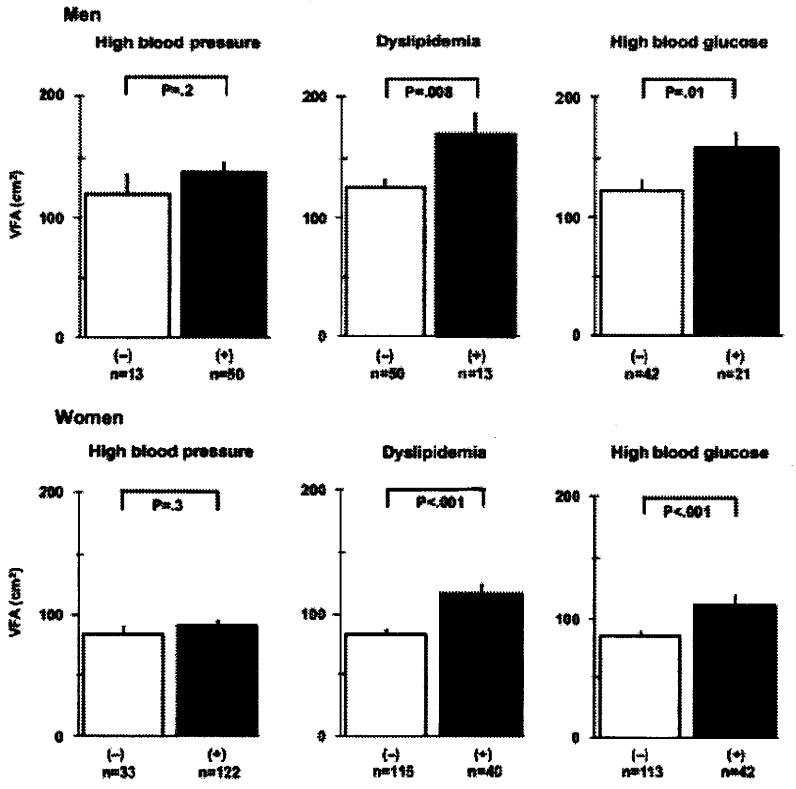

Figure 2. Visceral fat area (VFA) in the absence (–) and presence (+) of each metabolic risk factor. Dyslipidemia includes high triglycerides, low high-density lipoprotein cholesterol, or both. Data are expressed as means ± standard errors.

The relationship between each metabolic risk factor and VFA in elderly subjects was examined. As shown in Figure 2, men and women with dyslipidemia (high triglycerides, low HDL-C, or both) had a significantly greater mean VFA than those without dyslipidemia. Similar results were observed in subjects with and without high blood glucose, although there was no significant difference in VFA between subjects with and without high BP. Changing the cutoff values to 140/90 mmHg from 130/85 mmHg in this analysis made no difference in the results ($P = .25$ in men, $P = .41$ in women; data not shown). A simple regression analysis between VFA and SBP or DBP in subjects not receiving antihypertensive treatment showed no correlation (SBP: $P = .51$ in men, $P = .72$ in women; DBP: $P = .81$ in men, $P = .11$ in women; data not shown).

Finally, a significant negative correlation was observed between VFA and serum adiponectin and a positive correlation between VFA and HOMA-IR in men and women (Figure 3).

DISCUSSION

VFA is associated with metabolic abnormalities, as previously shown in studies of middle-aged populations.[7–9] This association was still observed after adjustment for age and BMI, suggesting that visceral fat accumulation might be a strong risk factor for the metabolic syndrome even in older adults. This association was observed even in subjects aged 75 and older, and VFA was correlated with components of the metabolic syndrome even in subjects who on average had a normal BMI.

Nevertheless, in multiple regression analysis, BMI was not correlated with number of metabolic risk factors in men or women. These results suggest that, for the evaluation of metabolic abnormalities in older adults, VFA is more useful than BMI because BMI in older adults might reflect not only visceral fat mass, but also lower muscle mass and intercellular fluid associated with aging. Thus, because of a reduction of muscle mass with aging, studies that use only BMI would underestimate the health effect of body fatness. Moreover, even if waist circumference was added in this multiple regression analysis, VFA was significantly correlated with number of metabolic risk factors in men and women, but waist circumference was not, suggesting that VFA rather than waist circumference may strongly predict metabolic abnormalities. Data from the Diabetes Prevention Program Research Group showed that visceral adipose tissue predicted the development of type 2 diabetes mellitus better than BMI or waist circumference, but analyses were not limited to older adults (only 20% were ≥60).[18] Thus, it would be important to assess the value of VFA prospectively in predicting the worsening of metabolic risk factors and age-related diseases (e.g., diabetes mellitus and cardiovascular disease).

A strength of this study is the precise assessment of visceral fat according to CT scanning instead of the generally used waist circumference for assessment of abdominal obesity. In many clinical studies, large waist circumference, representing visceral fat accumulation, has been reported to

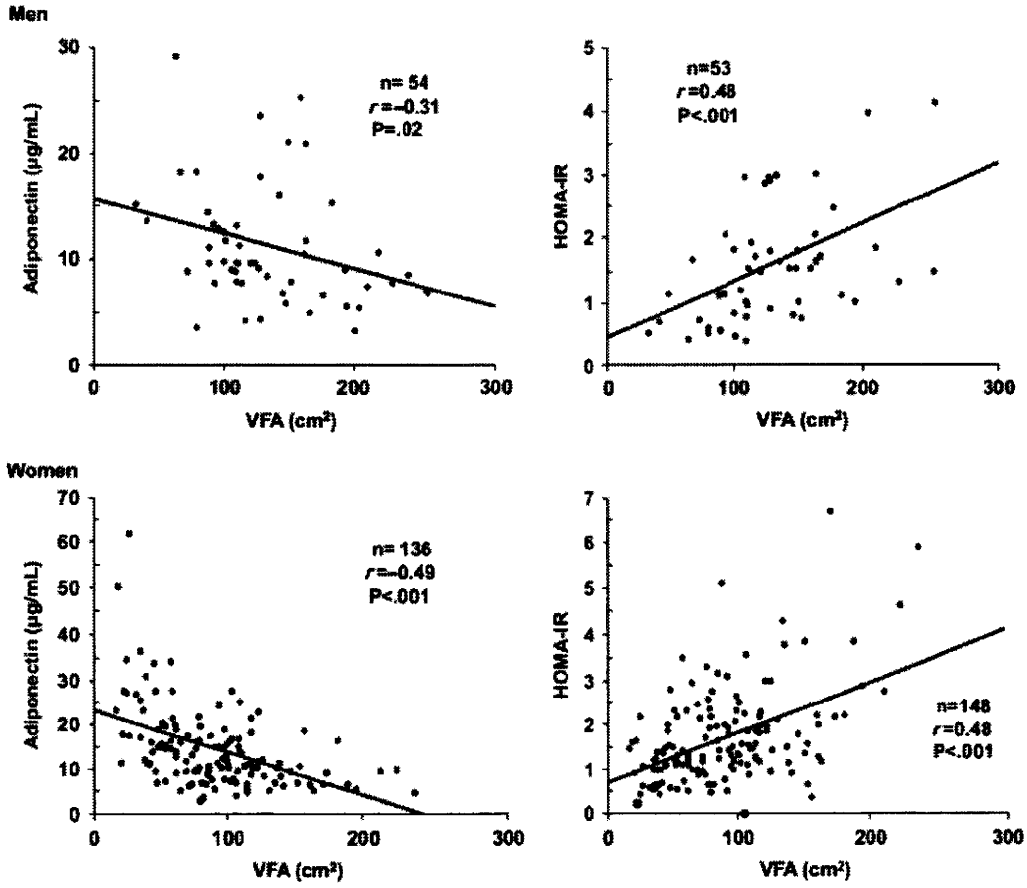

Figure 3. Correlation between visceral fat area (VFA) and serum adiponectin in all subjects and homeostasis model assessment of insulin resistance (HOMA-IR) in older men and women without diabetes mellitus. There was a significant negative correlation between VFA and serum adiponectin and a positive correlation between VFA and HOMA-IR in men and women. r = correlation coefficient.

be associated with greater cardiovascular disease and mortality.[19–21] As the mechanism of this association, it has been proposed that visceral fat accumulation is associated with metabolic abnormalities through insulin resistance and abnormal secretion of adipocytokines.[22,23] This study confirmed that visceral fat accumulation was negatively correlated with serum adiponectin level and positively correlated with insulin resistance as estimated by HOMA-IR in older adults. These findings suggest that older adults with visceral fat accumulation might tend to show metabolic abnormalities through decreased secretion of adiponectin and exacerbation of insulin resistance, similar to middle-aged adults with abdominal obesity.

