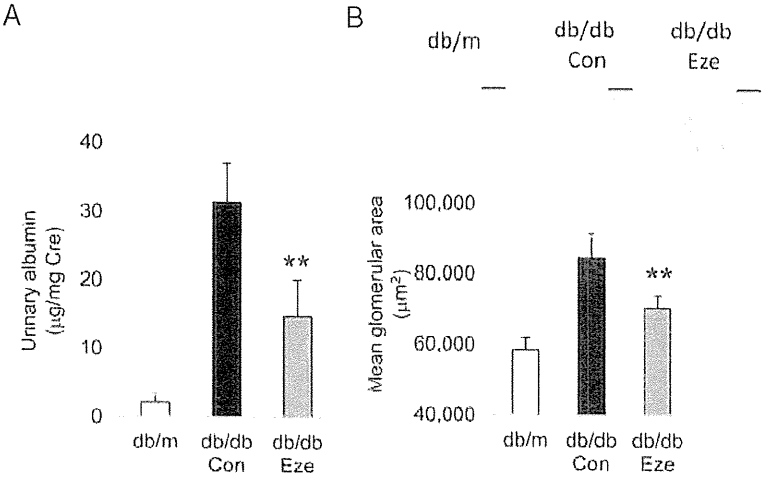


Fig. 2. Effect of ezetimibe on renal function in db/db mice at 16 weeks of age. Urinary excretion of albumin (A), HE staining of glomeruli (magnification ×400, bar; 50 μm) and mean glomerular surface area (B) of db/m mice, non-treated (Con), ezetimibe-treated (Eze) db/db mice. Fifty glomeruli per mouse were analyzed. Results are expressed as the mean ± S.D. $^{**}p<0.01$ vs. non-treated db/db mice ($n=6$ in each group).

Supplementary Table 1. Effect of Ezetimibe treatment on blood chemistry in db/db mice

	db/m	db/db Con	db/db Eze
Total protein (g/dL)	5.0 ± 0.5	5.9 ± 0.5	5.1 ± 0.7
BUN (mg/dL)	19.1 ± 3.5	20.1 ± 2.4	27.2 ± 7.6
Creatinine (μg/mL)	0.11 ± 0.03	0.08 ± 0.02	0.09 ± 0.03

Results are expressed as the means ± S.D. ($n=6$ in each group)

and cholesterol contents were expressed as mg/mg protein.

Measurement of Urinary Albumin and Creatinine

Urinary albumin and creatinine were measured at 16 weeks age using 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 Inc., Philadelphia, PA). Urinary creatinine was measured with a Hitachi Mode 736 analyzer (Hitachi, Tokyo, Japan). 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 (8OHdG Check; Japan Institute for the Control of Aging, Fukuroi, Japan). Urinary 8-OHdG excretion was expressed as the total amount excreted in 24 h.

Measurement of Glomerular Size

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. To measure glomerular size, paraffin sections were stained with hematoxylin and eosin. The glomerular area was measured using Image Pro plus software version 3.0.1 (Media Cybernetics Inc., Bethesda, MD).

Quantitative Real-Time PCR

Total RNA was extracted from frozen adipose tissue (100 mg) and kidney tissue (30 mg) using an RNeasy mini kit (Qiagen, Valencia, CA). The cDNA was synthesized from total RNA using Super Script III (Invitrogen). Real-time polymerase chain reaction was performed on an ABI PRISM 9700 using the SYBR GREEN polymerase chain reaction Master Mix

(Applied Biosystems, Warrington, UK). Primer sets were as follows: TNF alpha forward: CCCAGACCCTCACACTCAGATC, reverse: GCCACTCCAGCTGCTCCTC, Nox2 forward: TTGGGTCAGCACTGGCTCTG, reverse: TGGCGGTGTGCAGTGCTATC, Nox4 forward: ATTTGGATAGGCTCCAGGCAAAC, reverse: CACATGGGTATAAGCTTTGTGAGCA, $p22^{phox}$ forward: GTCCACCATGGAGCGATGTG, reverse: CAATGGCCAAGCAGACGGTC adiponectin receptor 1 (AdipoR1) forward: ACGTTGGAGAGTCATCCCGTA, reverse: CTCTGTGTGGATGCGGAAGAT, adiponectin receptor 2 (AdipoR2) forward: TGCCAGGAAGATGAAGGGTTTAT, reverse: TTCCATTCGTTCGATAGCATGA, β-actin forward: TACCACAGGCATTGTGATGG, reverse: TTTGATGTCACGCACGATTT. The mRNA levels were normalized relative to the amount of β-actin mRNA and expressed in arbitrary units.

Statistical Analysis

Data are expressed as the mean ± S.D. Multiple comparisons among the groups were conducted by one-way analysis of variance with Fisher's PLSD test for post-hoc analysis. Pearson's correlation was used to find a correlation between two continuous variables. $P<0.05$ was considered significant.

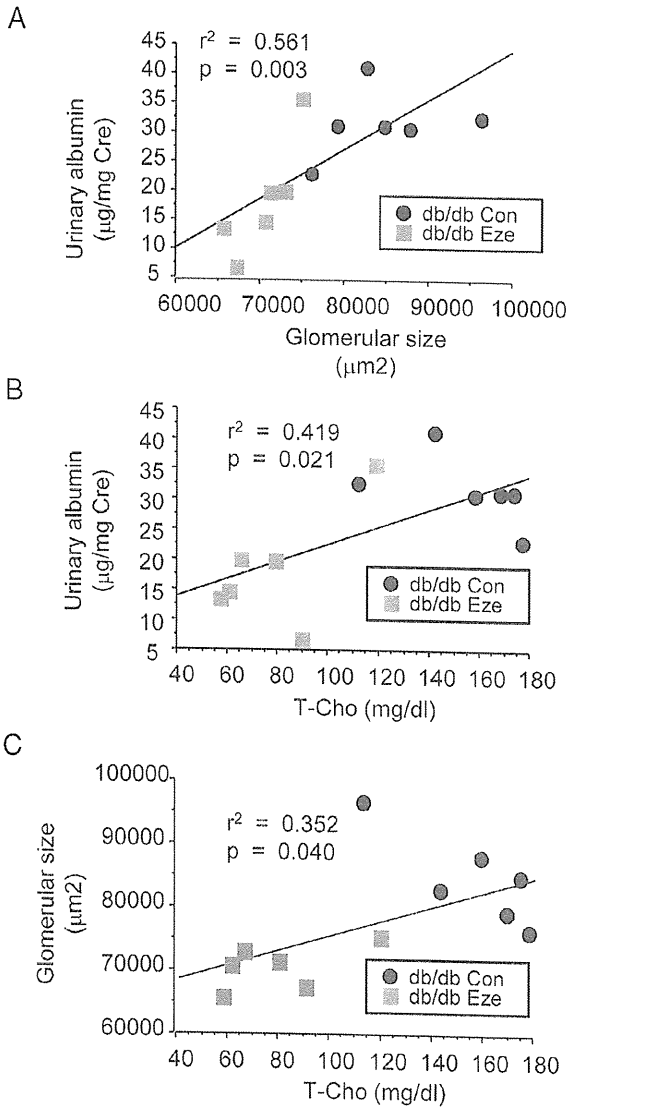
Results

Effect of Ezetimibe Treatment on Body Weight, Adiposity, and Systolic Blood Pressure

In db/db mice fed with a standard diet for 8 weeks until 16 weeks of age, body weight, epididymal white adipose tissue (eWAT) weight, liver weight, and kidney weight were increased compared with db/m mice (**Fig. 1A-E**). Although ezetimibe treatment reduced liver weight in db/db mice, body weight, food intake, eWAT weight, and kidney weight were not changed (**Fig. 1A-E**). In addition, there was no difference in systolic blood pressure between ezetimibe-treated and non-treated db/db mice (**Fig. 1F**).

