Original Article

Differential Effects of Atorvastatin and Pitavastatin on Inflammation, Insulin Resistance, and the Carotid Intima-Media Thickness in Patients with Dyslipidemia

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***Aims*: 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have multiple pleiotropic effects, such as anti-inflammatory and vascular endothelium protection, that are independent of their low-density-lipoprotein (LDL) cholesterol lowering effects. However, whether different statins exert diverse effects on inflammation, insulin resistance, and the progression of carotid atherosclerosis [as indicated by the intima-media thickness (CIMT)] in patients with dyslipidemia remains unclear.**
***Methods*: A total of 146 patients with hypercholesterolemia without known cardiovascular disease were randomly assigned to receive 5 mg/day of atorvastatin ($n=73$) or 1 mg/day of pitavastatin ($n=73$).**
***Results*: At baseline, age, gender, blood pressure, lipid profiles, and the serum monocyte chemoattractant protein (MCP)-1, homeostasis model assessment of insulin resistance (HOMA-IR) and CIMT values were comparable between the groups. After 12 months of treatment, atorvastatin and pitavastatin equally reduced the LDL cholesterol levels; however, atorvastatin increased the HOMA-IR by +26% and pitavastatin decreased this parameter by −13% ($p<0.001$). The MCP-1 values were reduced by −28% in the patients treated with pitavastatin and only −11% in those treated with atorvastatin ($p=0.016$). A greater percent decrease in the mean CIMT from baseline was observed in the patients treated with pitavastatin than in those treated with atorvastatin (−4.9% vs. −0.5%, $p=0.020$).**
***Conclusions*: These data indicate that, while these agents significantly and equally reduce the LDL cholesterol levels, atorvastatin and pitavastatin have different effects on inflammation, insulin resistance, and the progression of carotid atherosclerosis in patients with dyslipidemia.**

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Key words: Statins, Inflammation, Insulin resistance, Carotid intima-media thickness

Introduction

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been shown to reduce the incidence of cardiovascular disease (CVD) in primary and secondary prevention studies[1-4]. The cardiovascular benefits of statins are conventionally attributed to their ability to reduce the LDL-cholesterol level[5]. However, although statins reduce the values of LDL cholesterol and inflammatory markers, including C-reactive protein (CRP), the correlation coefficient between LDL cholesterol and CRP is weak (approximately 0.13)[6], suggesting that the reductions in CRP cannot be explained by the reductions in LDL cholesterol alone. In addition, patients treated with statins have a decreased rate of CVD than that predicted by their achieved LDL cholesterol levels, raising the possibility of a distinct mechanism of action independent of cholesterol reduction (cholesterol-independent or pleiotropic effects)[7]. In fact, numerous studies have confirmed that statins have pleiotropic actions, including reductions in inflammation and oxidative

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stress, as well as effects resulting in improvements in both the endothelial dysfunction and coagulation[7-10].

Inflammation plays a significant role in the pathogenesis and development of CVD, such as heart failure and acute coronary syndrome[10, 11]. Activated macrophages produce proinflammatory cytokines and chemokines, including tumor necrosis factor (TNF)-α and monocyte chemoattractant protein (MCP)-1, which play important roles in the pathogenesis and development of atherosclerosis and CVD[10, 11].

Arterial wall thickening may be assessed *in vivo* based on ultrasound measurements of the carotid intima-media thickness (CIMT). The CIMT is correlated with coronary and carotid atherosclerosis and is a significant predictor of future cardiovascular events. For these reasons, the CIMT has been widely used in many clinical studies as a surrogate marker of coronary and carotid atherosclerosis and the risk of CVD[12-14].

Clinical and experimental studies have demonstrated that statins attenuate inflammatory and oxidative stress markers and slow the progression of carotid atherosclerosis. However, there have been few studies regarding direct comparisons of the effects of distinct statins on insulin sensitivity as well as inflammatory and oxidative stress markers[15-17]. Furthermore, there have been no studies so far regarding direct comparisons of the differential effects of statins on inflammatory markers, insulin resistance, and the progression of carotid atherosclerosis in patients with dyslipidemia. Therefore, this study was conducted to examine whether atorvastatin and pitavastatin have different effects in dyslipidemic patients.

Methods

Study Subjects

This study was a prospective, randomized, open-label trial, and single-center study. The present study was originally designed to enroll more than 400 patients, because 200 patients were required in each group in order to achieve a power of 80% to detect a 20% difference in the percent change in the mean CIMT (mCIMT) from baseline to 12 months of treatment between the treatment groups. All patients were recruited from Tama-Nagayama Hospital, Nippon Medical School at an outpatient clinic between January 2009 and December 2011. Follow-up data were obtained (every 4−8 weeks) via direct contact with the patients at an outpatient clinic of our hospital until January 2014.

Drs. A.N. and T.S recruited the patients from an outpatient clinic and Dr. Y.K. blindly collected all patient data. Dr. M.K. performed the statistical analyses independent of the study group. Dr. W.S. was the chief investigator of this study, and Dr. H.A. made the final review of the manuscript.

This study included patients (≥20 years) with dyslipidemia. The patients were considered to have dyslipidemia if they had an overnight fasting serum total cholesterol (TC) level of ≥220 mg/dL, triglyceride (TG) level of ≥150 mg/dL, LDL cholesterol level of ≥140 mg/dL, or HDL cholesterol level of <40 mg/dL. The LDL cholesterol level was calculated using the Friedewald formula (LDL cholesterol=TC−HDL cholesterol−TG/5). The non-HDL cholesterol level was calculated using the following formula: non HDL cholesterol=TC−HDL cholesterol.

Subjects with clinical signs of acute infection, autoimmune disorders, severe renal (serum creatinine level >2.0 mg/dL) or hepatic disease, or with suspected malignancy were excluded from the present series. In addition, patients with a history of CVD, including coronary artery disease, cardiomyopathy, and valvular heart disease, or stroke and/or arteriosclerosis obliterans were also excluded from this study. None of the patients had received lipid modulating medications, including statins or fibrates before enrollment.

For equalization between the two groups, the patients were randomly assigned to either the atorvastatin group or pitavastatin group. The envelope method was employed using mathematical techniques, such as the use of a random number table by an independent administrator (Dr. K.K.) for group allocation. The present study does not have either a study registration number or URL.

The investigation protocol was approved by the institutional review board and ethics committee of Nippon Medical School, Tama-Nagayama Hospital and was performed in accordance with the Declaration of Helsinki. All subjects provided their written informed consent to participate in the study.