No association was observed between high BP and VFA. Although the high rate (nearly 80%) of high BP may have affected this result, an additional analysis of this study showed no association between VFA and high BP using a modified cutoff value (140/90 mmHg). Moreover, the simple regression analysis showed no correlation between VFA and SBP or DBP in subjects not receiving antihypertensive treatment. These results suggest that factors other than visceral fat accumulation, such as sclerosis of blood vessels and enhancement of salt sensitivity, both of which are associated with aging, might affect BP in older adults. To the contrary, impaired energy metabolism (e.g., high blood glucose and dyslipidemia) was closely associated with visceral fat accumulation.

It has been reported that weight-reduction therapy using diet, exercise, or both is efficacious in terms of improvement of insulin resistance and dyslipidemia even in older adults.[24,25] Thus, taking together the results of this study and these reports, it appears that the beneficial effects of weight-reduction therapy for older adults even with normal BMI might result from a reduction of visceral fat mass and subsequent improvement in energy metabolism. However, severe dietary therapy for weight reduction is difficult to achieve in elderly patients and has potential risks of causing micronutrient deficiencies,[26–28] generalized weakness, and loss of lean body mass.

There are some limitations of this study. First, because of exclusion criteria, the results of this study might not be generalizable to the general elderly population,. Second, this study did not determine the effects of other body parameters such as subcutaneous fat and nonfat mass on metabolic abnormalities. Third, with the cross-sectional design, causal relationships cannot be established between VFA and metabolic risk factors. Finally, it remains to be determined whether metabolic syndrome in older adults

contributes to cardiovascular events or mortality.[29,30] Confirmation by a large prospective study with precise assessment, such as CT scanning, will be needed to determine whether visceral fat accumulation in older adults directly contributes to cardiovascular events or mortality.

In conclusion, this study suggests that visceral fat accumulation is associated with metabolic risk factor clustering even in older adults with normal BMI. These results provide important insight into the management of metabolic abnormalities in older adults.

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Conflict of Interest: This study was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (18890055 and 20249041) and Mitsui Sumitomo Insurance Welfare Foundation.

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SHORT COMMUNICATION

Adiponectin in plasma and cerebrospinal fluid in MCI and Alzheimer's disease

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Keywords:
adipocytokine, adiponectin, Alzheimer's disease, cerebrospinal fluid, mild cognitive impairment

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Background and purpose: Life style-related disorders such as hypertension, diabetes, dyslipidemia, and obesity are reported to be a great risk of dementia. Adipocytokines released from adipose tissue are thought to modulate some brain functions including memory and cognition. We here analysed adiponectin, one of the most important adipocytokines, in plasma and cerebrospinal fluid (CSF) from cognitive normal controls (NC), mild cognitive impairment (MCI) subjects, and patients with Alzheimer's disease (AD) and discussed if/how adiponectin could relate to the pathogenesis of AD.

Methods: Normal controls (n = 28), MCI (n = 18), and AD (n = 27) subjects were recruited at Tohoku University Hospital. The diagnosis of AD was based on NINCDS-ADRDA criteria. All the blood and CSF samples were obtained from each fasted subject. Adiponectin was assayed using a sandwich ELISA system.

Results: The levels of adiponectin between in plasma and in CSF showed a positive correlation. Plasma adiponectin was significantly higher in MCI and AD compared to NC, whereas CSF adiponectin was significantly higher in MCI compared to NC.

Conclusion: It is possible that the level of adiponectin in plasma reflects its level in CSF. The tendency to have higher adiponectin in plasma and CSF from MCI and AD suggests that this molecule plays a critical role in the onset of AD.

Introduction

It is reported that life style-related diseases such as hypertension, diabetes, dyslipidemia, and obesity have been increasing especially in developed countries [1]. These diseases are suggested to be a great risk not only for vascular dementia but also for Alzheimer's disease (AD) [2]. Great attention has been paid to several cytokines that are supposed to be involved in the pathogenesis of AD. Several researchers reported that the levels of interleukin-1 (IL-1), IL-6, and TNFα are altered in cerebrospinal fluid (CSF) or blood in AD compared to normal control (NC) [3,4]. On the other hand, adipocytokines released from adipose tissue or pre-adipocytes are considered to play some critical roles in brain functions [5]. Therefore, it is suggested that adipocytokines are involved in the pathogenesis of dementia including AD. In this study, we focused on adiponectin, one of the most important adipocytokines, which modulates glucose metabolism, fatty acid catabolism, and the immune functions, to investigate if/how the level of this molecule is altered in plasma and CSF from patients with AD and subjects with mild cognitive impairment (MCI) compared to cognitively normal subjects. We quantified a level of adiponectin in each subject to discuss if/how adiponectin could contribute to the pathomechanism of AD.

Methods

Subjects with normal cognition, MCI, and AD were recruited at Tohoku University Hospital, Sendai, Japan. Twenty-eight normal controls (NCs), 18 subjects with MCI, and 27 patients with AD participated in this study. The demographic information of the subjects is shown in Table 1. The mean body mass indexes were not statistically different amongst the three groups. The diagnosis of MCI and probable AD followed the MCI

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Table 1 Demographic details of the subjects in this study

	N	Gender	Age	MMSE	ApoE4 allele (%)	BMI
Normal control	28	M/F = 12/16	72.5 ± 2.82	29.9 ± 0.3	0.14	21.8 ± 0.58
MCI	18	M/F = 9/9	74.2 ± 2.16	25.5 ± 2.5	0.25	21.9 ± 0.66
Alzheimer's disease	27	M/F = 8/19	77.4 ± 0.95	19.5 ± 3.7	0.32	21.7 ± 0.65

MCI, mild cognitive impairment; MMSE, mini-mental state examination; Apo E, apolipoprotein E; BMI, body mass index.

clinical criteria presented by Petersen *et al.* [6] and the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association [7], respectively. All the MCI subjects studied were amnestic. Mini-mental state examination (MMSE) scores were significantly different between 'NC and MCI', 'NC and AD', and 'MCI and AD'. The study protocol was approved by the Committee on Clinical Investigation at Tohoku University School of Medicine. After a complete description of the study to the patients and subjects, written informed consent was obtained. The concentrations of total adiponectin in plasma, serum, and CSF were quantified using an ELISA system (Daiichi Chemical. Co, Tokyo, Japan) [8].

For statistical comparison of adiponectin levels in the three groups, we applied one-way analysis of variance (ANOVA) followed by the Bonferroni-Dunn *post hoc* test using GRAPHPAD PRISM Version 5 (GraphPad Software Inc., San Diego, CA, USA) and SPSS version 14 (SPSS Inc., Chicago, IL, USA). Multivariable regression models were used to examine the effect of variables, age, and gender on adiponectin levels. Association between adiponectin levels in plasma and CSF was analysed using Pearson's correlation coefficient. Statistical significance was defined as $P < 0.05$.

Results

First, we analysed concentrations of total adiponectin in serum and plasma in the same 15 subjects. The concentrations in serum and plasma were well correlated with each other ($r = 0.9538$, $P < 0.0001$); therefore, we only analysed adiponectin in plasma in this study.

Second, concentrations of adiponectin in plasma and CSF were quantified, and their correlation was analysed. As shown in Fig. 1a, a positive correlation ($r = 0.4064$, $P = 0.0051$) was obtained between the levels of adiponectin in plasma and those in CSF, indicating the possibility that some amount of adiponectin passes between plasma and CSF through the blood–brain barrier (BBB).