Effect of Ezetimibe Treatment on Renal Dysfunction in db/db Mice

Because albuminuria reflects renal dysfunction at early diabetic nephropathy[14], we measured 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. 2**); however, ezetimibe treatment reduced urinary excretion of albumin by 50% in db/db mice (**Fig. 2**). There was no difference in serum total protein, creatinine, or BUN levels between db/m and non-treated db/db mice. Ezetimibe treatment also had no effect on these variables in db/db mice (**Supplementary Table 1**). These data suggest that ezetimibe ameliorates early diabetic nephropathy in db/db mice.



Supplementary Fig. 1. The correlation between the effect of ezetimibe on urinary albumin and glomerular size (A), urinary albumin and serum T-Cho level (B), glomerular size and serum T-Cho level (C) in db/db mice.

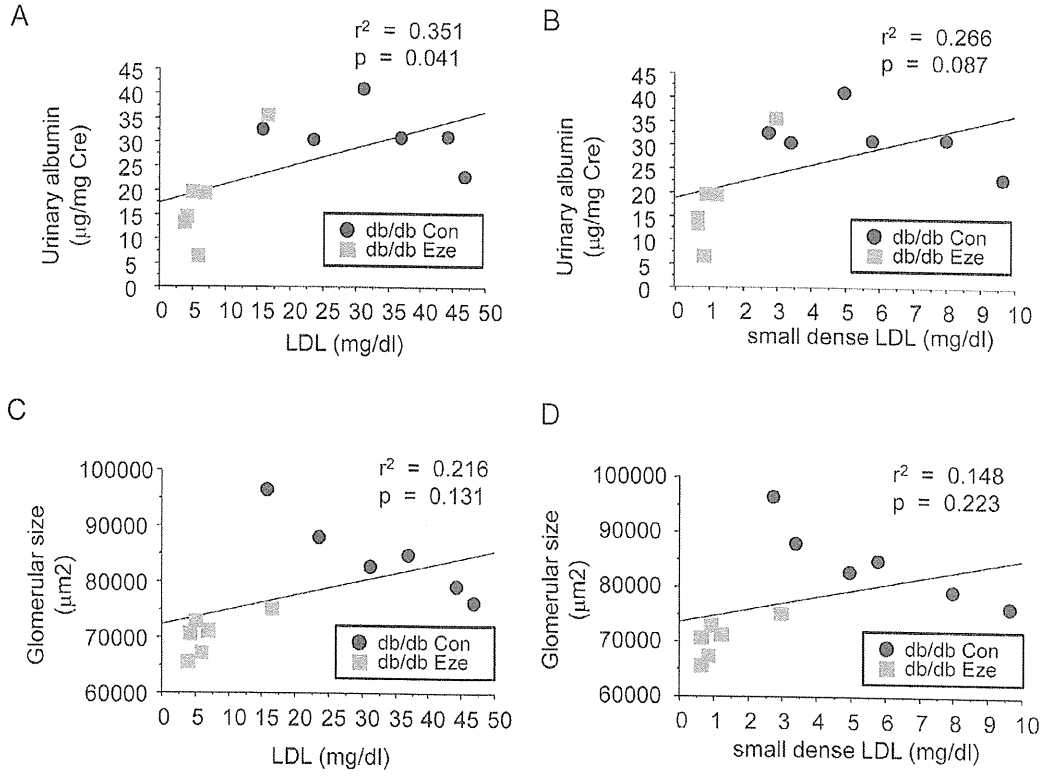
Effect of Ezetimibe Treatment on Glomerular Hypertrophy in db/db Mice

Glomerular hypertrophy is a marker of diabetic nephropathy along with albuminuria; therefore, we checked glomerular hypertrophy in db/db mice and

Table 1. Effect of ezetimibe treatment on serum lipid in db/db mice

	db/m	db/db Con	db/db Eze
Triglyceride (mg/dL)	50.9 ± 10.2	59.0 ± 23.3	64.8 ± 27.4
Total Cholesterol (mg/dL)	77.8 ± 2.2	150.3 ± 26.8	78.7 ± 23.1**
Chylomicron (mg/dL)	0.8 ± 0.5	1.9 ± 0.6	0.9 ± 0.5*
VLDL cholesterol (mg/dL)	4.2 ± 1.5	7.0 ± 1.6	4.3 ± 3.0
LDL cholesterol (mg/dL)	6.7 ± 1.1	30.4 ± 11.1	7.1 ± 4.8**
HDL cholesterol (mg/dL)	66.1 ± 1.5	111.0 ± 17.6	66.4 ± 16.2**
Small dense LDL cholesterol (mg/dL)	2.4 ± 0.4	5.0 ± 2.1	1.2 ± 0.9**

Results are expressed as the means ± S.D. (n=6 in each group)
*p<0.05, **p<0.01 vs db/db Con group

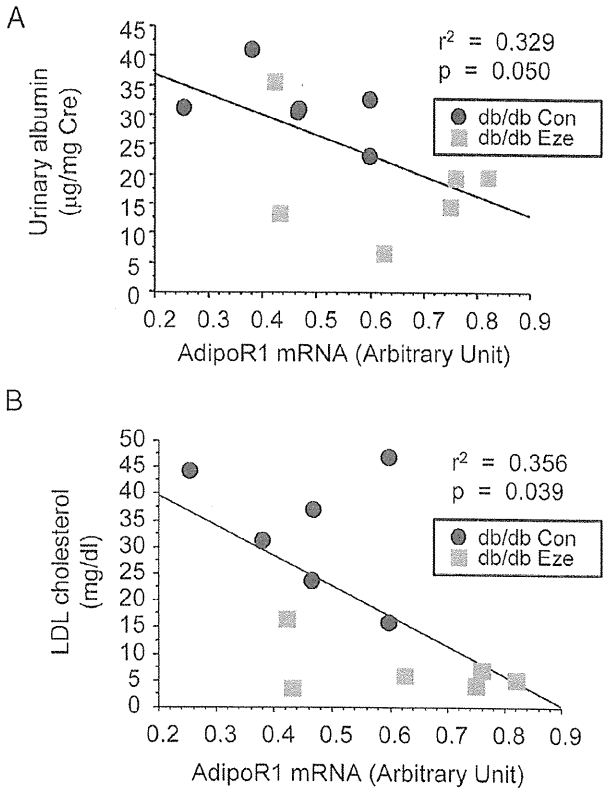


Supplementary Fig. 2. The correlation between the effect of ezetimibe on urinary albumin and LDL cholesterol (A), urinary albumin and small dense LDL cholesterol (B), glomerular size and LDL cholesterol (C), glomerular size and small dense LDL cholesterol (D) in db/db mice.