A total of 160 randomly selected patients with dyslipidemia (86 males and 74 females; mean age, 67.0±9.4 years) were enrolled in the current study. Three patients were excluded from randomization as a result of withdrawal of consent. After randomization, four patients were excluded due to non-compliance (**Fig. 1**). Therefore, 77 of the 153 remaining patients were randomly assigned to receive 5 mg/day of atorvastatin, while the remaining 76 patients were randomly assigned to receive 1 mg/day of pitavastatin. We were unable to follow-up two patients treated with atorvastatin and two patients treated with pitavastatin because they moved to other hospitals during the follow-up period. In addition, two patients discontinued atorvastatin treatment because of increases in their

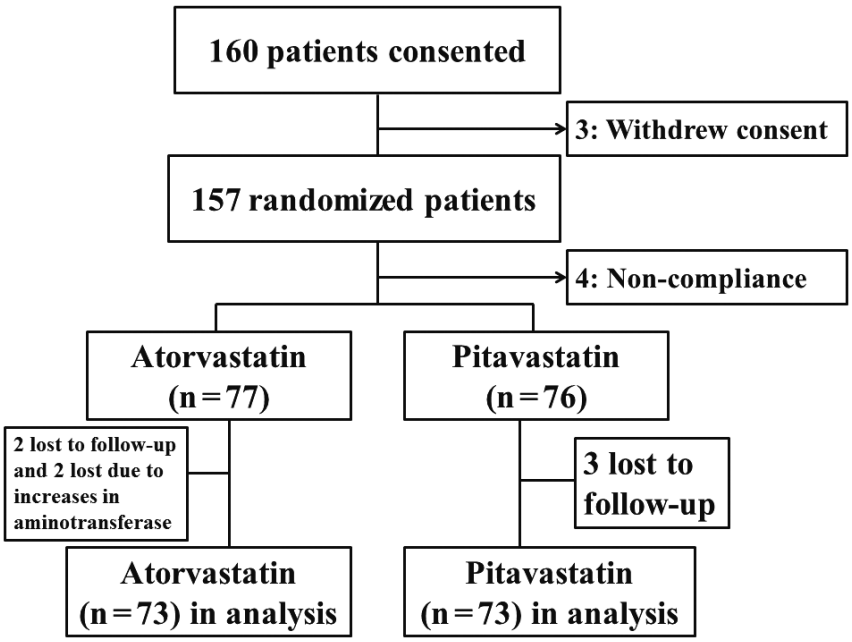

Fig. 1. Flow chart of the patients enrolled in the present study. This study was a prospective, randomized, and open-label trial.

aminotransferases values. Finally, 73 patients treated with atorvastatin and 73 patients treated with pitavastatin completed the present study (**Fig. 1**).

Laboratory Measurements

The serum levels of TNF-α and MCP-1 at baseline and after 12 months of treatment were measured with a specific enzyme-linked immunosorbent assay (ELISA) using commercially available systems (R&D Systems), and the results are expressed as the mean ± SD (pg/mL). The intra- and inter-assay coefficients of variation were less than 5% for all ELISAs, and all samples were analyzed in duplicate.

The hsCRP values were measured using an immunoturbidimetry assay. The homeostasis model assessment of insulin resistance [HOMA-IR; the score equals immunoreactive insulin (IRI; μU/mL) times fasting plasma glucose (FPG; mg/dL) divided by 405] was calculated and used as a marker of insulin resistance. To determine the renal function, the estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease prediction equation for Japanese subjects ($194 \times \text{serum creatinine}^{-1.094}$ (mg/dL) $\times \text{Age}^{-0.287}$ (years) $\times 0.739$, if female)[18].

Carotid Intima-media Thickness

The right and left carotid arteries were examined and the mean CIMT (mCIMT) was estimated according to a standardized protocol by one blinded trained sonographer using B-mode ultrasound with a 10 MHz linear probe (LOGIQ 7, GE, Milwaukee, WI). The CIMT was measured at three points in each common carotid artery 10 mm proximal to the site of bifurcation, and the mean value of six measurements for the right and left carotid arteries was calculated and used for the subsequent analysis. The progression of carotid atherosclerosis was defined as follows: a positive percent change in the mCIMT from baseline to 12 months of treatment, namely (mCIMT at 12 months minus baseline mCIMT)/baseline mCIMT $\times 100 > 0$. The intra-observer and inter-observer coefficients of variation for the repeated measurements of the CIMT in our laboratory were 2.9% and 3.2%, respectively.

Statistical Analysis

The results are presented as the mean ± SD for continuous variables and the percentage of the total number of patients for categorical variables. Student's *t*-test for independent samples and the chi-square test were used to compare continuous and categorical variables, respectively. The distributions of the TG, TNF-α, MCP-1, and hsCRP levels were skewed; hence, the Mann-Whitney test was used for unpaired comparisons between the two groups and Wilcoxon's signed-rank test was used for paired comparisons within the two groups, with the data expressed as the median (25th−75th percentile). In terms of the baseline and 12 month values, the data between groups were com-

Table 1. Clinical characteristics, blood chemical variables and mean carotid intima-media thickness in the patients treated with atorvastatin and pitavastatin

	Atorvastatin ($n=73$)	Pitavastatin ($n=73$)	p-value
Age (years)	65.9 ± 10.7	66.1 ± 9.5	0.870
Gender (male, %)	41 (53.2)	36 (46.8)	0.507
Body mass index (kg/m^2)	25.2 ± 3.1	24.5 ± 3.7	0.246
Waist circumference (cm)	87.7 ± 8.3	86.2 ± 9.9	0.320
Systolic blood pressure (mmHg)	130 ± 2	130 ± 4	0.250
Heart rate (beats/min)	72 ± 2	73 ± 2	0.080
Hemoglobin (g/dL)	14.3 ± 1.1	14.2 ± 1.1	0.316
High sensitivity-CRP (mg/L)	0.90 (0.35, 2.80)	0.58 (0.38, 2.26)	0.920
Total cholesterol (mg/dL)	244 ± 27	247 ± 25	0.378
LDL-C (mg/dL)	161 ± 29	162 ± 23	0.926
HDL-C (mg/dL)	55 ± 15	59 ± 17	0.143
Triglycerides (mg/dL)	132 (96, 164)	132 (91, 178)	0.788
LDL-C/HDL-C ratio	3.1 ± 0.9	2.9 ± 0.7	0.136
non HDL-C (mg/dL)	189 ± 27	189 ± 21	0.981
Fasting plasma glucose (mg/dL)	104 ± 15	104 ± 13	0.888
IRI (μU/mL)	8.6 ± 3.8	8.9 ± 7.3	0.765
HOMA-IR	2.2 ± 1.2	2.3 ± 2.2	0.842
HbA1c (JDS; %)	5.5 ± 0.6	5.4 ± 0.5	0.170
eGFR (mL/min/1.73 m^2)	68.6 ± 15.4	71.1 ± 16.1	0.332
Baseline TNF-α (pg/mL)	12.5 (8.5, 16.0)	15.2 (9.4, 17.3)	0.102
Baseline MCP-1 (pg/mL)	105.3 (67.8, 221.0)	133.0 (87.1, 254.0)	0.143
Mean CIMT (mm)	0.884 ± 0.166	0.902 ± 0.196	0.669

The data are expressed as the mean ± SD or median (interquartile range). CRP: C-reactive protein, C: cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, IRI: immunoreactive insulin, HOMA-IR: homeostasis model assessment of insulin resistance, eGFR: estimated glomerular filtration rate, TNF: tumor necrosis factor, MCP: monocyte chemoattractant protein, CIMT: carotid intima-media thickness

pared with a two-way analysis of variance followed by Bonferroni correction. To compare the percent changes in the mCIMT between the two groups, a graph was prepared using the box and whisker plots with the median levels and 25th and 75th interquartile ranges. The bivariate correlations between parameters were assessed with the Pearson or Spearman correlation (r) coefficient for normal or skewed distributions, respectively.

The associations between the percent change in the mCIMT from baseline to after 12 months of treatment and other variables were explored using a multiple linear regression analysis with forward stepwise selection of covariates. The percent (%) changes in various values were defined as follows: (values at each time points minus values at baseline/values at baseline) × 100. Univariate and multivariate logistic regression analyses were employed to calculate the estimated odds ratio (OR) with a 95% confidence interval (CI) where appropriate.