Third, we quantified the levels of adiponectin in plasma and CSF from NC, MCI, and AD and compared them carefully (Fig. 1b). As shown in the Fig. 1b, the levels of adiponectin in plasma from MCI and AD

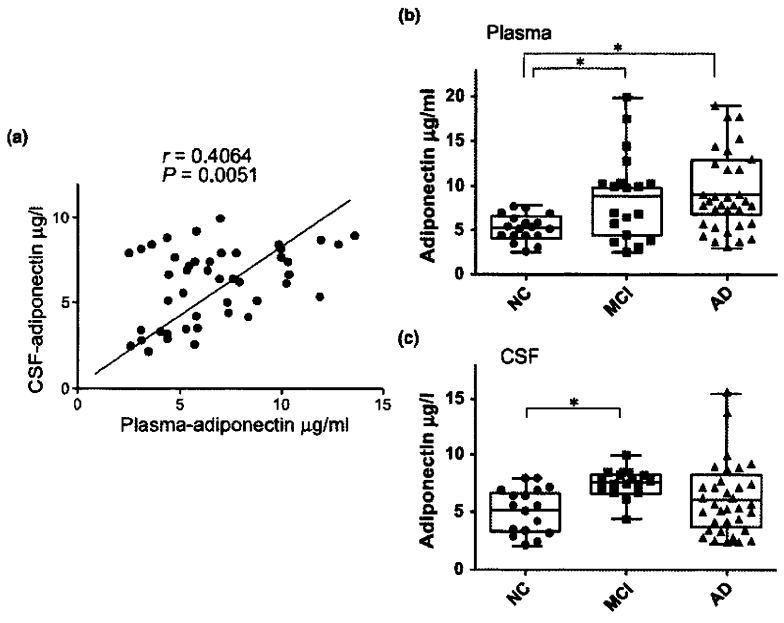

Figure 1 Concentrations of adiponectin in plasma and cerebrospinal fluid (CSF). Boxes indicate interquartile range. Vertical bars indicate minimum–maximum range. (a) Concentrations of adiponectin in CSF were plotted against those in plasma. A positive correlation was observed between them. (b) Adiponectin levels in plasma in normal control (NC), mild cognitive impairment (MCI), and Alzheimer's disease (AD) were plotted. The plasma adiponectin in MCI and AD were significantly higher than NC. $*P < 0.05$. (c) Adiponectin levels in CSF in NC, MCI, and AD were plotted. The CSF adiponectin in MCI was significantly higher than NC. $*P < 0.05$.

are significantly higher than that from NC (NC vs. MCI: $P = 0.015$; NC vs. AD: $P = 0.032$). Because the amount of body fat is the major predictor of adiponectin levels in plasma and adiponectin is primarily synthesized by fat cells, we calculated the amount, as 'plasma adiponectin (μg/l)/body weight (kg) (P-Adp/BW)', and compared it amongst the three groups (NC, MCI, and AD). The values of P-Adp/BW were also significantly higher in MCI (0.202 ± 0.031, $P < 0.05$) and AD (0.201 ± 0.019, $P < 0.05$) than in NC (0.109 ± 0.012). It has been reported that women have higher plasma adiponectin than men [9]. Although in this study plasma adiponectin level (8.32 ± 0.75, $n = 44$) was found higher in women than in men (7.87 ± 0.61, $n = 29$), the difference was not statistically significant between men and women. Significant differences were still obtained in plasma adiponectin between 'NC and MCI' and 'NC and AD' following multivariate regression analysis to adjust for age and gender.

Finally, CSF analyses indicated that only MCI showed a higher level of adiponectin compared to NC ($P = 0.027$) (Fig. 1c). The difference in CSF also remained following multivariate regression analysis to adjust for age and gender.

Discussion

It is well known that patients with AD often have problems with appetite and eating, resulting in several metabolic concerns including weight changes [10,11]. Great attention has recently been paid to adipocytokines released from adipose tissue in regard to metabolism of fat and sugar and also to brain functions. Adipocytokines, therefore, have a possibility of being involved in the pathogenesis of neurodegenerative disorders causing dementia and metabolic problems such as AD. Adiponectin is one of the most important adipocytokines because it is involved in a number of metabolic processes, and its concentration in plasma is one of the highest. Although adiponectin in CSF could not be quantified until recently because of the low sensitivity of detection methods, novel high-sensitive ELISA systems have allowed us to analyse adiponectin in CSF in recent years [8]. As far as we know, this is the first report that investigates adiponectin in the CSF and plasma in the subjects with MCI and AD.

Adiponectin in CSF was previously investigated in several neurological disorders. Hietaharju *et al.* [12] reported that CSF adiponectin is elevated in patients with multiple sclerosis (MS) and suggested that adiponectin in CSF is related to immuno-reaction to induce MS relapses. In addition, Ball *et al.* [13] reported no change in CSF adiponectin in idiopathic intracranial hypertension (IIH), although CSF leptin was elevated in IIH. Patients with IIH tend to be obese; therefore, the authors concluded that adipocytokines, especially leptin, are involved in the pathophysiology of IIH in addition that obesity in IIH may occur as a result of hypothalamic leptin resistance.

In this study, concentrations of adiponectin in plasma and CSF showed a moderate positive correlation. On the other hand, Hietaharju *et al.* [12] suggested that a possible intrathecal synthesis of adiponectin exists because the adiponectin level in CSF did not correlate with the level in plasma. Because of the limited data, it is hard to lead to a conclusion whether adiponectin is synthesized intrathecally or whether it flows into the intrathecal space from plasma passing through BBB. It is definite, however, that adiponectin exists in CSF, and further investigations will be needed to clarify where adiponectin is produced, and how it circulates.

We have not completely elucidated the pathomechanism of the high adiponectin levels in MCI and AD. It was reported that lower body mass index predicts dementia in the elderly, and weight loss may precede the onset of AD [11]. Therefore, the high level of adiponectin especially in MCI, which is regarded as a prodromal state of AD, could play a role in weight loss observed in the early stage of dementia.

We conclude that the level of adiponectin is higher in plasma in MCI and AD in addition to that CSF adiponectin is elevated in MCI. This finding could be related to the manifestations, which are weight loss, decrease in fat tissue, and appetite change, observed in the early stage of AD. It is considered that further investigations will be needed to elucidate more detailed functions of adiponectin in the pathomechanisms of AD.

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Original Article

Effects of Pitavastatin (LIVALO Tablet) on the Estimated Glomerular Filtration Rate (eGFR) in Hypercholesterolemic Patients with Chronic Kidney Disease

— Sub-analysis of the LIVALO Effectiveness and Safety (LIVES) Study

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Aim: **In addition to the risk of progression to end-stage renal disease (ESRD), chronic kidney disease (CKD) is also known to be associated with an elevated risk of cardiovascular disease (CVD). Statins may improve renal function in CKD patients.**

Methods: **The database of the LIVALO Effectiveness and Safety (LIVES) Study, a large-scale (n=20,279), long-term (104 weeks), prospective post-marketing surveillance study of hypercholesterolemic patients treated with pitavastatin, was used to evaluate the effects of pitavastatin on the estimated glomerular filtration rate (eGFR).**

Results: **Of the 19,925 patients enrolled in the aforementioned study, data from 3,119 patients were analyzed to evaluate the effects of pitavastatin treatment for 104 weeks on the eGFR. In this sub-analysis, 958 patients with a baseline eGFR of less than 60 mL/min/1.73 m^2 (30.7%) were analyzed. A significant increase of the eGFR (+5.4 mL/min/1.73 m^2) was observed after 104 weeks of pitavastain treatment (p<0.001; one-sample t-test). In the analysis of the time-course of changes in the eGFR in response to pitavastatin treatment, the eGFR was elevated by 2.4 mL/min/1.73 m^2 after 12 weeks' treatment, and by 5.6 mL/min/1.73 m^2 after 104 weeks' treatment (p<0.001; repeated measures ANOVA). The results of multivariate analysis identified the presence/absence of proteinuria and the amount change of HDL-C as clinical factors associated with increased eGFR during pitavastatin treatment.**

Conclusions: **Increased eGFR was noted after 104 weeks of treatment with pitavastatin, which suggests a possible effect of the statin on CKD.**

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Key words; Statin, HMG-CoA reductase inhibitor, Estimate of glomerular filtration rate, Urinary protein

Introduction

In addition to the risk of progression to end-stage renal disease (ESRD), chronic kidney disease (CKD) has also been reported to be associated with an elevated risk of cardiovascular disease (CVD)[1-3]. A recent study reported an increased risk of coronary heart disease (CHD) in patients with CKD[4]. In Japan, patients with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 have been estimated to account for about 10% of the entire population[5, 6]. Early diagnosis and prompt treatment of

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CKD are important for the prevention of CVD and reduction of mortality and morbidity[1].

In a sub-analysis of the Treating to New Targets (TNT) study, treatment with 10 mg and 80 mg atorvastatin was found to increase the eGFR by 3.5 mL/min/1.73 m^2 and 5.2 mL/min/1.73 m^2, respectively[7]. In contrast, in the Prevention of Renal and Vascular ENd-stage Disease Intervention trial (PREVEND-IT), treatment with 40 mg pravastatin did not result in any change of the eGFR[8]. Thus, the beneficial effect of statins on the eGFR remained controversial.