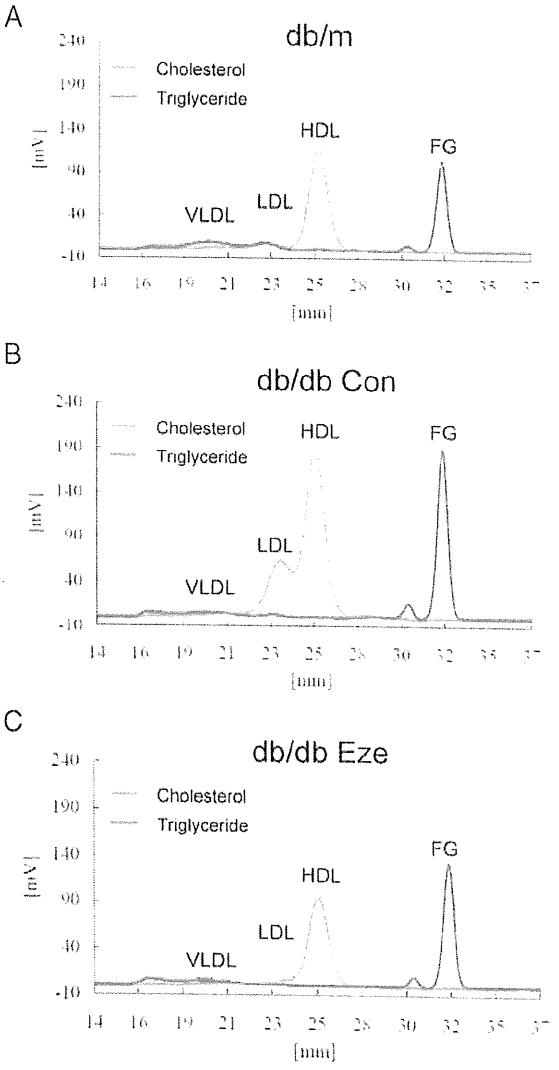
the effect of ezetimibe by measuring the glomerular surface area. Mean glomerular surface area size in db/db mice was increased compared with db/m mice; however, ezetimibe treatment suppressed glomerular hypertrophy in db/db mice (**Fig. 2B**). Furthermore, there was a significant correlation in the effect of ezetimibe treatment on glomerular hypertrophy and albuminuria in db/db mice (**Supplementary Fig. 1A**).

Effect of Ezetimibe Treatment on Lipid Metabolism in db/db Mice

To clarify the mechanisms by which ezetimibe improves renal dysfunction, we next examined the effect of ezetimibe treatment on lipid metabolism in db/db mice. Serum TG levels were not affected by ezetimibe treatment in db/db mice (**Table 1** and **Supplementary Fig. 4**). Serum T-Cho levels were



Supplementary Fig. 3. The correlation between the effect of ezetimibe on urinary albumin and AdipoR1 expression in the kidney (A), LDL cholesterol and AdipoR1 expression in the kidney (B) of db/db mice.



Supplementary Fig. 4. Graph of cholesterol (pink line) and triglyceride (blue line) contents in each fraction of lipoprotein in db/m (A), non-treated db/db mice (B) and ezetimibe-treated db/db mice (C). FG: free glycerol.

increased in non-treated db/db mice compared with in db/m mice; however, ezetimibe treatment normalized T-Cho levels in db/db mice (**Table 1** and **Supplementary Fig. 4**). Furthermore, ezetimibe treatment reduced chylomicron, LDL, small dense LDL, and HDL cholesterol levels in db/db mice (**Table 1** and **Supplementary Fig. 4**). In addition, hepatic TG and T-Cho contents in db/db mice were reduced by ezetimibe treatment (**Fig. 3**), suggesting that ezetimibe treatment improves hepatic steatosis.

Effect of Ezetimibe Treatment on Insulin Resistance in db/db Mice

It has been reported that ezetimibe treatment improves insulin resistance, which is associated with the development of diabetic nephropathy[15, 16]; therefore, we next examined the effect of ezetimibe treatment on glucose metabolism in db/db mice. Fasted plasma glucose, the 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. 4**); however, ezetimibe treatment had no effect on glucose metabolism in db/db mice.

Effect of Ezetimibe Treatment on Oxidative Stress in Kidney of db/db Mice

To examine the effect of ezetimibe treatment on oxidative stress, we measured urinary 8-OHdG levels in db/db mice. Urinary 8-OHdG levels in non-treated db/db mice were significantly higher than those in db/m mice; however, ezetimibe had no effect on urinary 8-OHdG levels in db/db mice (**Fig. 5A**). Furthermore, mRNA expressions of Nox2 and Nox4, the substrate

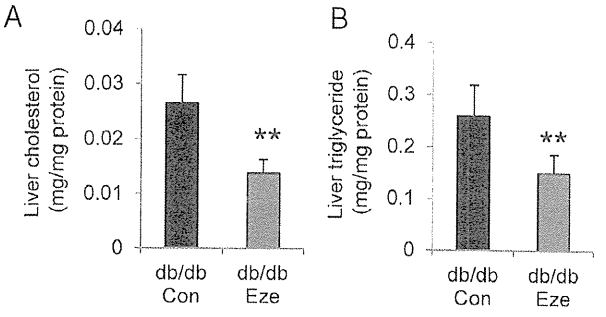


Fig. 3. Effect of ezetimibe on hepatic steatosis in db/db mice at 16 weeks of age. Hepatic triglyceride content (A), hepatic cholesterol content (B) in db/m mice, non-treated (Con), ezetimibe-treated (Eze) db/db mice. Results are expressed as the mean ± S.D. $^{**}p < 0.01$ vs. non-treated db/db mice ($n = 6$ in each group).

of NADPH oxidase, were not altered by ezetimibe treatment in the whole kidney of db/db mice (**Supplementary Fig. 5**). These data suggest that ezetimibe has no effect on oxidative stress in the kidney of db/db mice.

Effect of Ezetimibe Treatment on Hypoadiponectinemia

Because hypoadiponectinemia is associated with the development of kidney disease[17], we examined the effect of ezetimibe treatment on serum adiponectin levels in db/db mice. In non-treated db/db mice, serum adiponectin levels were decreased compared with db/m mice; however, ezetimibe treatment normalized serum adiponectin levels in db/db mice (**Fig. 5B**).

Effect of Ezetimibe on Inflammation and Oxidative Stress in Adipose Tissue

Because inflammation and oxidative stress in adipose tissue are a major cause of hypoadiponectinemia[18], we examined the effect of ezetimibe treatment on the expression of inflammatory cytokines and an oxidative stress marker in db/db mice. TNF-α mRNA expression was markedly increased in non-treated db/db mice compared with in db/m mice (**Fig. 6A**); however, ezetimibe treatment reduced TNF-α mRNA expression in db/db mice, suggesting that it suppresses adipose tissue inflammation in db/db mice. Furthermore, oxidative stress markers such as Nox2 and $p22^{phox}$ mRNA expression were decreased by ezetimibe treatment in db/db mice (**Fig. 6B, C**), suggesting that ezetimibe treatment suppresses oxidative stress in adipose tissue of db/db mice.

Effect of Ezetimibe Treatment on the Expression of Adiponectin Receptor (AdipoR) in the Kidney and Adipose Tissue in db/db Mice

We next examined the effect of ezetimibe on the expression of AdipoR1 and AdipoR2 in the kidney and adipose tissue of db/db mice. AdipoR1, but not AdipoR2, was abundantly expressed in the kidney as well as in adipose tissue (**Fig. 7**). There were no differences in mRNA expression of AdipoR1 and AdipoR2 in adipose tissue and the expression of AdipoR2 in the kidney among db/m mice, non-treated and ezetimibe-treated db/db mice; however, mRNA expression of AdipoR1 was decreased in the kidney of db/db mice compared with db/+m mice. Intriguingly, ezetimibe treatment significantly increased mRNA expression of AdipoR1 in the kidney of db/db mice (**Fig. 7**).