Potential predictors of the progression of carotid atherosclerosis (defined as a positive percent change in mCIMT from baseline to 12 months) included age, gender, active smoking status, and the percent changes in the SBP, heart rate, waist circumference, TG, LDL cholesterol, HDL cholesterol, HOMA-IR, hsCRP, TNF-α, and MCP-1 levels, as well as the use of pitavastatin, angiotensin-converting inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), β-blockers, or sulfonylureas. The variables were entered into a multivariate model of factors with a p-value of ≤ 0.05 in the univariate analysis. The Statistical software Package for Social Science (SPSS) for Windows, version 22.0 (IBM, Japan) was used for the statistical analyses. A p-value of ≤ 0.05 was considered to be statistically significant.

Results

The baseline characteristics of the patients treated with atorvastatin and those treated with pitavastatin are shown in **Table 1**. Overall, the clinical characteris-

Table 2. Prevalence of coronary risk factors and concomitant medications in the patients treated with atorvastatin and pitavastatin

	Atorvastatin ($n=73$)	Pitavastatin ($n=73$)	p-value
Diabetes (%)	30 (41.1)	21 (28.8)	0.165
Hypertension (%)	54 (74.0)	60 (82.2)	0.317
Smoker (%)	24 (32.9)	15 (20.5)	0.134
CCBs (%)	39 (53.4)	50 (68.5)	0.089
ACEIs (%)	17 (23.3)	14 (19.2)	0.686
ARBs (%)	16 (21.9)	26 (35.6)	0.100
β-blockers (%)	9 (12.3)	7 (9.6)	0.792
Sulfonylureas (%)	1 (1.4)	2 (2.7)	0.560
α-glucosidase inhibitors (%)	4 (5.5)	0 (0)	0.120
Metformin (%)	14 (19.2)	9 (12.3)	0.364
Pioglitazone (%)	6 (8.2)	9 (12.3)	0.587
Insulin(%)	0 (0)	0 (0)	1.000

CCBs: calcium channel blockers, ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers

tics were comparable between the groups. The prevalence of treatment with CCBs showed a tendency to be higher in the patients treated with pitavastatin than in those treated with atorvastatin (68.5% vs. 53.4%, $p=0.089$, **Table 2**); however, the frequencies of diabetes, hypertension, and active smokers and the use of concomitant medications, including ACEIs, ARBs, β-blockers, and/or anti-diabetic medications, were similar between the groups (**Table 2**).

Lipid Parameters and Insulin Resistance

At baseline, there were no significant differences in the serum lipid, glycated hemoglobin (HbA1c), FPG, fasting IRI, or HOMA-IR values between the groups (**Table 1**). After 12 months of treatment, atorvastatin and pitavastatin significantly and equally reduced the total TC (−21.3% vs. −19.5%, $p=0.234$), LDL cholesterol (−29.2% vs. −28.6%, $p=0.772$), TG (−17.6% vs. −15.2%, $p=0.556$), and non-LDL cholesterol levels (−28.2% vs. −27.5%, $p=0.718$), as well as the LDL-cholesterol/HDL-cholesterol ratio (−30.2% vs. −33.0%, $p=0.193$) (**Fig. 2A** and **Table 3**). However, the patients treated with pitavastatin exhibited an increase in the HDL cholesterol values of +6.8%, in comparison to only a +1.8% increase in the patients treated with atorvastatin ($p=0.001$, **Fig. 2A** and **Table 3**).

After 12 months, the FPG, IRI, and HbA1c levels in the patients treated with pitavastatin were significantly lower than those in the patients treated with atorvastatin (**Table 3**). The values of HOMA-IR, a marker of insulin resistance, increased by +25.6% in the patients receiving atorvastatin, whereas these values decreased by −13.0% in those receiving pitavastatin ($p<0.001$, **Fig. 2A** and **Table 3**).

Inflammatory Markers

There were no significant differences in terms of the baseline hsCRP, TNF-α, and MCP-1 levels between the groups (**Tables 1** and **3**). After 12 months of treatment, atorvastatin significantly reduced the hsCRP, TNF-α, and MCP-1 levels by −23.6%, −21.1%, and −10.9%, respectively, while pitavastatin significantly reduced the hsCRP, TNF-α, and MCP-1 levels by −32.1%, −36.0%, and −27.9%, respectively (**Fig. 2B** and **Table 3**). In addition, a significant reduction in the percent (%) change from baseline to 12 months in TNF-α and MCP-1 was observed in the patients treated with pitavastatin compared to those receiving atorvastatin (TNF-α; −36.0% vs. −21.1%, $p<0.001$, MCP-1; −27.9% vs. −10.9%, $p=0.016$). Pitavastatin treatment also tended to reduce the hsCRP levels more than atorvastatin therapy ($p=0.096$, **Fig. 2B** and **Table 3**).

Relationships between the Clinical Characteristics, Lipid Parameters, Inflammatory Markers, and CIMT in the Patients with Dyslipidemia

The mean CIMT (mCIMT) values in the patients treated with atorvastatin and pitavastatin at baseline and after 12 months of treatment are shown in **Tables 1** and **3**. The mCIMT at baseline was comparable between the groups. However, after 12 months of treatment, a greater decrease in the mCIMT was observed in the patients treated with pitavastatin than in those treated with atorvastatin (−4.9% vs. −0.5%, $p=0.020$, **Table 3** and **Fig. 3**).

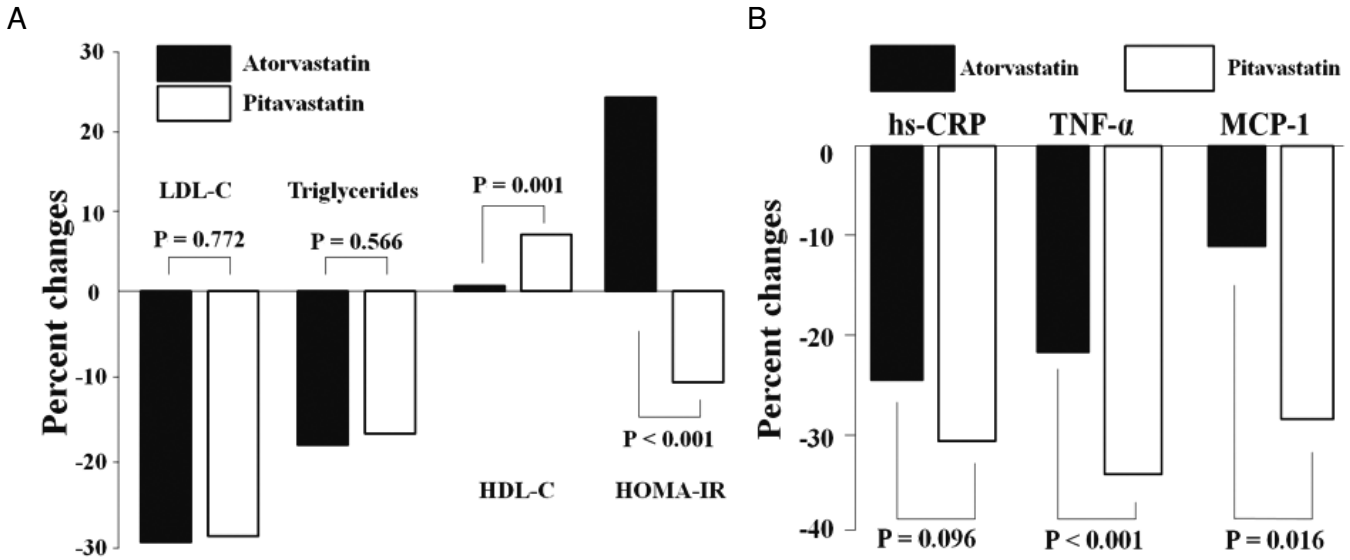

Fig. 2. Percent (%) changes in the lipid profiles and HOMA-IR (A) from baseline to after 12 months of treatment in the atorvastatin (black bars) and pitavastatin (white bars) groups and % changes from baseline in the hs-CRP, TNF-α, and MCP-1 values (B) in the atorvastatin (black bars) and pitavastatin (white bars) groups. HOMA-IR; homeostasis model assessment of insulin resistance, hs-CRP; high-sensitivity C-reactive protein, TNF; tumor necrosis factor, MCP; monocyte chemoattractant protein.