The LIVALO Effectiveness and Safety (LIVES) Study was a large-scale, long-term, prospective post-marketing surveillance study of pitavastatin[9]. Since it included more than 20,000 hypercholesterolemic patients and was a prospective surveillance study, the database of the LIVES Study is considered to be useful for evaluation of the efficacy and safety of pitavastatin in routine clinical practice. Sub-analysis of the LIVES Study showed that pitavastatin significantly increased serum HDL-C[10]. In the present study, using the LIVES Study database, we analyzed the effect of pitavastatin on the eGFR in patients with a baseline eGFR of < 60 mL/min/1.73 m^2.

Subjects and Methods

Survey Participants

The design and results of the LIVES Study have been reported previously[9]. Patients with hypercholesterolemia, including familial hypercholesterolemia, were enrolled in this study using a central registration system, with each patient enrolled within 14 days of the start of treatment with pitavastatin. Patients were observed for 2 years after the start of treatment. Of the 20,279 patients recruited, 19,925 were included in the safety analysis and 18,031 in the efficacy analysis of pitavastatin.

The major objective of the LIVES Study was to investigate the occurrence of any unknown adverse reactions and to evaluate the incidence and pattern of adverse reactions of pitavastatin. In the 19,925 patients included in the safety analysis, the eGFR was calculated in patients for whom all data were available after 104 weeks' treatment with pitavastatin. Seven patients with serum creatinine levels above the normal range were excluded from the analysis as outliers.

eGFR Analysis

eGFR was assessed using the new Japanese revised equation[11], as follows:

$$eGFR\ (mL/min/1.73\ m^2) = 194 \times Cr^{-1.094} \times Age^{-0.287}$$

($\times 0.739$, if female).

According to the baseline eGFR, the patients were classified into CKD stages as defined in the K/DOQI guideline[12], as follows: stage 1 (≥ 90), stage 2 (≥ 60–< 90), stage 3 (≥ 30–< 60), stage 4 (≥ 15–< 30), and stage 5 (< 15). Patients with baseline eGFR values < 60 mL/min/1.73 m^2 were enrolled for sub-analysis. Furthermore, the time-course of changes in the eGFR was evaluated at 0, 12, 28, 52 and 104 weeks in patients with a baseline eGFR of 60 mL/min/1.73 m^2 for whom all data were available after 104 weeks of pitavastatin treatment. The time-course of changes in the eGFR was analyzed using repeated measures ANOVA.

Lipid Profile Analysis

The percent changes of serum TC, LDL-C, TG (in the entire study population and in the high TG group (≥ 150 mg/dL) at baseline), HDL-C (in the entire study population and in the low HDL-C group (< 40 mg/dL) at baseline), non-HDL-C and LDL-C/HDL-C were calculated in patients with a baseline eGFR of < 60 mL/min/1.73 m^2. The serum concentration of LDL-C was estimated using the Friedewald formula (LDL-C = TC-HDL-C-TG $\times$ 0.2)[13] in patients with serum TG concentrations of less than 400 mg/dL. Correlations between the degree of change in the eGFR and that of the changes in the serum TC, LDL-C, TG, HDL-C, non-HDL-C and LDL-C/HDL-C were analyzed in patients with a baseline eGFR of less than 60 mL/min/1.73 m^2.

Analysis of the Clinical Factors Affecting Changes in the eGFR during Pitavastatin Treatment

The clinical factors affecting the changes in the eGFR during pitavastatin treatment were analyzed in patients with a baseline eGFR of < 60 mL/min/1.73 m^2. The patient baseline characteristics (gender, age, BMI and smoking history), presence/absence of underlying diseases (hypertension, diabetes and heart disease), presence/absence of proteinuria by the urinary dipstick test (+- or more), history/no previous history of lipid-lowering medication, the initial dose of pitavastatin, and the amount change of serum lipids (LDL-C, TG, and HDL-C) were entered into a multivariate regression model for this analysis.

Statistical Analysis

All data were expressed as the mean ± standard deviation. Statistical analysis was performed with a one-sample *t* test or paired *t* test, or a two-sample *t* test, as appropriate. One-way analysis of variance (ANOVA) and linear regression analysis were performed to analyze the time-course of changes in the

eGFR. In factorial analysis, changes in the eGFR were analyzed after adjustment for the baseline eGFR by ANOVA (*F*-test). Furthermore, multivariate analysis was applied by the stepwise method to identify factors that affected changes in the eGFR during treatment. JMP ver. 5.1.1 was used for all statistical analyses. The significance level was set at 0.05 (two-sided).

Results

Effects on Renal Function

Of the 19,925 patients, 3,119 for whom the relevant data were available were included to evaluate changes in the eGFR after 104 weeks pitavastatin treatment. The patients were classified into CKD stages according to the baseline eGFR. The number of patients in each stage is shown in **Table 1**. Of the patients included in this analysis, the baseline eGFR was ≥60 mL/min/1.73 m^2 in 2,161 patients and <60 mL/min/1.73 m^2 in 958 patients. The demographic characteristics of these patients are shown in **Table 2**. The two groups were similar except for the mean age, hyperlipidemia phenotype, and prevalence of hypertension and renal disease. Patients with an eGFR of <60 mL/min/1.73 m^2 were included for the following analysis as cases of impaired renal function.

Table 1. Distribution of eGFR

eGFR (mL/min/1.73 m^2)	patients	%	mean eGFR (mL/min/1.73 m^2)
≧90	421	13.5	102.2
60≦<90	1,740	55.8	72.7
30≦<60	888	28.5	50.3
15≦<30	41	1.3	24.6
<15	29	0.9	5.2

The changes in the eGFR at 104 weeks are shown in **Fig. 1**. A significant increase in the eGFR from 47.8 ± 11.5 to 53.2 ± 18.6 mL/min/1.73 m^2 (+5.4 mL/min/1.73 m^2) was observed at 104 weeks ($p<0.001$). The average increase of the eGFR at 104 weeks was 6.3 mL/min/1.73 m^2 in treatment-naive patients ($n=731$, $p<0.001$) and 2.3 mL/min/1.73 m^2 in patients with a history of treatment with other cholesterol-lowering drugs ($n=227$, $p<0.01$) (data not shown). The increase in the eGFR at 104 weeks was 3.2 mL/min/1.73 m^2 in patients under treatment with an ACE inhibitor or ARB (baseline eGFR=45.9 ± 12.6 mL/min/1.73 m^2, $n=470$, $p<0.001$), and 7.5 mL/min/1.73 m^2 in patients not under treatment with these classes of drugs (baseline eGFR=49.7 ± 10.1 mL/min/

Table 2. Patient demographic characteristics

Item		Patients with eGFR ≧60 mL/min/1.73 m^2	Patients with eGFR <60 mL/min/1.73 m^2
No. of patients surveyed		2,161	958
Female		1,451 (67.1)	621 (64.8)
Age (years)		62.9 ± 10.8	68.8 ± 10.2
BMI (kg/m^2)		24.4 ± 3.7	24.4 ± 3.3
Hyperlipidemia phenotype	IIa	1,161 (53.7)	460 (48.0)
	IIb	907 (42.0)	436 (45.5)
Co-morbid conditions		1,810 (83.8)	836 (87.3)
Hypertension		1,134 (52.5)	583 (60.9)
Diabetes		759 (35.1)	308 (32.2)
Heart disease		329 (15.2)	207 (21.6)
Liver disease		211 (9.8)	73 (7.6)
Renal disease		43 (2.0)	124 (12.9)
Smoking history		261 (12.1)	105 (11.0)
Previous history of lipid-lowering medication		502 (23.2)	227 (23.7)
Initial daily dose	1 mg	845 (39.1)	374 (39.0)
	2 mg	1,305 (60.4)	577 (60.2)
	4 mg	11 (0.5)	6 (0.6)
Most frequent daily dosage	1 mg	855 (39.6)	380 (39.7)
	2 mg	1,267 (58.6)	557 (58.1)
	4 mg	32 (1.5)	8 (0.8)