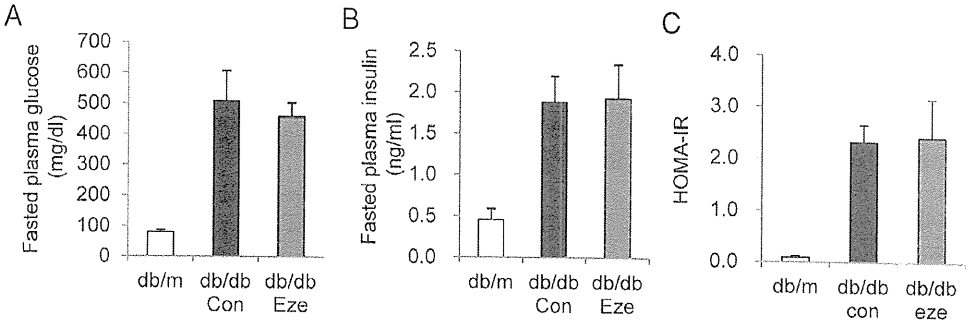


Fig. 4. Effect of ezetimibe on glucose metabolism in db/db mice at 16 weeks of age. Fasted plasma glucose (A), Fasted plasma insulin level (B) and HOMA-IR (C) in db/m mice, non-treated (Con), ezetimibe-treated (Eze) db/db mice. Results are expressed as the mean ± S.D. $^{*}p < 0.05$ vs. non-treated db/db mice ($n = 6$ in each group).

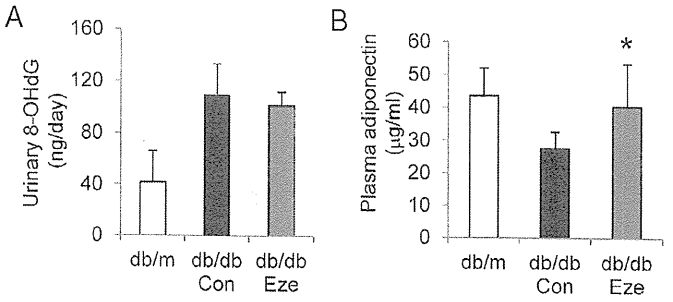
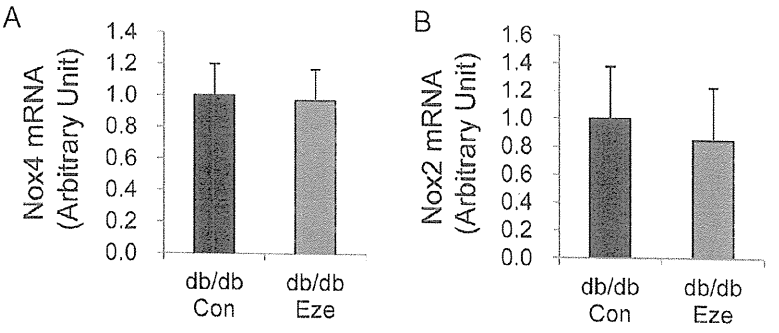


Fig. 5. Effect of ezetimibe on renal oxidative stress and hypoadiponectinemia in db/db mice at 16 weeks of age. Urinary 8-OHdG level (A) and serum adiponectin level (B) in db/m mice, non-treated (Con), ezetimibe-treated (Eze) db/db mice. Results are expressed as the mean ± S.D. $^{*}p<0.05$ vs. non-treated db/db mice ($n=6$ in each group).



Supplementary Fig. 5. Effect of ezetimibe on oxidative stress in whole kidney of db/db mice. Expression of Nox4 mRNA (A) and Nox2 mRNA (B) in non-treated (Con) or ezetimibe-treated (Eze) db/db mice. Results are expressed as the mean ± S.D.

Discussion

In the present study, we showed that ezetimibe treatment improved hyperlipidemia, albuminuria, and glomerular hypertrophy in db/db mice, implying a beneficial role of ezetimibe in early diabetic nephropathy[19].

Ezetimibe is an anti-hyperlipidemic medication that is used to lower cholesterol levels in addition to statins[9]. Specifically, it appears to bind to a critical mediator of cholesterol absorption, NPC1-L1, on gastrointestinal tract epithelial cells[10]. In the present study, we observed a correlation between the effect of ezetimibe on albuminuria and on the T-Cho level in db/db mice (**Supplementary Fig. 1B**). These data suggest that ezetimibe improves diabetic nephropathy through its hypolipidemic action, and provide further evidence for the importance of hyperlipidemia in the development of diabetic nephropathy. Ezetimibe treatment also markedly reduced LDL cholesterol and small dense LDL cholesterol in db/db mice, consistent with the effect in humans[8, 20]. In the present study, we found a correlation between the effect of ezetimibe treatment on albuminuria and on the LDL cholesterol level, but not on the small dense LDL cholesterol level in db/db mice; therefore, the effect of ezetimibe on LDL cholesterol might be associated with the amelioration of diabetic nephropathy in this model.

In this study, we found no effect of ezetimibe on the urinary 8-OHdG level and the expression of oxidative stress markers in the kidney of db/db mice, whereas ezetimibe significantly reduced oxidative stress in the adipose tissue of db/db mice, suggesting that the renoprotective effect of ezetimibe is not directly due to reduced oxidative stress in the kidney. Nevertheless, ezetimibe has been reported to have an anti-oxidative effect in non-diabetic individuals[11].

Several human and animal studies have reported

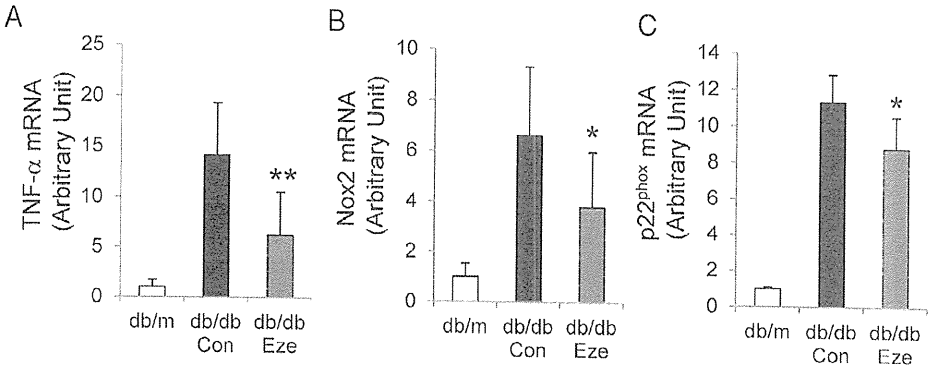


Fig. 6. Effect of ezetimibe on inflammation and oxidative stress in adipose tissue of db/db mice. The mRNA expression of TNF-α (A), Nox2 (B) and $p22^{phox}$ (C) in db/m mice, non-treated (Con), ezetimibe-treated (Eze) db/db mice. Results are expressed as the mean ± S.D. $^{*}p<0.05$ vs. non-treated db/db mice ($n=6$ in each group).