Table 3. Changes in the clinical characteristics and blood chemistry parameters from baseline to after 12 months of treatment in the patients treated with atorvastatin and pitavastatin

	Atorvastatin (n=73)		Pitavastatin (n=73)	
	Baseline	At 12 months (the % change)	Baseline	At 12 months (the % change)
Total-C (mg/dL)	244±27	190±25 (−21.3)$^{\&}$	247±25	199±22 (−19.5)$^{\&}$
LDL-C (mg/dL)	161±29	113±29 (−29.2)$^{\&}$	162±23	113±29 (−28.6)$^{\&}$
HDL-C (mg/dL)	55±15	55±15 (+1.8)	59±17	62±16 (+6.8)$^{\$\ \#}$
TG (mg/dL)	132 (96, 164)	108 (86, 126) (−17.6)$^{\&}$	132 (91, 178)	108 (73, 124) (−15.2)$^{\&}$
LDL-C/HDL-C ratio	3.1±0.9	2.2±0.8 (−30.2)$^{\&}$	2.9±0.7	2.0±0.5 (−33.0)$^{\$\ \#}$
non HDL-C (mg/dL)	189±27	135±27 (−28.2)$^{\&}$	189±21	137±22 (−27.5)$^{\&}$
FPG (mg/dL)	104±15	107±18 (+3.3)$^{\$}$	104±13	101±14 (−3.1)$^{\$\ \#}$
IRI (μU/mL)	8.6±3.8	9.9±6.0 (+21.9)$^{\&}$	8.9±7.3	7.5±5.8 (−9.4)$^{\$\ \#}$
HOMA-IR	2.2±1.2	2.6±1.7 (+25.6)$^{\&}$	2.3±2.2	1.9±1.7 (−13.0)$^{\&\ *}$
HbA1c (JDS; %)	5.5±0.6	5.5±0.6 (−0.2)	5.4±0.5	5.3±0.4 (−2.5)$^{\#}$
hs-CRP (mg/L)	0.90 (0.35, 2.80)	0.50 (0.24, 2.20) (−23.6)$^{\&}$	0.58 (0.38, 2.26)	0.50 (0.24, 2.20) (−32.1)$^{\&}$
TNF-α (pg/mL)	12.5 (8.5, 16.0)	9.5 (6.1, 11.3) (−21.1)$^{\&}$	15.2 (9.4, 17.3)	9.5 (6.1, 11.3) (−36.0)$^{\&\ *}$
MCP-1 (pg/mL)	105.3 (67.8, 221.0)	78.0 (55.7, 152.3) (−10.9)$^{\&}$	133.0 (87.1, 254.0)	78.0 (55.7, 152.3) (−27.9)$^{\&\ \#}$
Mean CIMT (mm)	0.884±0.166	0.875±0.180 (−0.4)	0.902±0.196	0.857±0.212 (−4.9)$^{\$\ \#}$

$^{\$}p<0.05$ vs. baseline, $^{\&}p<0.01$ vs. baseline $^{\#}p<0.05$, $^{*}p<0.001$ vs. patients treated with atorvastatin at 12 months, The values in *parentheses* represent the percent changes from baseline to after 12 months of treatment, The data are expressed as the mean±SD or median (interquartile range), C: cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, FPG: fasting plasma glucose, IRI: immunoreactive insulin, HOMA-IR: homeostasis model assessment of insulin resistance, JDS: Japan Diabetes Society, hs-CRP: high-sensitivity C-reactive protein, TNF: tumor necrosis factor, MCP: monocyte chemoattractant protein, CIMT: carotid intima-media thickness

In the multivariate linear regression analysis, the use of pitavastatin and percent changes in the waist circumference and MCP-1 values from baseline to 12 months were significantly and independently associated with the percent change in the mCIMT from baseline (**Table 4**). Further adjustment for various medications, such as CCBs, ACEIs, ARBs, β-blockers, and sulfonylureas, did not eliminate the associa-

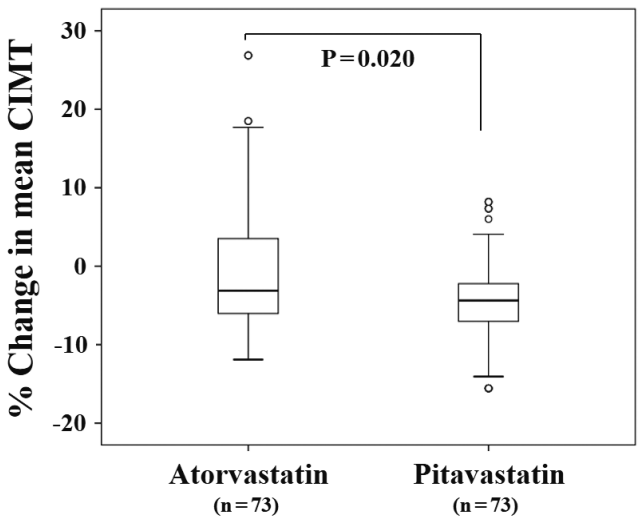

Fig. 3. Percent (%) change in the mean CIMT from baseline to after 12 months of treatment in the atorvastatin and pitavastatin groups. The box and whisker plots show the median levels and 25th and 75th interquartile ranges (delineated by the bottom and top of each box), and the circles represent outliers that are >1.5% of the 75th confidence interval. CIMT; carotid intima-media thickness, $p=0.020$; atorvastatin vs. pitavastatin.

tion with pitavastatin use or the percent change in the mCIMT from baseline to 12 months (β coefficient = −0.221, $p=0.030$).

The multivariate logistic regression analysis showed that the use of pitavastatin (OR (odds ratio) 0.228, 95% confidence interval (CI) 0.093−0.557, $p=0.001$) and plasma levels of MCP-1 (OR 1.022, 95% CI 1.008−1.035, $p=0.002$) were strongly and independently associated with the progression of carotid atherosclerosis, which was defined as the positive percent change in the mCIMT from baseline to 12 months (**Table 5**).

In order to elucidate the pathophysiological mechanisms by which pitavastatin and/or atorvastatin treatment is useful for suppressing the progression of carotid atherosclerosis, we investigated the relationships between the percent change in the mCIMT from baseline and the percent changes in the various parameters from baseline, including blood pressure, lipid profiles, and inflammatory markers, such as the hsCRP, MCP-1, and TNF-α levels.