( ): %

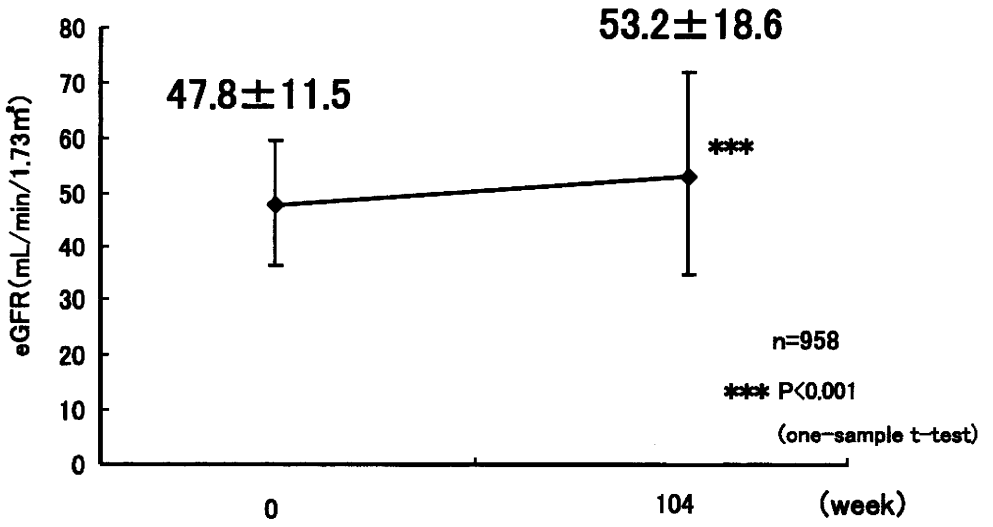
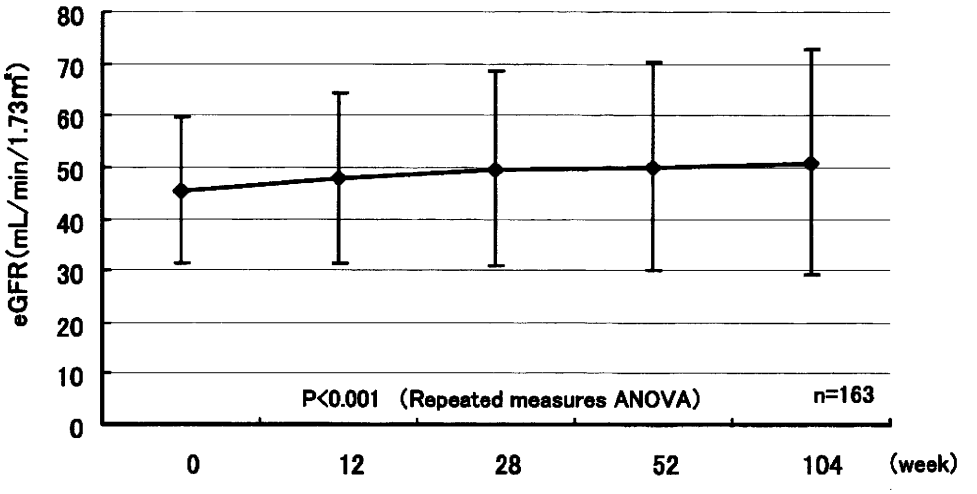


Fig. 1. Effect of pitavastatin on the eGFR. Baseline eGFR <60 mL/min/1.73 m^2. Values are the mean ± SD



Degree of change of the eGFR (mL/min/1.73m²)	0	2.4±7.6	4.4±10.7	4.8±13.2	5.6±15.0
Percent change of the eGFR (%)	0	4.8±17.0	8.8±24.2	9.9±31.3	10.5±33.0

Fig. 2. Time-course of changes of the eGFR.Baseline eGFR <60 mL/min/1.73 m^2. Values are the mean ± SD

1.73 m^2, n=488, p<0.001) (data not shown). Furthermore, in regard to the time-course of changes in the eGFR during pitavastatin treatment, the increase in the eGFR was 2.4 mL/min/1.73 m^2 at 12 weeks, and 5.6 mL/min/1.73 m^2 at 104 weeks (p<0.001; Repeated measures ANOVA) (**Fig. 2**).

Effects of Pitavastatin Treatment on Plasma Lipid Levels

The percent changes in serum lipid levels at 104 weeks are listed in **Table 3**. A significant reduction of the serum TC (−22.5%) and LDL-C (−31.3%) was observed at 104 weeks. Serum non-HDL-C and LDL-C/HDL-C were also reduced significantly (p<0.0001)

Table 3. Changes in lipid levels (eGFR < 60 mL/min/1.73 m²)

	No. of patients	Period	Lipid value (mg/dL) (Mean ± SD)	% change from baseline (Mean ± SD)	*p* value*
TC	914	Baseline 104 weeks	254.0 ± 41.6 193.4 ± 34.3	−22.5 ± 15.5	<0.0001
LDL-C#	341	Baseline 104 weeks	165.7 ± 37.4 109.0 ± 28.5	−31.3 ± 24.1	<0.0001
TG	903	Baseline 104 weeks	186.8 ± 126.7 152.1 ± 88.2	−6.4 ± 50.6	<0.001
TG (Baseline value ≧ 150 mg/dL)	494	Baseline 104 weeks	253.3 ± 137.7 182.5 ± 98.3	−21.8 ± 38.1	<0.0001
HDL-C	739	Baseline 104 weeks	56.8 ± 16.7 59.2 ± 16.0	6.6 ± 20.5	<0.0001
HDL-C (Baseline value < 40 mg/dL)	91	Baseline 104 weeks	34.7 ± 4.0 41.9 ± 7.7	21.5 ± 22.3	<0.0001
non-HDL-C	714	Baseline 104 weeks	197.6 ± 42.7 133.8 ± 32.9	−30.2 ± 19.5	<0.0001
LDL-C#/HDL-C	341	Baseline 104 weeks	3.1 ± 1.2 1.9 ± 0.8	−33.1 ± 26.5	<0.0001

#LDL-C was estimated by the Friedewald formula. *one-sample *t*-test

at 104 weeks. The percent reduction of serum TG was 6.4% in the entire population, but 21.8%, much higher, in the high TG group (≥150 mg/dL). The percent increase of serum HDL-C was 6.6% ($p<0.0001$) in the entire population, but 21.5%, much higher ($p<0.0001$), in the low HDL-C group (<40 mg/dL).

There were no significant correlations between the changes of the eGFR and those of serum TC, LDL-C, TG, non-HDL-C or LDL-C/HDL-C (**Table 4**). A weak correlation was observed between the change in the eGFR and that of serum HDL-C following pitavastatin treatment ($r=0.092$; $p=0.013$).

Table 4. Correlation between eGFR and lipid level changes (eGFR < 60 mL/min/1.73 m²)

Variable	No. of patients	Coefficient (r)	*p* value*
TC	914	−0.049	0.136
LDL-C#	341	−0.049	0.365
TG	903	−0.047	0.160
HDL-C	739	0.092	0.013
non-HDL-C	714	−0.068	0.071
LDL-C#/HDL-C	341	−0.057	0.297

#LDL-C was estimated by the Friedewald formula. *t-test

Analysis of the Clinical Factors Affecting Changes in the eGFR During Pitavastatin Treatment

The clinical factors affecting changes in the eGFR during pitavastatin treatment are shown in **Table 5**. According to the results of ANOVA (F-test), gender, age, presence/absence of hypertension, diabetes, heart disease, proteinuria, and history/no previous history of lipid-lowering medication were identified as significant factors affecting changes in the eGFR during pitavastatin treatment.

Multivariate analysis by the stepwise method was used to identify the factors influencing changes in the eGFR during pitavastatin treatment. The results identified the presence/absence of proteinuria and the amount change of HDL-C as significant factors influencing changes in the eGFR during pitavastatin treatment (**Table 6**). Changes in the eGFR in the presence/absence of hypertension, diabetes, and proteinuria are shown in **Fig. 3**. The increase in the eGFR in patients with diabetes/hypertension was less than that in patients without diabetes/hypertension. Similar results were obtained in patients with/without proteinuria.

Safety

Of the 19,925 patients included in the safety evaluation in the LIVES study, 2,069 patients (10.4%) developed adverse drug reactions[9]. Of the 3,119 patients included in the present analysis, 173 (5.5%) developed adverse drug reactions. Myopathy-associated adverse reactions were seen in 74 patients (2.4%), and hepatic adverse reactions in 68 patients (2.2%).