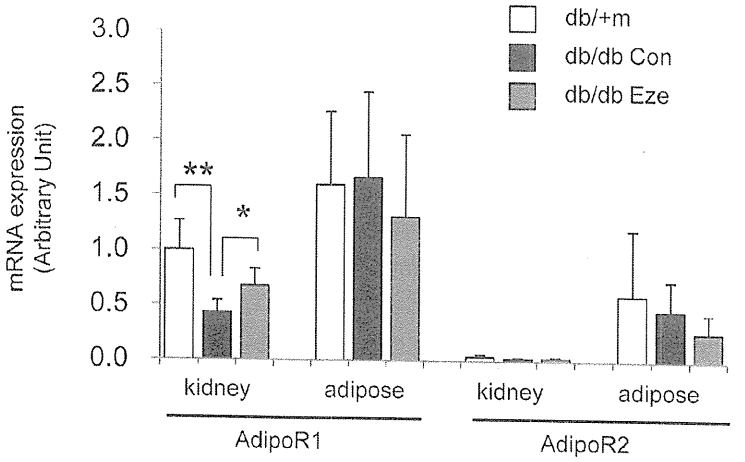


Fig. 7. Effect of ezetimibe on mRNA expression of adiponectin receptor 1 (AdipoR1) and 2 (AdipoR2) in the kidney and adipose tissue of db/m mice and non-treated (Con) and ezetimibe-treated (Eze) db/db mice. Results are expressed as the mean ± S.D. $^{*}p<0.05$, $^{**}p<0.01$ ($n=6$ in each group).

that hypoadiponectinemia is associated with renal dysfunction[21-23]. In the present study, we observed the improvement of hypoadiponectinemia by ezetimibe treatment in db/db mice; however, we did not find a correlation between the effect of ezetimibe on albuminuria and on adiponectin in db/db mice (data not shown), suggesting that improvement of hypoadiponectinemia may not be responsible for the renoprotective effect of ezetimibe in db/db mice. In contrast, we found a negative correlation between the effect of ezetimibe on albuminuria and AdipoR1 expression in the kidney of db/db mice (**Supplementary Fig. 3A**). Furthermore, we also observed a negative correlation between the effect of ezetimibe on AdipoR1 expression in the kidney and the LDL cholesterol level in db/db mice (**Supplementary Fig. 3B**). Guo *et al.* reported decreased adipoR1 expression in the kidney of diabetic rats, suggesting the existence of adiponectin resistance in diabetic nephropathy[24]. Taken together, whether renoprotection by ezetimibe occurs through alteration of the adiponectin effect remains to be determined.

We also observed that ezetimibe treatment suppressed the expression of pro-inflammatory cytokines such as TNF-α in adipose tissue of db/db mice. TNF-α can dose-dependently reduce the expression of

adiponectin in adipocytes by suppressing its promoter activity[25]; however, we did not find any correlations among the effect of ezetimibe on the serum adiponectin level, TNF-α expression in adipose tissue, and serum lipid profiles in db/db mice. We thus speculate that ezetimibe has pleiotropic effects, which might not be mutually interrelated.

Insulin resistance is also 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 non-diabetic subjects[16]. In the present study, we observed marked elevation of plasma glucose and insulin in db/db mice, indicating the development of insulin resistance. Because it has been reported that ezetimibe improved hepatic insulin resistance[15], we examined the effect of ezetimibe on the glucose metabolism; however, ezetimibe had no effect on systemic insulin resistance in db/db mice despite the increase in serum adiponectin. These data indicate that the renoprotective effect of ezetimibe in db/db mice was independent of systemic insulin-sensitizing action.

Ezetimibe can be used for hypercholesterolemic patients who exhibit statin resistance or suffer adverse effects of statin treatment[26]. Recently, combination therapy with a statin and ezetimibe showed efficacy and safety compared with high-dose statin therapy in patients with hypercholesterolemia[27]. Therefore, combination therapy of statins and ezetimibe as well as ezetimibe monotherapy might be useful for the treatment of diabetic nephropathy associated with hyperlipidemia[28].

In conclusion, our data suggest that ezetimibe can improve diabetic nephropathy through its hypolipidemic action, and the amelioration of adiponectin resistance may be responsible for the renoprotective effect of ezetimibe as its underlying mechanism.

Acknowledgements

We thank Nami Sawada (Kyoto University) for excellent technical assistance. This study was supported by Takeda Science Foundation.

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Geriatr Gerontol Int 2012

ORIGINAL ARTICLE

Indications and practice for tube feeding in Japanese geriatricians: Implications of multidisciplinary team approach

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Aim: The aim of this study was to examine how geriatricians decide the indication of tube feeding in the elderly with eating difficulty as a result of several disorders, and to determine the factors associated with their decision making and interventions for dysphagia.

Methods: The design was a cross-sectional study. All board-certified geriatricians in the Japan Geriatrics Society were recruited to this study in September 2010. We sent questionnaires to 1469 geriatricians. Among them, 629 agreed to participate. The survey consisted of self-administered questionnaires regarding demographic information, indications of tube feeding and interventions for dysphagia before tube feeding.

Results: We analyzed the remaining 555 questionnaires after excluding incomplete ones. Over 90% of geriatricians answered that "neurological disorder" and "stroke" are indications, whereas 46.8% of them answered that "dementia" is an indication for tube feeding. Geriatricians who organize a multidisciplinary team conference tended to carry out more "interventions for dysphagia before the prescription of tube feeding" compared with the reference group (odds ratio 2.1–8.7) after multivariate adjustment.

Conclusions: The results show that approximately half of the geriatricians prescribe tube feeding when the patient has dementia with loss of appetite or apraxia for eating. There is no consensus among Japanese geriatricians about the indication of tube feeding for demented people. We suggest that guidelines for tube feeding in the elderly should be established. Furthermore, a multidisciplinary approach would be desirable for decision making for tube feeding. **Geriatr Gerontol Int 2012; ••: ••–••.**

Keywords: elderly, geriatrician, multidisciplinary team, percutaneous endoscopic gastrostomy, tube feeding.

Introduction

Many older patients have nutritional problems caused by eating difficulties as a result of stroke, cancer, dementia and other conditions. When the patients have a functional gastrointestinal tract and they cannot take sufficient nutrition orally, tube feeding is an option. Percutaneous endoscopic gastrostomy (PEG) is the preferential route when enteral nutrition is expected to last for a longer period of time, because it is associated with better nutritional status and a lower incidence of aspiration than nasogastric tube (NGT).[1] PEG was originally developed for pediatric use by Gauderer in 1980.[2] However, thereafter PEG has become the most

Accepted for publication 2011 December 25.

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doi: 10.1111/j.1447-0594.2011.00831.x

common way to supply artificial enteral nutrition in the elderly, including dementia patients. The number of people on PEG is increasing because of the improved simplicity and safety. Approximately 5–30% of the advanced dementia patients in nursing homes are on tube feeding in Europe and the USA; whereas, in Japan, approximately 50% of those are on tube feeding.[3–6] Thus, the percentage of tube feeding including PEG for dementia patients is higher in Japan than that in Western countries. However, recent studies have questioned the appropriateness of tube feeding in these patients. The decision of the practice or the withholding of tube feeding in patients with dementia is a difficult challenge among geriatricians and many other health-care professionals, as they need to make a decision with clinical ethical dilemmas. Furthermore, the quality of life (QOL) in the elderly with tube feeding and its effect on long-term survival have not yet been clarified,[7–13] and neither has a guideline for tube feeding in the elderly, especially in dementia patients. Accordingly, tube feeding is the focus of some extremely complex legal and ethical questions. Therefore, it is important to study the current situation of tube feeding for the elderly in Japan.