In the patients treated with atorvastatin, the percent change in the mCIMT from baseline to 12 months of treatment was significantly but weakly associated with the percent change from baseline in MCP-1 ($r=0.250$, $p=0.033$, **Fig. 4A**) and negatively associated with the percent change from baseline in the systolic

Table 4. Multivariate logistic regression analysis of the percent change from baseline to 12 months in the mean carotid intima-media thickness

	β	p value
Age (age)	0.001	0.999
Gender (male)	0.076	0.362
Active smoking	−0.022	0.790
Pitavastatin use (vs. atorvastatin)	−0.221	0.030
Calcium channel blockers use	0.049	0.590
ACEIs or ARBs use	0.103	0.263
β-blockers use	−0.081	0.359
Sulfonylurea use	0.018	0.848
Percent change in SBP	0.155	0.129
Percent change in heart rate	−0.166	0.158
Percent change in waist circumference	−0.270	0.011
Percent change in LDL cholesterol	0.093	0.305
Percent change in HDL cholesterol	−0.028	0.798
Percent change in Triglycerides	−0.049	0.589
Percent change in HOMA-IR	−0.064	0.536
Percent change in hsCRP	0.133	0.182
Percent change in MCP-1	0.352	<0.001
Percent change in TNF-α	−0.022	0.822
	Model adjusted $R^2=0.291$	

β: regression coefficient, ACEis: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, SBP: systolic blood pressure, LDL: low-density lipoprotein HDL: high-density lipoprotein, HOMA-IR: hemostasis model assessment of insulin resistance, hsCRP: high sensitivity C reactive protein, lVlCP: monocyte chemoattractant proten, TNF: tumor necrosis factor

blood pressure (SBP; $r=-0.273$, $p=0.020$), waist circumference ($r=-0.288$, $p=0.014$), FPG ($r=-0.428$, $p<0.001$), and HOMA-IR ($r=-0.351$, $p=0.002$) values. However, the percent change in the mCIMT from baseline was not related to the percent changes from baseline in the TNF-α ($r=-0.090$, $p=0.451$, **Fig. 4C**), hsCRP ($r=0.163$, $p=0.168$, **Fig. 5A**), LDL cholesterol ($r=0.095$, $p=0.425$, **Fig. 5C**), HDL cholesterol ($r=-0.041$, $p=0.729$), TG ($r=-0.147$, $p=0.214$), or non-HDL cholesterol ($r=0.035$, $p=0.768$) levels or the LDL-cholesterol/HDL-cholesterol ratio ($r=0.108$, $p=0.365$).

In the patients treated with pitavastatin, the percent change in the mCIMT from baseline to 12 months was significantly and positively associated with the percent changes from baseline in the MCP-1 ($r=0.729$, $p<0.001$, **Fig. 4B**), TNF-α ($r=0.576$, $p<0.001$, **Fig. 4D**), and hsCRP ($r=0.360$, $p=0.002$, **Fig. 5B**) levels and negatively associated with the percent change from baseline in FPG ($r=-0.232$, $p=0.049$). However, the percent change in the mCIMT values from baseline was not correlated with the percent changes

Table 5. Multivariate regression analysis of the progression of carotid atherosclerosis

	Univariate			Multivariate		
	OR	95% C.I.	*p* value	OR	95% C.I.	*p* value
Age (years)	0.99	0.95 – 1.02	0.436			
Gender (male)	1.38	0.69 – 2.75	0.359			
Active smoking	0.90	0.41 – 1.98	0.788			
Diabetes	0.62	0.30 – 1.30	0.207			
Hypertension	0.99	0.44 – 2.27	0.986			
Pitavastatin use (vs. atorvastatin)	0.18	0.08 – 0.39	< 0.001	0.23	0.09 – 0.56	0.001
Calcium channel blockers use	1.03	0.52 – 2.06	0.935			
ACEIs or ARBs use	0.89	0.45 – 1.76	0.727			
β-blockers use	0.41	0.11 – 1.50	0.178			
Sulfonylurea use	0.96	0.09 – 10.84	0.959			
Change in waist circumference (cm)	0.82	0.68 – 0.99	0.035	0.79	0.62 – 1.01	0.057
Change in SBP (mmHg)	0.89	0.73 – 1.08	0.223			
Change in heart rate (beats/min)	1.01	0.89 – 1.15	0.857			
Change in triglycerides (mg/mL)	0.99	0.98 – 1.01	0.359			
Change in LDL cholesterol (mg/dL)	1.02	0.99 – 1.04	0.209			
Change in HDL cholesterol (mg/dL)	0.96	0.93 – 1.00	0.049	1.01	0.96 – 1.06	0.656
Change in HOMA-IR	1.00	0.99 – 1.01	0.988			
Change in hsCRP (mg/L)	1.01	0.99 – 1.02	0.220			
Change in MCP-1 (pg/mL)	1.03	1.01 – 1.04	< 0.001	1.02	1.01 – 1.04	0.002
Change in TNF-α (pg/mL)	1.01	0.99 – 1.02	0.375			

OR: odds ratio, C.I.: confidence interval, ACEIs: angiotensin-converting inhibitors, ARBs: angiotensin receptor blockers, SBP: systolic blood pressure, LDL: low-density lipoprotein, HDL: high-density lipoprotein, HOMA-IR: homeostasis model assessment of insulin resistance, hsCRP: high-sensitivity C-reactive protein, MCP: monocyte chemoattractant protein, TNF: tumor necrosis factor

from baseline in the SBP ($r = -0.013$, $p = 0.916$), waist circumference ($r = -0.207$, $p = 0.080$), LDL cholesterol ($r = -0.049$, $p = 0.683$, **Fig. 5D**), HDL cholesterol ($r = -0.085$, $p = 0.477$), TG ($r = -0.069$, $p = 0.562$), non-HDL cholesterol ($r = -0.107$, $p = 0.368$), LDL-cholesterol/HDL-cholesterol ratio ($r = 0.094$, $p = 0.430$), or HOMA-IR ($r = -0.024$, $p = 0.839$) values.

Safety

All patients tolerated the treatment well, without any serious side effects during the follow-up period. None of the patients experienced cardiovascular events, including acute coronary syndrome, heart failure, arrhythmia, stroke, or peripheral artery disease, during the follow-up period. In addition, none of the patients died from any causes, including CVD or cancer. Two patients treated with atorvastatin discontinued the treatment because of increases in their aminotransferases levels (alanine aminotransferase increased in one patient from 12 IU/mL to 120 IU/mL, aspartate aminotransferase increased in one patient from 22 IU/mL to 98 IU/mL, **Fig. 1**). However, none of the patients developed rhabdomyolysis during the follow-up period.

Discussion

The cardiovascular benefits of statins are conventionally attributed to reductions in the LDL cholesterol level[5]. However, the nature of the correlation between the extent of cholesterol reduction induced by statins and the degree of clinical benefit remains controversial[8, 9]. The post hoc analyses of the West of Scotland Coronary Prevention Study (WOSCOPS)[1], Cholesterol and Recurrent Events (CARE)[2], and Scandinavian Simvastatin Survival Study (4S)[3] studies have resulted in conflicting reports. In the WOSCOPS study, the reduction in the rates of fatal and nonfatal coronary heart disease was related to LDL cholesterol-lowering effects of up to 24%; however, no additional benefits were observed for further reductions in the LDL cholesterol levels, even up to 39%[1]. Similarly, the relative risk of the endpoint in the CARE study was progressively reduced, with the LDL cholesterol levels declining from 140 to 120 mg/dL; however, additional lowering of LDL cholesterol did not produce additional risk reduction[2].