Table 5. Analysis of the clinical factors affecting the eGFR Adjusted eGFR baseline

Variable	Number of patients		Difference or Level	Difference in the degree of change of the eGFR	*p* value*
Gender	Female/male	621/337	Female	2.39	0.0076
Age	≧65/<65	672/286	≧65	−1.92	0.0401
BMI	≧25 kg/m²/<25 kg/m²	265/412	≧25 kg/m²	−0.68	0.5263
Hypertension	Yes/No	583/375	Yes	−3.68	<0.0001
Diabetes	Yes/No	308/650	Yes	−4.31	<0.0001
Heart disease	Yes/No	207/751	Yes	−3.22	0.0021
Smoking history	Yes/No	105/851	Yes	−0.79	0.5635
Proteinuria	Yes/No	156/407	Yes	−6.83	<0.0001
Previous history of lipid-lowering medication	Yes/No	227/731	Yes	−3.73	0.0002
Initial daily dose	2 mg/day/1 mg/day	577/374	2 mg/day	0.88	0.3166

*ANOVA (*F* test)

Table 6. Analysis to identify the clinical factors affecting the eGFR (multivariable analysis) Adjusted eGFR baseline

Variable		Difference or Level	Difference in the degree of change of the eGFR	*p* value*
Previous history of lipid-lowering medication	Yes/No	Yes	−1.98	0.2013
Diabetes	Yes/No	Yes	−2.74	0.0512
Proteinuria	Yes/No	Yes	−4.65	0.0029
HDL-C		1 mg/dL	0.17	0.0032

*ANOVA (*F* test)

Discussion

In this study, a significant increase of the eGFR was seen after pitavastatin treatment for 104 weeks in hypercholesterolemic patients with a baseline eGFR of <60 mL/min/1.73 m². In view of the decrease of the eGFR by 0.36 mL/min/1.73 m² per year in healthy Japanese subjects[14], the increase in eGFR by 5.4 mL/min/1.73 m² induced by pitavastatin treatment after 104 weeks in patients with a baseline eGFR of <60 mL/min/1.73 m² is noteworthy. The increase in the eGFR observed after pitavastatin treatment in the present study is similar to that reported for other statins, i.e. 3.5 and 5.2 mL/min/1.73 m² for 10 mg and 80 mg atorvastatin[7] and 4.8 mL/min/1.73 m² for rosvastatin[15]. Thus, it was confirmed in this study that the increase in eGFR is a class effects of statins. Athyros *et al.* reported that the increase in the eGFR induced by statins was also related to a reduction in the hazard ratio for CHD[16]. In sub-analysis of the TNT trial[4, 7], 80 mg atorvastatin produced greater elevation of the eGFR and reduction of the CVD risk than 10 mg atorvastatin in patients with CKD.

The possible mechanisms underlying the increase in the eGFR induced by statins have been reported in several papers and include improvement of the endothelial function[17]. Statins have also been suggested to increase renal blood flow and suppress monocyte recruitment, mesangial cell proliferation, and inflammation[18]. Nakamura *et al.* reported that pitavastatin reduced urinary albumin and liver-type fatty acid-binding protein (L-FABP) in patients with early diabetic nephropathy, which might be attributable to the antioxidant effects of pitavastatin[19]. In spontaneously hypercholesterolaemic Imai rats, pitavastatin showed a renal protective effect via reduction of the urinary protein and antioxidant actions, independent of the lipid-lowering effects[20]. Thus, we assume that the increased eGFR observed in the present study could be attributed to the pleiotropic effects of pitavastatin. Meanwhile, changes in the eGFR were significantly related with those of serum HDL-C in this analysis, although the correlation coefficient was small. Also, the amount change of HDL-C was identified as a significant factor

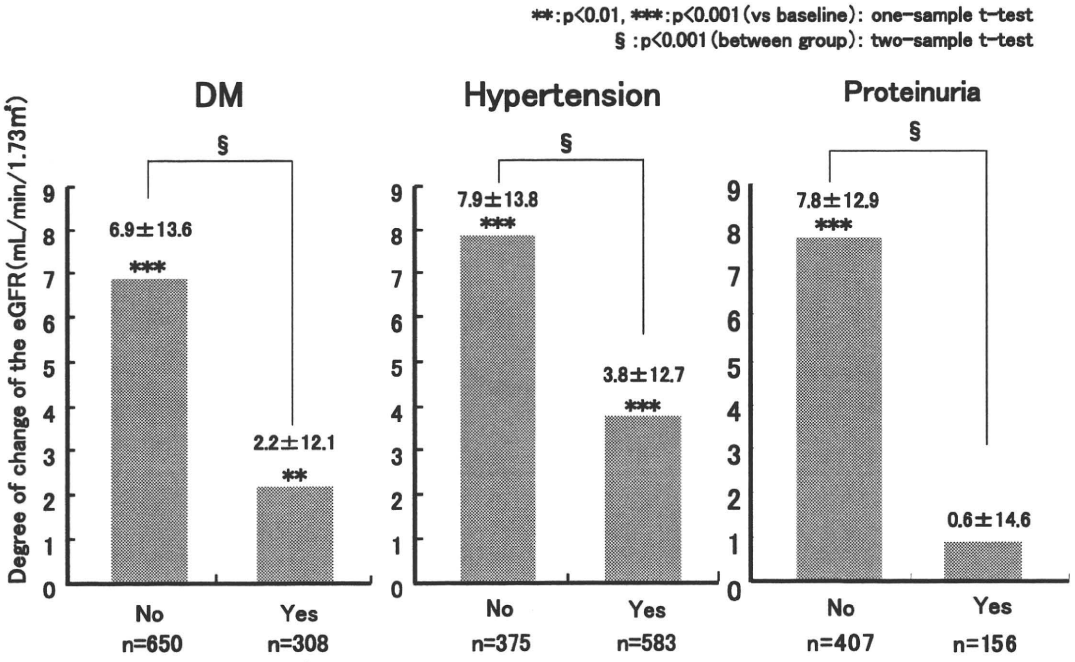


Fig. 3. Change of the eGFR in patients with each factor. Baseline eGFR < 60 mL/min/1.73 m^2. Values are the mean ± SD

influencing changes in the eGFR during pitavastatin treatment; therefore, the increase of HDL-C might be attributed to the increase of the eGFR. In fact, the results of sub-analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study suggested a relation between increased serum HDL-C and increased eGFR following atorvastatin treatment[21]. The antioxidant effects of HDL-C were considered to possibly underlie this correlation[22]; however, further analysis is needed to clarify the mechanism underlying the increase of the eGFR induced by pitavastatin.

At the baseline, the percentage of patients with an eGFR < 60 mL/min/1.73 m^2 was 30.7% in this sub-analysis, higher than that estimated in the Japanese general population, which is about 10%[5, 6]. Therefore, it may be assumed that CKD is more prevalent in hypercholesterolemic patients than in the general population. Indeed, in a sub-analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study[23] conducted in mild hypercholesterolemic patients, the percentage of patients with an eGFR between 30 and 60 mL/min per 1.73 m^2 was higher than in the general population.

In factorial analysis of the current sub-analysis, proteinuria was identified as a significant factor attenuating the elevation of the eGFR observed during pitavastatin treatment. Proteinuria is known as a major factor related to the decline of eGFR and the progression of renal disease[14, 24]; therefore, it is understandable why patients with proteinuria showed a less pronounced effect of pitavastatin in increasing the eGFR in this study. Diabetes was identified as a factor attenuating the elevation of eGFR during pitavastatin treatment with borderline significance (p=0.0512). Diabetes is well known to be associated with the progressive impairment of renal function. The rate of renal function deterioration in CKD patients is higher in those with than without diabetes[25]. The increase of the eGFR in patients taking an ACE inhibitor or ARB was lower than in patients not under treatment with these classes of drugs. The baseline eGFR in patients with an ACE inhibitor or ARB was significantly lower than in patients without an ACE inhibitor or ARB; therefore, patients taking an ACE inhibitor or ARB might show less increase of eGFR because of severe renal dysfunction; however, it is also possible that ACE-I/ARB treatment affects the potency of pitavastatin for the eGFR directly.

In this study, we analyzed the effects of pitavastatin on the eGFR under actual use conditions using the database of the LIVES Study. Since the LIVES Study is post-marketing surveillance study, there is no

control group; thus, a further randomized controlled trial is needed to confirm the effects of pitavastatin on the eGFR.

In conclusion, pitavastain showed a significant increase of the eGFR after treatment for 104 weeks, suggesting that pitavastatin might maintain the glomerular filtration rate and also contribute to reduce the risk of CVD in patients with CKD. Further prospective long-term clinical trials are needed for more precise evaluation of the effects of pitavastatin on renal function.