When we make a decision on tube feeding, comprehensive assessment of the patient, such as nutrition, cognition and swallowing function, is important and the assessment should be based on a multidisciplinary team approach. Previous studies showed the effectiveness of inpatient geriatric evaluation and management; that is, comprehensive geriatric assessment (CGA).[14] A multidisciplinary approach might be required for medical and nursing care of elderly patients, especially when we need to make a complicated decision, such as that of tube feeding. However, it is unknown whether the team approach can affect the decision making for tube feeding and interventions for dysphagia.

Therefore, the aim of the present study was to examine how geriatricians decide on the indication of tube feeding in the elderly with eating difficulty as a result of various disorders, and to determine whether the team approach can affect their decision making and interventions for dysphagia.

Methods

The design was a cross-sectional study. All board-certified geriatricians in the Japan Geriatrics Society were recruited to the present study in September 2010. We separately sent self-administered questionnaires to 1469 geriatricians by post and collected them from October to December 2010. These geriatricians were chosen because of their experience in taking care of patients who require tube feeding, and carry out CGA by organizing multidisciplinary team conferences. The present study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (no. E984, 2010).

The questionnaires included demographic information, such as age, sex, place of employment, and clinical experience, reference guidelines for tube feeding, aims and indications of tube feeding in geriatrics, interventions for dysphagia before tube feeding, and multidisciplinary team approach if tube feeding is indicated. It was explained in the questionnaires that the term "elderly" was defined as people over the age of 75 years and those who require nursing care, and tube feeding included NGT, PEG and enterostomy tube.

We carried out descriptive analyses for each item in the questionnaire. The χ^2-test or t-test was used to compare the differences of place of employment and clinical experience. Logistic regression analyses were carried out to evaluate the differences of the frequencies and conference members according to the indication for tube feeding, and the interventions for dysphagia before tube feeding. Each item in the indication for tube feeding or interventions for swallowing disorder was adjusted for sex, working place and clinical experience of geriatricians. The frequency and number of members in a multidisciplinary conference were divided into five categories: not at all, occasional and less than five different health-care professionals, occasionally and ≧5 different health-care professionals, every time and less than five different health-care professionals, and every time and ≧5 different health-care professionals. The Statistical Package for Social Sciences version 18.0J (SPSS Japan, Tokyo, Japan) was used for statistical analysis. All probability values were two-tailed with a significant level of $P < 0.05$, and all confidence intervals were estimated at the 95% level.

Results

We sent a questionnaire to 1469 board-certified geriatricians, and 51 were returned as a result of being undeliverable because of wrong address. Among the rest, 629 agreed to participate in the present study. The response rate was 44.4%. After excluding the questionnaires with missing data, we analyzed the remaining 555 questionnaires. The prevalence of doctors aged over 60 years and male doctors was 34.6% and 89.2%, respectively. We found that 43.8% of the geriatricians had a clinical experience of more than 30 years, and 63.7% were working in acute hospitals, 30.7% in a clinic and 3.9% in long-term care facilities.

Table 1 shows the percentage of geriatricians who follow the guidelines and the purpose for tube feeding according to the geriatrician's place of employment and clinical experience. A total of 68% of geriatricians did not use any guideline for tube feeding. Among geriatricians following guidelines for tube feeding, 137 used "Guideline of Parenteral and Enteral Nutrition (EN) in

Table 1 Use of guidelines and the aims of tube feeding according to place of employment and clinical experience

Questions	Characteristics of geriatricians								Total
	Place of employment					Clinical experience			
	Hospital $n = 360$	Clinic $n = 166$	Long-term care $n = 20$	Other† $n = 9$	*P*-value	<30 years $n = 317$	≧30 years $n = 238$	*P*-value	$n = 555$
Do you use any guidelines for TF in geriatrics?‡									
Guideline of Parenteral and EN in Japan*1	84 (23.3)	48 (28.9)	4 (20.0)	1 (11.1)	ND	87 (27.4)	50 (21.0)	0.082	137 (24.7)
Guideline of PEG in Japan*2	51 (14.2)	21 (12.7)	4 (20.0)	1 (11.1)	ND	41 (12.9)	36 (15.1)	0.460	77 (13.9)
Guideline of Parenteral and EN in America*3	13 (3.6)	11 (6.6)	0 (0.0)	0 (0.0)	ND	11 (3.5)	13 (5.5)	0.253	24 (4.3)
Guideline of Parenteral and EN for elderly in Europe*4	9 (2.5)	11 (6.6)	0 (0.0)	1 (1.1)	ND	9 (2.8)	12 (5.0)	0.178	21 (3.8)
Not using guideline for TF	253 (70.3)	106 (63.9)	10 (50.0)	7 (77.8)	ND	209 (65.9)	167 (70.2)	0.291	376 (67.7)
What are the aims of TF in geriatrics?§									
Improvement of survival	63 (17.5)	29 (17.5)	6 (30.0)	0 (0.0)	ND	54 (17.0)	44 (18.5)	ND	98 (17.7)
Improvement of general condition and prevention of complications	201 (55.8)	93 (56.0)	12 (60.0)	3 (33.3)	–	163 (51.4)	146 (61.3)	–	309 (55.7)
Improvement of activities of daily living	17 (4.7)	9 (5.4)	0 (0.0)	1 (11.1)	–	22 (6.9)	5 (2.1)	–	27 (4.9)
Improvement of quality of life	24 (6.7)	9 (5.4)	2 (10.0)	2 (22.2)	–	24 (7.6)	13 (5.5)	–	37 (6.7)
Satisfaction of patient	15 (4.2)	13 (7.8)	0 (0.0)	2 (22.2)	–	19 (6.0)	11 (4.6)	–	30 (5.4)
Burden of caregiver	5 (1.4)	9 (5.4)	0 (0.0)	0 (0.0)	–	6 (1.9)	8 (3.4)	–	14 (2.5)
Length of hospital stay	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	–	3 (0.9)	0 (0.0)	–	3 (0.5)
Living will	27 (7.5)	3 (1.8)	0 (0.0)	1 (11.1)	–	20 (6.3)	11 (4.6)	–	31 (5.6)
Other	5 (1.4)	1 (0.6)	0 (0.0)	0 (0.0)	–	6 (1.9)	0 (0.0)	–	6 (1.1)

Number (%). *P*-values were tested by χ^2-test. †Other included part-time doctors, retired doctors, researchers and so on. ‡Multiple answers were allowed. §Simple answer was allowed for nine items. *1 From Japanese Society for Parenteral and Enteral Nutrition *2 From Japan Gastroenterological Endoscopy Society *3 From American Society for Parenteral and Enteral Nutrition *4 From European Society for Gastroenterological Endoscopy Society. EN, enteral nutrition; ND, not determined; PEG, percutaneous endoscopic gastrostomy; TF, tube feeding.

Japan" from the Japanese Society for Parenteral and EN. For the purpose for tube feeding, more than half of the geriatricians chose "improvement of general condition or prevention of complications." However, a few geriatricians chose "improvement of QOL," "satisfaction of patient" or "living will." The working place or clinical experience did not affect the aims of tube feeding placement.