On the other hand, the relationship between

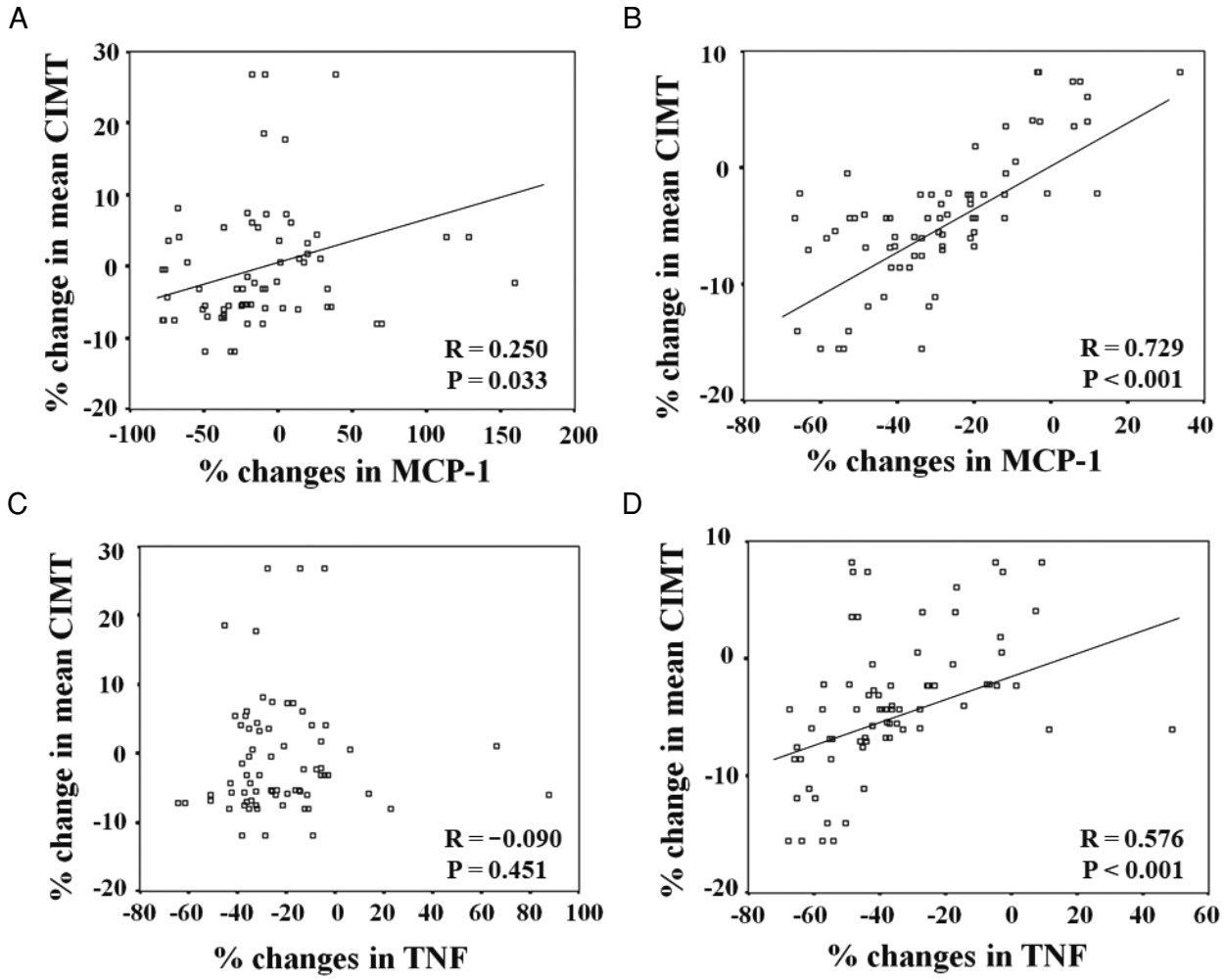

Fig. 4. Relationship between the percent (%) change from baseline to after 12 months of treatment in the MCP-1 values and the % change from baseline in the mean CIMT in the atorvastatin ($r=0.250$, $p=0.033$; A) and pitavastatin ($r=0.729$, $p<0.001$; B) groups. Relationship between the % change from baseline in the TNF-α values and the % change from baseline in the mean CIMT in the atorvastatin ($r=-0.090$, $p=0.451$; C) and pitavastatin ($r=0.576$, $p<0.001$; D) groups. CIMT; carotid intima-media thickness.

cholesterol reduction and event reduction in the 4S trial was curvilinear and did not reach a threshold[3]. Although apparently divergent, these results may be a function of the global risk and baseline LDL cholesterol levels in the population studied[7-9]. In addition, many clinical trials have shown that more significant reductions in the risk of CVD are associated with only minimal changes in the coronary luminal dimensions estimated on coronary angiography[7-9]. These data suggest that the benefits of the reductions in the risk of CVD achieved with statins cannot be explained by simple plaque regression due to reductions in the LDL cholesterol level alone.

Therefore, other mechanisms (LDL cholesterol-independent effects or pleiotropic effects) may be involved in these benefits. Potential mechanisms that may mediate these effects include improved endothelial dysfunction, plaque stabilization, attenuated atherogenesis, and anti-inflammatory and anti-thrombotic actions[7-10].

It has been reported that statins attenuate inflammatory and oxidative stress markers and slow the progression of carotid atherosclerosis[17]; however, there have been few studies regarding the effects of distinct statins on insulin sensitivity, inflammatory, and oxidative stress markers, and the progression of carotid atherosclerosis[15-17]. In addition, there have been no studies thus far regarding the differential effects of statins on inflammatory markers, insulin resistance, and the progression of carotid atherosclerosis (as indicated by