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Echocardiography

Transthoracic Tissue Doppler Assessment of Left Atrial Appendage Contraction and Relaxation: Their Changes with Aging

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Aim: We assessed left atrial appendage (LAA) function using transthoracic tissue Doppler echocardiography (TDE), and examined the influence of aging on LAA contraction and relaxation. Methods: The subjects were 45 consecutive patients with heart disease and 110 healthy individuals. LAA wall motion velocity (LAAWV) at the tip of the LAA was measured using transthoracic echocardiography (TTE) and/or transesophageal echocardiography (TEE). Results: We successfully recorded and measured LAAWV using TTE in 105 (95%) of the 110 healthy subjects. When angle correction was applied for the Doppler beam in TTE, LAAWV during contraction (LAAWVc) measured by TTE closely correlated with that measured by TEE ($r = 0.97$), and LAAWV during relaxation (LAAWVr) measured by TTE closely correlated with that measured by TEE ($r = 0.95$). LAAWVc and LAAWVr measured by TTE correlated significantly with the LAA flow velocities during LAA contraction and LAA relaxation measured by TEE ($r = 0.64$, $P < 0.001$; $r = 0.53$, $P = 0.001$). In healthy subjects, although LAAWVc remained unchanged with aging, LAAWVr significantly declined with aging ($r = -0.48$, $P < 0.001$) and had a significant negative correlation with left atrial dimension and a significant positive correlation with transmitral flow and annulus velocity during early diastole. Conclusion: Transthoracic TDE can provide information on LAA function. LAA relaxation may be impaired with aging and may be accompanied by early diastolic left ventricular dysfunction and chronic overload to the left atrium. (Echocardiography 2010;27:839-846)

Key words: left atrial appendage function, aging, tissue Doppler echocardiography, transthoracic echocardiography, left atrial appendage wall velocity

Left atrial (LA) size increases and contractile function enhances with aging.[1–3] There have been very few studies concerning left atrial appendage (LAA) function in relation to normal aging. LAA function may be slightly different from LA body function. Some investigators have suggested that the LAA is more compliant than the LA body and plays an important role in LA reservoir function.[4,5] LAA flow velocity, as assessed by transesophageal echocardiography (TEE), decreases with aging.[1,2] However, TEE cannot be performed in a physiologically static state. Insertion of the transesophageal probe is semi-invasive; hence, we hesitate to examine healthy subjects using TEE. Recent development in transthoracic echocardiography (TTE) has facilitated evaluation of the transverse size of the orifice and determination of flow velocities in the LAA, and in some reports, the efficacy of this method has been reported.[6,7] Recently, Uretsky et al. demonstrated that transthoracic tissue Doppler echocardiography (TDE) could provide noninvasive physiological analysis of LAA function, and that LAA wall velocity decreased in patients with atrial fibrillation.[8] However, there is no information on changes in LAA relaxation function with aging. The present study aimed at analyzing LAA contraction and relaxation function in the physiological noninvasive state by transthoracic TDE and examination of changes in LAA contraction and relaxation due to aging.

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Methods:

Study Population:

The study population comprised 45 consecutive patients with sinus rhythm (15 valvular disease, 16 paroxysmal atrial fibrillation, 4 valve replacement, 7 cerebral infarction, and 3 others) who underwent both TEE and TTE between November 2006 and August 2008 in our laboratory. The mean (standard deviation [SD]) age of the patients was 70 (11) years (Table I). The TTE method

TABLE I

Characteristics of Patients

Variable	
Number	45
Men	27
Age (years)	70 (11)
LAAVc (cm/sec)	55 (25)
LAAVr (cm/sec)	51 (22)
LAAFC (%)	43 (23)
LAAWVc by TEE (cm/sec)	15.6 (6.1)
LAAWVr by TEE (cm/sec)	12.9 (4.6)
LAAWVc by TTE (cm/sec)	15.8 (6.2)
LAAWVr by TTE (cm/sec)	13.5 (4.3)
E (cm/sec)	55 (31)
A (cm/sec)	51 (32)
LAD (mm)	42 (8)

LAAVc = left atrial appendage (LAA) flow velocity during atrial contraction; LAAVr = LAA flow velocity during atrial relaxation; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; LAAFC = LAA fractional change during atrial contraction; LAAWVc = LAA wall velocity during LAA contraction; LAAWVr = LAA wall velocity during LAA relaxation; E = peak transmitral velocity during early diasole; A = peak trasmitral velocity during atrial contraction. LAD = left atrial dimension.

TABLE II

Characteristics in Healthy Individuals

Variable	
Number	105
Men	61
Age (years)	50 (22)
Heart Rate (bpm)	68 (15)
LAAWVc (cm/sec)	21.8 (3.2)
LAAWVr (cm/sec)	19.5 (3.9)
E (cm/sec)	81 (20)
A (cm/sec)	65 (19)
E′ (cm/sec)	12 (4)
A′ (cm/sec)	9 (3)
LAD (mm)	32 (4)

bpm = beats per minute; E′ = peak mitral annular motion velocity during early diastole; A′ = peak mitral annular motion velocity during atrial contraction. Refer to the footnote to Table I for additional abbreviations.

for assessing LAA function was validated in these patients. The purpose, methods, and risks of TEE were conveyed to the patients, and written informed consent was obtained.

In addition, between April 2007 and September 2007, 110 healthy individuals with a mean age of 50 (22) years (age range, 12–87 years) were examined in our laboratory using TTE, and changes in LAA contraction and relaxation function with aging were studied. Routine physical examinations, electrocardiography (ECG), echocardiography, or chest radiography revealed no abnormal findings in these individuals, and their history showed no evidence of treatment for angina pectoris, hypertension, or diabetes mellitus (Table II).

Echocardiographic Apparatus:
Studies were conducted using an ultrasound system (Vivid 7; GE Yokogawa Medical Systems, Tokyo, Japan) for both TEE and TTE examinations. The measurement specifications for transthoracic TDE were as follows: frame rate, 141 frames per second; frequency, 2.6 MHz; sampling volume width, 3.3 mm. The measurement specifications for transesophageal TDE were as follows: frame rate, 78 frames per second; frequency, 3.9 MHz; and sampling volume width, 3.2 mm.

Transesophageal Echocardiography:
The transesophageal probe was inserted after pharyngeal local anesthesia of lidocaine spray, intramuscular injection of 1 mg of glucagon, and intravenous injection of 3–4 mg of diazepam. To assess LAA function, the LAA flow velocities in the LAA during LAA contraction (LAAVc) and LAA relaxation (LAAVr) and the change in LAA fractional area during atrial contraction (LAAFC) were recorded using TEE in the long-axis view. The sample volume for the LAA flow velocity measurement was placed in the center of the LAA. LAA wall velocities at the tip of the LAA during atrial contraction (LAAWVc) and atrial relaxation (LAAWVr) were also obtained using pulsed transesophageal TDE. LAAWVc and LAAWVr were identified with reference to the P-wave of ECG. Because the Doppler beam was almost parallel to the direction of the LAA flow velocities and the longitudinally contracting appendage motion, angle correction was not performed (Figs. 1 and 2).

Transthoracic Echocardiography:
The LAA wall velocity (LAAWV) was measured using TTE within 1 hour after examination by TEE. The LAA at the left side of the aortic root in the parasternal short-axis view was sought, and the triangular-shaped LAA was carefully identified. The sample volume was placed as close as possible to the tip of the LAA, and LAAWVc and LAAWVr were measured using pulsed transthoracic TDE. The LAAWVc and LAAWVr were identified with reference to the P-wave of ECG. Correction of the Doppler beam angle was performed by observing the direction of the longitudinally contracting appendage (Figs. 1 and 3).

The LA dimension (LAD) was conventionally measured using M-mode TTE. The peak transmitral flow during early diastole (E) and the peak transmitral flow during atrial contraction (A) were also conventionally measured using TTE.

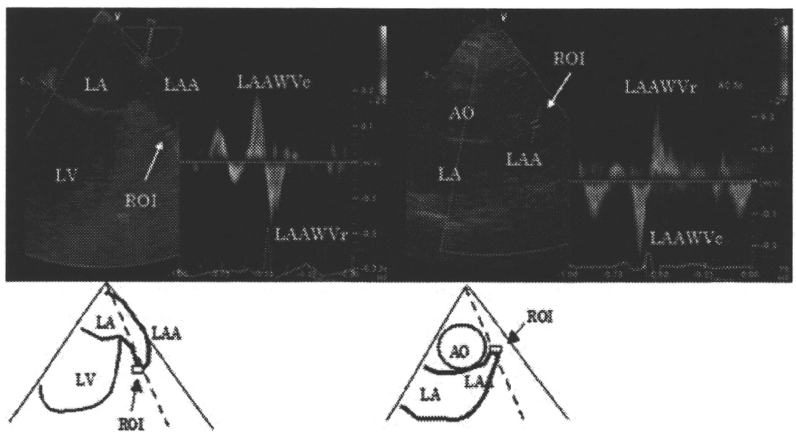

Figure 1. Measurement of left atrial appendage wall velocity (LAAWV) using pulsed tissue Doppler with transesophageal (TEE) (left panel) and transthoracic (TTE) (right panel) echocardiography. The sample volume (white arrows) for the measurement of LAAWV is placed at the tip of the LAA. The peak wave during the LAA contraction phase is designated as LAAWVc, and the peak wave during the LAA relaxation phase is designed as LAAWVr. ROI = region of interest.