Table 2 shows the indication for tube feeding and the interventions for dysphagia before tube feeding according to place of employment and clinical experience. Among the seven target indications for tube feeding in the elderly, over 90% of the geriatricians answered that "neurological disorders other than dementia" and "stroke" are indications for tube feeding. Over 80% of the geriatricians answered that "head injury or facial trauma" and "oropharyngeal malignancy" are also an indication. In contrast, 46.8% of the geriatricians answered that "dementia" is an indication for tube feeding, and 65.9% of the geriatricians answered that "aspiration-prone frail elderly without comorbidites" is an indication. The place of employment was not associated with the judgment for the indication. The percentage of geriatricians who answered that "head injury or facial trauma" and "neurological disorders other than dementia" were an indication for tube feeding was significantly higher in those with less than 30 years of clinical experience than in those with more than 30 years of clinical experience" (head injury or facial trauma; $P = 0.012$, neurological disorder; $P = 0.049$). However, following guideline for tube feeding did not affect the decision making of tube feeding for these disorders (data not shown). We also asked about the life expectancy of the patient after PEG placement, and 79.5% answered that at least more than 12 weeks were expected.

Next, we asked how many interventions they carried out for swallowing disorder before tube feeding. The mean number of interventions was 6.22, and geriatricians with less than 30 years of experience carried out significantly more interventions than those with more than 30 years (6.49 ± 3.2 *vs* 5.86 ± 2.8, $P = 0.015$). The number of interventions was not significantly different between geriatricians working in an acute hospital and those working in a clinic. Among 15 items of interventions for swallowing disorder, over 70% of geriatricians answered that "thickening agent" and "using semi-solid and liquid foods" were afforded to patients with swallowing disorder.

Figure 1 shows the percentage of geriatricians organizing a multidisciplinary conference for tube feeding. A total of 63% of geriatricians discussed with other health-care professionals every time or occasionally. They also answered that physicians including themselves (95.4%), primary nurses (84.9%), dieticians (49.7%) and speech therapists (42.0%) were the members of the conference. The place of employment was not associated with the number of conference members (Table 3).

Table 4 shows the multiple logistic regression analysis for the frequencies and conference members according to the indication for tube feeding and interventions for dysphagia before tube feeding. More "interventions for dysphagia before introducing tube feeding" were carried out in geriatricians organizing a multidisciplinary team conference than the reference group after multivariate adjustment (odds ratio 2.1–8.7). We also found that geriatricians who always organize a conference with many types of health-care professionals (multidisciplinary) carried out more tests for the assessment of swallowing function and interventions for dysphagia before introducing tube feeding, such as oral ice massage, than the reference group. However, the indications for tube feeding were not affected by a multidisciplinary conference.

Discussion

In the present study, we found that approximately 70 % of board-certified geriatricians did not use any guidelines for tube feeding in their practice. We also noted that the use of guidelines was not associated with the decision making for tube feeding in the elderly, because "Guideline of Parenteral and EN in Japan" or "Guideline of PEG in Japan" does not describe the indications for tube feeding in elderly patients, especially in dementia patients.[15,16] Furthermore, more than half of the geriatricians consider that the purpose of tube feeding is to improve the general condition or to prevent complications in the elderly with eating problems. In contrast, only a few geriatricians selected living will or patient satisfaction. Decision making of geriatricians for tube feeding did not seem to be related to their working place or clinical experiences. Although the guideline describes that "respecting the wishes of the family or living will of the patient when nutrition therapy is needed for the elderly at the terminal stage or with dementia,"[15] most geriatricians who decide the indication of tube feeding might not have a chance to care for patients' living will. Although there is an ideal description in the guideline, it might be difficult for doctors to obtain a patient's living will beforehand, even if they understand the importance of respecting the living will of the patient. Therefore, comprehensive approaches not only from the field of nutrition and gastroenterology, but also from the experience and know-how from the professionals involved in medicine, nursing and care for the elderly, such as geriatricians, nurses, speech therapists, caregivers and care managers, would be expected to make a new guideline for tube feeding in the elderly.

Several studies have shown that there is no survival benefit in dementia patients who receive artificial

Table 2 Indications for tube feeding and interventions for dysphagia before introducing tube feeding according to place of employment and clinical experiences

Questions	Characteristics of geriatricians Place of employment Hospital $n = 360$	Clinic $n = 166$	Long-term care $n = 20$	Other† $n = 9$	*P*-value	Clinical experience <30 years $n = 317$	≧30 years $n = 238$	*P*-value	Total $n = 555$
Is the following disorder an indication for TF?									
Head injury or facial trauma	313 (86.9)	144 (86.7)	8 (40.0)	7 (77.8)	ND	208 (88.3)	192 (80.7)	0.012	472 (85.0)
Oropharyngeal malignancy	286 (79.4)	143 (86.1)	13 (65.0)	7 (77.8)	ND	258 (81.4)	191 (80.3)	0.736	449 (80.9)
Neurological disorder	328 (91.1)	155 (93.4)	15 (75.0)	7 (77.8)	ND	295 (93.1)	210 (88.2)	0.049	505 (91.0)
Stroke	334 (92.8)	147 (88.6)	18 (90.0)	8 (88.9)	ND	290 (91.5)	217 (91.2)	0.899	507 (91.4)
Dementia	177 (49.2)	66 (39.8)	13 (65.0)	4 (44.4)	ND	1156 (49.2)	104 (43.7)	0.198	260 (46.8)
Aspiration-prone frail elderly without comorbidity	238 (66.1)	108 (65.1)	15 (75.0)	5 (55.6)	ND	216 (68.1)	150 (63.0)	0.208	366 (65.9)
Malnutrition in frail elderly without comorbidity	115 (31.9)	58 (34.9)	9 (45.0)	5 (55.6)	ND	115 (36.3)	72 (30.3)	0.137	187 (33.7)
How long does a patient need to survive after PEG placement?‡									
2 weeks	3 (0.8)	2 (1.2)	0 (0.0)	0 (0.0)	ND	3 (0.9)	2 (0.8)	ND	5 (0.9)
4 weeks	19 (5.3)	16 (9.6)	1 (5.0)	2 (22.2)	–	18 (5.7)	20 (8.4)	–	38 (6.8)
6 weeks	4 (1.1)	2 (1.2)	1 (5.0)	1 (11.1)	–	7 (2.2)	1 (0.4)	–	8 (1.4)
8 weeks	39 (10.8)	21 (12.7)	3 (15.0)	0 (0.0)	–	37 (11.7)	26 (10.9)	–	63 (11.4)
12 weeks	295 (81.9)	125 (75.3)	15 (75.0)	6 (66.7)	–	252 (79.5)	189 (79.4)	–	441 (79.5)
Interventions for swallowing disorder before introducing TF									
No. Interventions; mean ± standard deviation (total 15 items)	6.44 ± 3.12*	5.83 ± 2.93	6.70 ± 2.00	3.67 ± 3.32*	0.010§	6.49 ± 3.20	5.86 ± 2.82	0.015	6.22 ± 3.06
No. interventions, ≧6 items¶ (total 15 items)	211 (58.6)	84 (50.6)	14 (70.0)	2 (22.2)	ND	188 (59.3)	123 (51.7)	0.073	311 (56.0)
Consultation									
To otolaryngologist	131 (36.4)	60 (36.1)	3 (15.0)	4 (44.4)	ND	123 (38.8)	75 (31.5)	0.076	198 (35.7)
To speech therapist	166 (46.1)	31 (16.7)	7 (35.0)	1 (11.1)	ND	131 (41.3)	74 (31.1)	0.013	205 (36.9)
To certified nurse of dysphagia nursing	77 (21.4)	25 (15.1)	4 (20.0)	2 (22.2)	ND	67 (21.1)	41 (17.2)	0.250	108 (19.5)
Test									
Repetitive saliva swallowing test	111 (30.8)	63 (38.0)	4 (20.0)	2 (22.2)	ND	109 (34.4)	71 (29.8)	0.257	180 (32.4)
Water swallowing test	243 (67.5)	104 (62.7)	13 (65.0)	5 (55.6)	ND	210 (66.2)	155 (65.1)	0.783	365 (65.8)
Video endoscopy	55 (15.3)	26 (15.7)	1 (5.0)	0 (0.0)	ND	50 (15.8)	32 (13.4)	0.444	82 (14.8)
Video fluorography	163 (45.3)	47 (28.3)	4 (20.0)	2 (22.2)	ND	140 (64.8)	76 (31.9)	0.003	216 (61.1)
Practice and education									
Oral ice-massage	102 (28.3)	23 (13.9)	5 (25.0)	0 (0.0)	ND	86 (27.1)	44 (18.5)	0.017	130 (23.4)
Swallowing exercise	72 (20.0)	40 (24.1)	5 (25.0)	0 (0.0)	ND	70 (22.1)	47 (19.7)	0.505	117 (21.1)
Vocalization exercise	50 (13.9)	20 (12.0)	1 (5.0)	0 (0.0)	ND	44 (13.9)	27 (11.3)	0.376	71 (12.8)
Using semi-solid and liquid foods	267 (74.2)	120 (72.3)	18 (90.0)	3 (33.3)	ND	236 (74.4)	172 (72.3)	0.565	408 (73.5)
Thickening agent	308 (85.6)	131 (78.9)	20 (100.0)	3 (33.3)	ND	267 (84.2)	195 (81.9)	0.474	462 (83.2)
Positioning	235 (65.3)	106 (63.9)	17 (85.0)	4 (44.4)	ND	215 (67.8)	147 (61.8)	0.138	362 (65.2)
Appropriate approach for swallowing	161 (44.7)	80 (48.2)	12 (60.0)	2 (22.2)	ND	153 (48.3)	102 (42.9)	0.206	255 (45.9)
Ways of coping with aspiration	161 (44.7)	85 (51.2)	17 (85.0)	4 (44.4)	ND	142 (44.8)	125 (52.5)	0.071	267 (48.1)