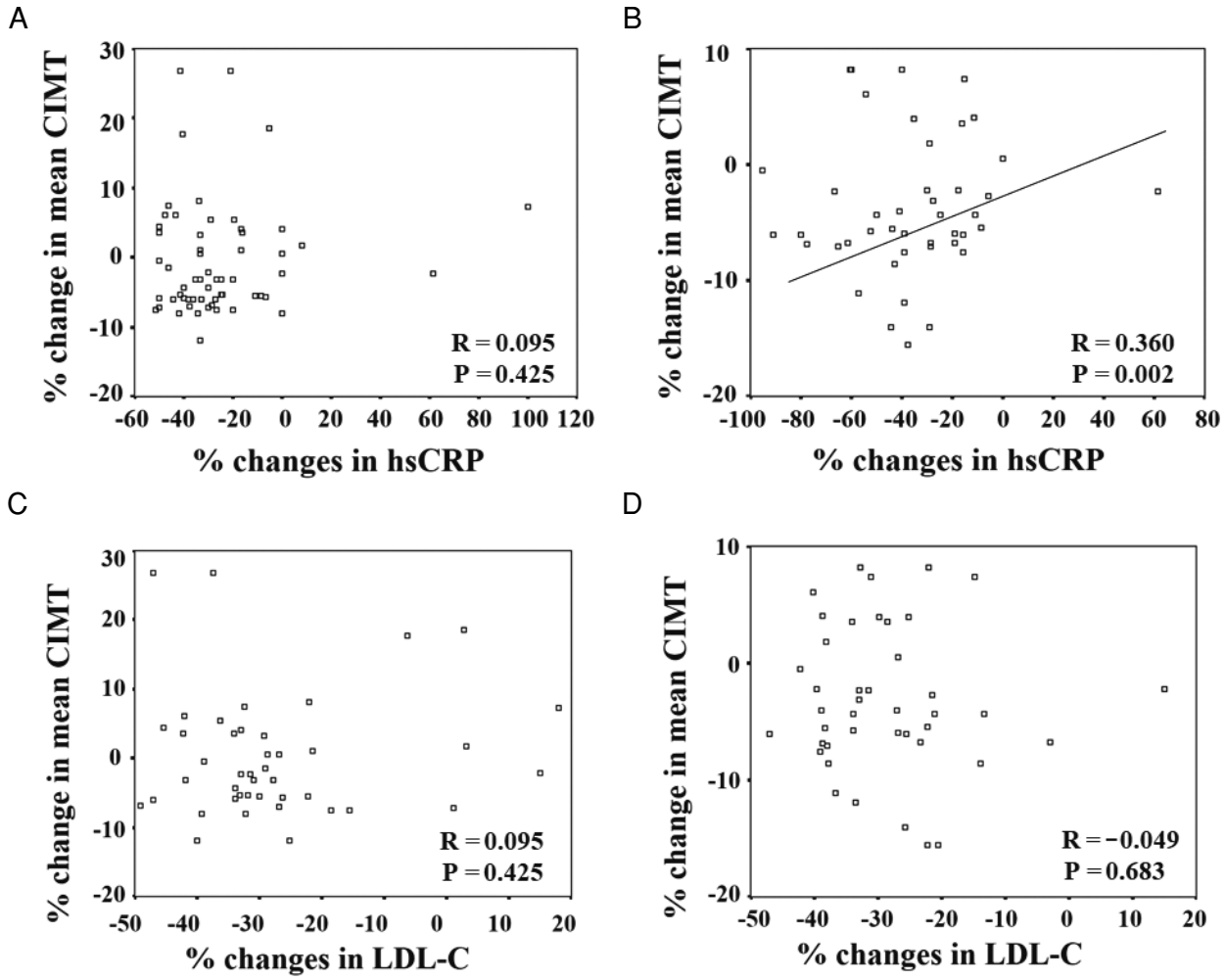

Fig. 5. Relationship between the % change from baseline to after 12 months of treatment in the hs-CRP values and the % change from baseline in the mean CIMT in the atorvastatin ($r=0.163$, $p=0.168$; A) and pitavastatin ($r=0.360$, $p=0.002$; B) groups. Relationship between the % change from baseline to after 12 months of treatment in the LDL cholesterol values and the % change from baseline in the mean CIMT in the atorvastatin ($r=0.095$, $p=0.425$; C) and pitavastatin ($r=-0.049$, $p=0.683$; D) groups. hs-CRP; high-sensitivity C-reactive protein, CIMT; carotid intima-media thickness, LDL; low-density lipoprotein.

an increased CIMT) in patients with dyslipidemia.

The present study demonstrated that atorvastatin and pitavastatin equally reduce the LDL cholesterol levels after 12 months of treatment, although atorvastatin increased the HOMA-IR by +26%, whereas pitavastatin decreased this parameter by −13%. These data suggest that pitavastatin may have greater benefits for improving insulin resistance than atorvastatin. Therefore, pitavastatin may be preferable to atorvastatin in diabetic/MS patients with dyslipidemia.

In the present study, the TNF-α and MCP-1 levels were reduced by −36%, and −28%, respectively, in the patients treated with pitavastatin, compared to only −21% and −11%, respectively, in those receiving atorvastatin. A greater decrease in the mean CIMT was also observed in the patients treated with pitavastatin than in those treated with atorvastatin. These data suggest that pitavastatin may be more beneficial than atorvastatin for reducing inflammation in patients with dyslipidemia.

In addition, in the patients treated with pitavastatin, the percent change in the mean CIMT from baseline to after 12 months of treatment was significantly associated with the percent changes from baseline in several markers of inflammation, including the hsCRP, TNF-α, and MCP-1 levels. The percent change in the CIMT from baseline was not related to the percent changes from baseline in blood pressure or the

LDL cholesterol levels.

In the patients treated with atorvastatin, the percent change in the mean CIMT from baseline to 12 months was significantly but weakly associated with the percent change from baseline in the MCP-1 levels, but not the hsCRP or TNF-α levels. In addition, the percent change in the mean CIMT from baseline was significantly and negatively correlated with the percent changes from baseline in systolic blood pressure and HOMA-IR.

These data suggest that the decrease in the mean CIMT may be, at least in part, due to reductions in inflammation in the patients treated with pitavastatin, while the decrease in the mean CIMT in the patients treated with atorvastatin may have been closely associated with the effects on the cholesterol levels, with no major effects on inflammation. In addition, the increases in the FPG and HOMA-IR values may be associated with the progression of carotid atherosclerosis in the patients treated with atorvastatin.

The present study showed, for the first time, that, despite reductions in the LDL cholesterol levels, atorvastatin and pitavastatin nevertheless have different effects on inflammatory markers, insulin resistance, and the progression of CIMT in patients with dyslipidemia. These findings may provide hypothesis-generating data for future large-scale studies with a longer follow-up period.

Effects of Concomitant Medications on the Inflammatory Markers, Insulin Resistance, and CIMT in Patients with Dyslipidemia

Clinical studies have shown that CCBs[19] and ACEIs[20] significantly decreased the progression of carotid atherosclerosis. However, the present study showed that pitavastatin treatment was significantly and negatively associated with the progression of carotid atherosclerosis, whereas other concomitant medications were not. Therefore, concomitant medications may not have affected the progression of carotid atherosclerosis in our patients with dyslipidemia.

Mechanisms Underlying the Progression of Carotid Atherosclerosis

The mechanisms underlying the progression of carotid atherosclerosis (increased CIMT) are complicated. However, some investigators have shown that the patient age, gender, total and LDL cholesterol, SBP, BMI, low HDL cholesterol, and elevated hsCRP and insulin levels are independently associated with the CIMT[21, 22]. We have also previously shown that the patient age, HDL cholesterol level, and insulin resistance estimated according to the HOMA-IR are independently associated with the mean CIMT[23]. In addition, we reported that patients with carotid atherosclerosis show significantly higher hsCRP levels and have lower overall HDL cholesterol levels in comparison to those without carotid atherosclerosis, thus indicating that inflammation and insulin resistance play significant roles in the pathogenesis and progression of carotid atherosclerosis in patients with MS[24]. Therefore, resistance to insulin-mediated glucose disposal and/or compensatory hyperinsulinemia may contribute to the progression of carotid atherosclerosis.

An association between lower HDL cholesterol levels and a higher incidence of CIMT was also found in our study. HDL cholesterol has potential anti-inflammatory and anti-oxidative effects, which may suppress the progression of carotid atherosclerosis[25, 26]. The present study also showed that 12 months of pitavastatin treatment improves insulin resistance and increases the HDL cholesterol levels, whereas atorvastatin therapy actually worsened the insulin resistance and did not affect the HDL cholesterol levels.

In the multivariate regression analysis, the percent changes in waist circumference and MCP-1 from baseline to 12 months were each significantly and independently associated with the percent change in the mCIMT from baseline to 12 months. In addition, the multivariate logistic analysis showed that the percent change in the MCP-1 values from baseline was a strong and independent determinant of the progression of carotid atherosclerosis. Therefore, inflammation may play an important role in the pathogenesis and progression of carotid atherosclerosis in patients with dyslipidemia. Very importantly, pitavastatin treatment significantly and independently correlated with slowing the progression of carotid atherosclerosis in this population.