The mitral-annular motion velocity during early diastole (E′) and that during atrial contraction (A′) were measured in the four-chamber view using pulsed transthoracic TDE. E′ and A′ were acquired by placing the sample volume at the septal annulus.

Statistical Analysis:
Variables were averaged over five cardiac cycles. Values were shown as mean (SD). Simple linear regression analysis was used to correlate two parameters. Agreement analysis between two parameters was performed according to the Bland-Altman technique. Differences in the values between two groups were assessed using an unpaired *t*-test and Fisher's exact test. The changes of LAA function with aging were determined using a one-way analysis of variance (ANOVA). The Statistical Package for the Social Sciences (SPSS version 11.0J; SPSS Japan Inc., Tokyo, Japan) software was used for statistical analysis. A P-value of less than 0.05 was considered statistically significant. Interobserver variability for measurements of LAAWV was calculated as the difference between two measurements of the same subject

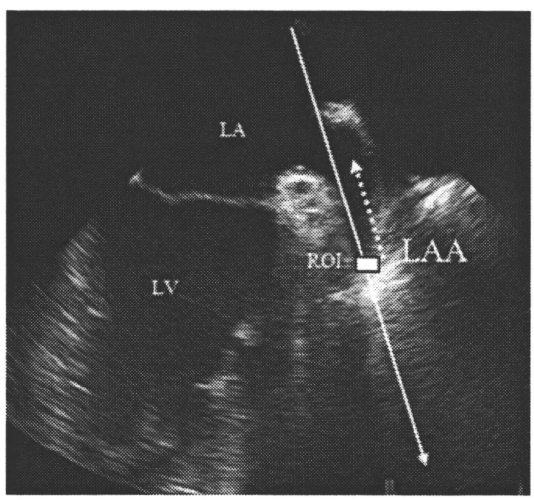

Figure 2. The Doppler beam (white arrows) was almost parallel to the direction of LAA wall motion (dotted arrows) in the long-axis view in TEE. AO = aorta; LA = left atrium; LAA = left atrial appendage; LV = left ventricle.

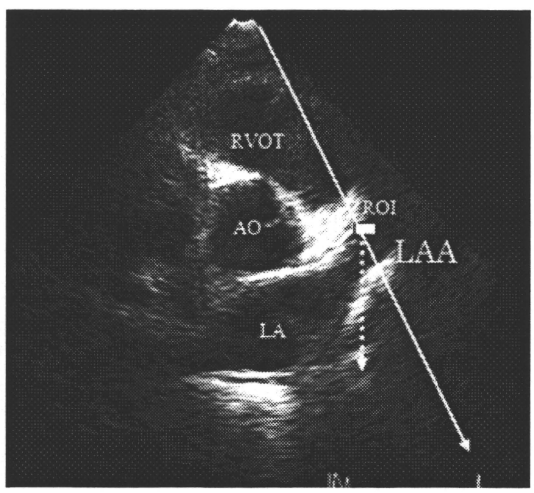

Figure 3. The direction of the Doppler beam (white arrows) was different from that of LAA wall motion (dotted arrows) in the long-axis view in TTE, even after aligning the Doppler beam as parallel as possible to the longitudinally contracting appendage. AO = aorta; LA = left atrium; LAA = left atrial appendage; RA = right atrium.

by two different observers divided by the mean value, and intraobserver variability for the same was calculated as the difference between two measurements of the same subject by one observer divided by the mean value. The study protocol was approved by our institutional review board, and informed consent was obtained from all patients.

Results:

Validation of Transthoracic LAAWV Measurement:

Transesophageal TDE patterns of LAA were reproducible and similar to Doppler flow patterns of LAA, and transthoracic TDE patterns of LAA were reproducible and similar to those of transesophageal TDE patterns of LAA (Fig. 1).

When no angle correction was applied for the Doppler beam in TTE, LAAWVc and LAAWVr measured by TTE were lower than LAAWVc and LAAWVr measured by TEE (13.4 [5.7] cm/sec vs. 15.6 [6.1] cm/sec; P = 0.007 and 11.4 [3.6] cm/sec vs. 12.9 [4.6] cm/sec; P = 0.05). The correlation coefficient between TTE and TEE for LAAWVc was r = 0.90, and that between TTE and TEE for LAAWVr was r = 0.78. According to the Bland-Altman analysis, the mean difference in the LAAWVc values measured by TTE and TEE was 2.1 cm/sec, and the mean difference in the LAAWVr values measured by TTE and TEE was 1.4 cm/sec (Fig. 4). When angle correction was applied for the Doppler beam in TTE, TTE and TEE gave similar values for LAAWVc and LAAWVr (15.8 [6.2] cm/sec vs. 15.6 [6.1] cm/sec and 13.5 [4.3] cm/sec vs. 12.9 [4.6] cm/sec). The correlation coefficients between TTE and TEE for LAAWVc was r = 0.97, and that between TTE and TEE for LAAWVr was r = 0.95. According to the Bland-Altman analysis, the mean difference in the LAAWVc value measured by TTE and TEE was −0.3 cm/sec, and the mean difference in the LAAWVr value measured by TTE and TEE was −0.6 cm/sec. (Fig. 5). When angle correction was applied for the Doppler beam in TTE, the correlation coefficients were better, and mean differences revealed narrow distribution in comparison with the correlation coefficients and mean differences obtained without angle correction. Moreover, when angle correction was applied for the Doppler beam in TTE, LAAWVc and LAAWVr measured by TTE correlated significantly with LAAVc and LAAVr measured by TEE, respectively (r = 0.64, P < 0.001 and r = 0.53, P = 0.001). LAAWVc measured by TTE correlated significantly with LAAFC measured by TEE (r = 0.61, P = 0.001).

The intraobserver and interobserver variabilities were low for LAAWVc (2.9% and 4.3%,

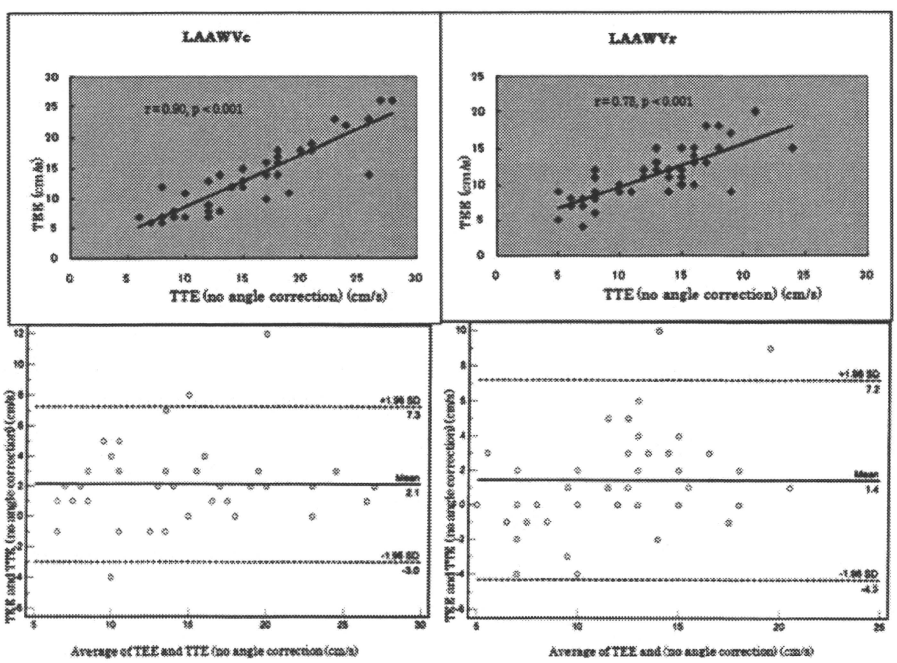

Figure 4. Regression analysis (left upper panel) and Bland-Altman plot (left lower panel) for LAA wall velocity during contraction (LAAWVc) measured by TEE and TTE when the angle correction was not applied for the Doppler beam in TTE. Regression analysis (right upper panel) and Bland-Altman plot (right lower panel) for LAA wall velocity during relaxation (LAAWVr) measured by TEE and TTE when the angle correction was not applied for the Doppler beam in TTE.