Number (%), *P*-values were tested by χ^2-test and Student's *t*-test, †Other included part-time doctors, retired doctors, researchers and so on. ‡Single answer was allowed for five items, and the other questions were allowed to select more than one. §*P*-values were tested by ANOVA, *$P < 0.05$ by Bonferroni. ¶Number of intervention items were divided into two groups, which used median value (≧6 *vs* <6). ND, not determined; PEG, percutaneous endoscopic gastrostomy; TF, tube feeding.

feeding by PEG.[7,8,10,12] In addition, "Guideline of parenteral and EN for elderly in Europe" does not recommend enteral nutrition to persons with severe dementia as a result of more risks than benefits for persons with severe dementia, and occasionally in early and moderate dementia to ensure energy and nutrient supply and to prevent undernutrition.[17,18] In the present study, we found that approximately 45% of the geriatricians considered that dementia patients with loss of appetite or apraxia for eating should be on tube feeding and that 65% of the geriatricians considered that aspiration-prone frail elderly without comorbidities should also be on tube feeding, which is a relatively high percentage. In a previous study, approximately 60% of physicians in the USA answered that aspiration pneumonia was the indication for PEG placement, and was the most common medical indication.[19] The present finding are consistent with other results; therefore the medical situation in Japan might be quite similar to that in the USA. Indeed, PEG placement to the elderly with repeating aspiration pneumonia or not eating voluntarily with cerebrovascular disease or dementia is indicated in "Guideline of PEG in Japan."[16] In the present study, the questions did not specify the stage of disorders or the level of conditions; therefore our results should be interpreted with caution. However, it is certain that there is no consensus among Japanese geriatricians about tube feeding for the elderly with advanced dementia and there is an urgent need to develop guidelines to decide the risk/benefit ratio in the individual patient to optimize the timing and route of nutritional support. Thus, the indication for tube feeding in the elderly should be widely discussed in the future and hence a guideline should be established to describe the indication of tube feeding in more detail.

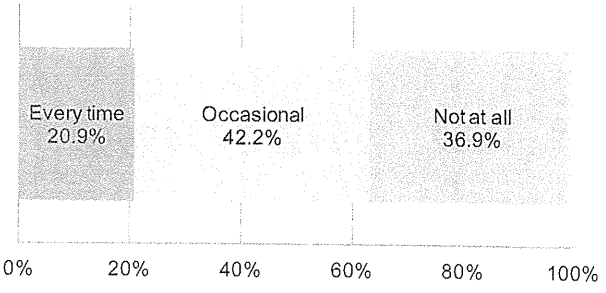

Figure 1 Do you organize a multidisciplinary conference before introducing tube feeding?

"Guideline of parenteral and EN for elderly in Europe" indicates PEG placement if EN is anticipated for longer than 4 weeks.[17,18] In contrast, the present study showed that approximately 80% of the geriatricians consider that survival more than 12 weeks should be expected for PEG placement. PEG is better than NGT for swallowing rehabilitation, and PEG placement

Table 3 Conference members for decision making of tube feeding according to place of employment

	Place of employment of geriatricians					Total
	Hospital $n = 249$	Clinic $n = 80$	Long-term care $n = 17$	Other† $n = 3$	*P*-value	$n = 350$
No. conference members; mean ± standard deviation (total 12 occupations)	4.4 ± 2.0	4.2 ± 1.8	4.3 ± 1.5	4.8 ± 4.2	0.864	4.31 ± 1.9
Conference members						
Attending physician	238 (95.2)	75 (92.6)	17 (100)	3 (100)	–	334 (95.4)
Primary nurse	224 (89.6)	54 (66.7)	15 (88)	3 (100)	–	297 (94.9)
Otolaryngologist	27 (10.8)	10 (12.3)	0 (0)	0 (0.0)	–	37 (10.6)
Certified nurse of dysphagia nursing	42 (16.8)	18 (22.2)	3 (18)	0 (0.0)	–	63 (18.0)
Physical therapist	55 (22.0)	12 (14.8)	4 (24)	1 (33.3)	–	72 (20.6)
Occupational therapist	37 (14.8)	8 (9.9)	4 (24)	1 (33.3)	–	50 (14.3)
Speech therapist	118 (47.2)	23 (28.4)	5 (29)	1 (33.3)	–	147 (42.0)
Dietician	126 (50.4)	37 (45.7)	9 (53)	2 (66.7)	–	174 (49.7)
Pharmacist	37 (14.8)	12 (14.8)	1 (5.9)	1 (33.3)	–	51 (14.6)
Discharge planning coordinator‡	26 (10.4)	14 (17.3)	2 (12)	1 (33.3)	–	43 (12.3)
Medical social worker	89 (35.6)	24 (29.6)	4 (24)	2 (66.7)	–	119 (34.0)
Care manager	46 (18.4)	39 (48.1)	5 (29)	1 (33.3)	–	91 (26.0)

Number (%), *P*-values were tested by ANOVA, $^*P < 0.05$ by Bonferroni. Of the 555 geriatricians, 350 (63.1%) carried out a conference at least once. Respectively, hospital: 249 (69.2%), clinic: 80 (48.2%), long-term care: 17 (85.0%), other: 3 (33.3%). Multiple answers were allowed. †Other included part-time doctors, retired doctors, researchers and so on. ‡They are a registered nurse and work for discharge planning and coordination in the hospital.