Taken together, these findings indicate that the patient age, hypertension, dyslipidemia, insulin resistance, and inflammation may contribute to the pathogenesis and progression of carotid atherosclerosis. These data suggest that pitavastatin is therefore preferable to atorvastatin in diabetic/MS patients with dyslipidemia.

Differential Effects of Statins on Lipid Metabolism, Inflammatory Markers, Insulin Resistance, and Progression of Carotid Atherosclerosis in Patients with Dyslipidemia

Chapman[27] demonstrated that 52 months of pitavastatin treatment significantly increases the HDL cholesterol levels by up to +14.3% vs. the initial baseline values. Kurogi *et al.*[28] recently reported a greater increase in the HDL cholesterol levels after long-term treatment in patients with dyslipidemia and coronary

artery disease treated with pitavastatin compared with atorvastatin. Consistent with these findings, the present study showed that pitavastatin treatment significantly increases the HDL cholesterol levels in comparison with atorvastatin. The pitavastatin-induced elevation of HDL cholesterol may have anti-inflammatory effects on the endothelium and possibly increase atherosclerotic plaque stability, which may slow the progression of carotid atherosclerosis[25, 26].

Recent epidemiological studies[29-31] have suggested that long-term statin treatment increases the risk of new-onset diabetes. Some investigators have compared the metabolic effects of atorvastatin and pravastatin in hypercholesterolemic patients[17, 32, 33] and found that the HbA1c levels in the atorvastatin group significantly increase after treatment, whereas no increases are observed in the pravastatin group[32]. Meanwhile, Koh *et al.*[34] showed that treatment with various doses of atorvastatin significantly increases the HbA1c and fasting IRI levels, consistent with the status of insulin resistance, whereas pravastatin therapy significantly improves insulin sensitivity[34]. The present study showed that pitavastatin treatment significantly improves insulin resistance; however, atorvastatin worsened insulin resistance in our study population. In agreement with these findings, Carter *et al.*[30] showed that, compared with pravastatin, there is an increased risk of incident diabetes in patients treated with atorvastatin (hazard ratio (HR) 1.22, 95% confidence interval (CI) 1.15–1.29).

The present study demonstrated that pitavastatin treatment significantly attenuates the levels of inflammatory markers, including TNF-α and MCP-1, in comparison to atorvastatin.

The differential effects of statin therapy on the progression of carotid atherosclerosis remain unclear. A meta-analysis of randomized controlled trials performed by Huang *et al.*[35] showed a significant decrease in the mean CIMT in patients treated with lovastatin, simvastatin, pravastatin, and rosuvastatin; however, this finding was not observed for atorvastatin or fluvastatin. A significant association between the change in the CIMT and the decrease in the TG levels was found. In addition, a similar but not statistically significant, trend was observed between the decrease in the CIMT and the decreases in the LDL cholesterol levels or increases in the HDL cholesterol levels. The present study also identified a greater decrease in the mean CIMT in the pitavastatin group than in the atorvastatin group. In addition, the present findings indicated that the percent change in the mean CIMT from baseline to after 12 months of treatment was significantly and positively associated with the percent changes from baseline in the hsCRP, TNF-α, and MCP-1 levels in the patients treated with pitavastatin, while the percent change in the mean CIMT from baseline was significantly but weakly related to the percent change in the MCP-1 levels in the patients treated with atorvastatin. Interestingly, the percent change in the mean CIMT from baseline was not associated with the percent change from baseline in the LDL cholesterol levels in either the atorvastatin or pitavastatin groups.

These data indicate that pitavastatin treatment slows the progression of carotid atherosclerosis, partially due to a reduction in inflammation. However, progression of the CIMT may not be related to the changes in LDL cholesterol in patients with dyslipidemia. In addition, despite the equivalent reductions in the LDL cholesterol levels, atorvastatin and pitavastatin had different effects on the levels of inflammatory markers as well as insulin resistance and the progression of carotid atherosclerosis in patients with dyslipidemia. These data provide the first evidence supporting the use of different therapeutic strategies for the treatment of diabetic/MS patients with dyslipidemia compared to those without these conditions.

Mechanisms Underlying the Differential Effects of Statins on Inflammatory Markers and the Progression of Carotid Atherosclerosis in Patients with Dyslipidemia

The mechanisms by which statins exert differential effects on inflammation, insulin resistance, and CIMT in patients with dyslipidemia are unclear. Statins inhibit the HMG-CoA reductase activity and decrease the isoprenylation of intracellular signaling molecules, including Rho[10, 36, 37]. Rho kinases (ROCKs) are protein serine/threonine kinases of approximately 160 kDa that act as downstream effectors of the small glutamyltranspeptidase (GTPase) Rho. Statins prevent the membrane targeting of Rho and its subsequent activation of ROCKs by inhibiting mevalonate synthesis. At clinically relevant concentrations, statins have been shown to inhibit the isoprenylation of Rho and activity of ROCK[36, 37].

The Rho/ROCK pathway is involved in the onset of hypertension and cardiac hypertrophy and progression of atherosclerosis[36, 37]. These data suggest that the Rho/ROCK pathway plays significant roles in the pathogenesis and progression of carotid atherosclerosis.

Masamura *et al.*[38] showed that pitavastatin regulates the thrombomodulin expression via the inhibition of small G proteins of the Rho family. Furthermore, Hamano *et al.*[39] reported that pitavastatin

decreases the tau levels (an important protein associated with Alzheimer's disease) via inactivation of the Rho/ROCK pathway. These data suggest that atorvastatin and pitavastatin attenuates inflammation via the Rho/ROCK pathway.

Rawlings *et al.*[40] showed that atorvastatin and rosuvastatin inhibit the ROCK activity; however, rosuvastatin more significantly reduces the ROCK activity than atorvastatin, thus suggesting that rosuvastatin reduces the ROCK activity and inflammation more effectively than atorvastatin. We speculate that pitavastatin may more strongly attenuate inflammation via the Rho/ROCK pathway than atorvastatin. However, we did not measure the ROCK activity in the present study. Further studies are thus needed to clarify the exact mechanisms underlying these findings.

Study Limitations

There are several limitations associated with this study. First, this study was performed with a small sample population, and future large-scale clinical studies are therefore required to confirm our findings. Second, although this study was prospective and randomized, it was also an open-label study, which may have induced bias in terms of the progression of carotid atherosclerosis. Third, we did not measure the ROCK activity or compare this finding between the patients treated with atorvastatin and pitavastatin. Fourth, we did not have any data on the CIMT at later time points, because this was a 12-month study. Hence, the long-time effects of different statins remain unclear.

Conclusions

In conclusion, while these agents significantly and equally reduce the LDL cholesterol levels, atorvastatin and pitavastatin exhibit different effects on inflammation, insulin resistance, and the progression of carotid atherosclerosis in patients with dyslipidemia. Pitavastatin may be superior to atorvastatin in slowing the progression of carotid atherosclerosis in dyslipidemic patients without known cardiovascular diseases. Further studies are needed to confirm these findings.

Conflicts of Interest

Dr. Wataru Shimizu has received lecture fees from Astellas Pharma, Inc. The other doctors have no conflicts of interest.

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