Original Article

Effects of Pitavastatin on Serum Lipids and High Sensitivity C-Reactive Protein in Type 2 Diabetic Patients

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Aim: Previous studies have been inconsistent results about the effects of statins on serum triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and high sensitivity C-reactive protein (hsCRP) levels. We therefore investigated the effects of pitavastatin on serum lipid profiles and hsCRP levels in patients with type 2 diabetes mellitus.

Methods: The study population was 65 Japanese type 2 diabetic patients who had been administered 2 mg daily of pitavastatin and completed a 6-month follow-up. Serum lipids and hsCRP were measured before and after treatment for 1, 3, and 6 months.

Results: Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and TG had significantly reduced after 1 month and remained reduced for 6 months, while HDL-C levels had significantly increased after 1 month and remained at the higher level for 6 months. Baseline median levels of hsCRP were 0.49 mg/L and showed a significant reduction to 0.37 mg/L at 6 months' treatment ($p < 0.001$). Six-month changes in hsCRP levels were not associated with those in TC, LDL-C, HDL-C or TG.

Conclusion: Pitavastatin improved serum lipid profiles and reduced serum hsCRP levels in type 2 diabetic patients with relatively low inflammation. The effect on hsCRP was not related to the effects on serum lipid profiles.

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Key words; Statin, Pitavastatin, C-reactive protein, Diabetes mellitus, Inflammation

Introduction

The prevention of cardiovascular diseases is one

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of the most important targets for the treatment of diabetic patients, because these disorders are a major contributor to morbidity and direct and indirect costs of diabetes¹. Besides blood glucose control for this purpose, the need to manage blood pressure and serum lipids, aspirin therapy, and smoking cessation has also been demonstrated¹⁻⁴. Lipid management aims at lowering low-density lipoprotein cholesterol (LDL-C), raising high-density lipoprotein cholesterol (HDL-C),

and lowering triglycerides (TG). Some but not all studies of pharmacological treatments of lipid abnormalities have shown that they can reduce the incidence of atherosclerotic vascular diseases in type 2 diabetic patients⁵⁻⁹.

Inflammation is known to play an important role in the etiology of atherosclerosis¹⁰. Of various circulating inflammatory markers, high sensitivity C-reactive protein (hsCRP) has been the most intensively studied. Circulating hsCRP levels have been shown to be associated with cardiovascular diseases as well as asymptomatic atherosclerosis¹¹⁻¹⁶. They are also related to age, sex, race (African-American), body mass index, smoking, serum lipids, blood pressure, frequency of exercise, and cardiorespiratory fitness¹⁷⁻²⁰. Considerable evidence is accumulating that HMG-CoA reductase inhibitors (statins), which are potent lipid-lowering agents, lower hsCRP levels in patients with hypercholesterolemia as well as those with coronary artery disease, and the reduction of hsCRP after statins therapy is associated with a better clinical outcome in addition to a reduced rate of atherosclerosis progression²¹⁻²³.

Elevation of circulating hsCRP has been observed in patients with diabetes mellitus²⁴⁻²⁶. Since statins are most widely used for the lipid management of patients with type 2 diabetes mellitus⁵⁻⁸, investigation is warranted of whether statins therapy can lower circulating hsCRP levels in these patients. Atorvastatin treatment (20 mg daily) for 3 months failed to lower hsCRP levels in type 2 diabetic patients²⁷, but administration of 10 mg daily for 3 months, followed by 20 mg daily for 3 months, lowered hsCRP in type 2 diabetes patients after 6 months²⁸. It has also been reported that pravastatin treatment for 8 weeks lowered hsCRP levels in patients with type 2 diabetes mellitus by 13%²⁹. Treatment with simvastatin was found to reduce circulating hsCRP within 14 days but it had returned to baseline levels by day 28³⁰. The findings of studies examining the effect of statins on hsCRP levels in patients with type 2 diabetes show various discrepancies, which may be the result of differences in the statins used, baseline hsCRP levels and patients studied.

Pitavastatin has been available in Japan since 2003³¹. In the present study we aimed to evaluate the effects of pitavastatin on serum lipids as well as on serum hsCRP levels in Japanese patients with type 2 diabetes mellitus accompanied by elevated serum LDL-C, which has not yet been proved. Our study patients showed much lower hsCRP levels than subjects in most studies conducted in western countries^{27, 29, 30}.

Table 1. Baseline characteristics of 65 patients with type 2 diabetes mellitus

Age (years)	62 ± 9
Males (%)	30 (46.0)
Body mass index (kg/m ²)	24.4 ± 3.2
Current smoker (%)	13 (20.0)
Hypertension (%)	29 (44.6)
Diabetes treatment (diet/OHA/insulin/OHA plus insulin)	14/41/8/2

Figures show the means ± SD or numbers (%)

Subjects and Methods

Study Patients

For this 6-month, multi-center, prospective, open-label study, we recruited 91 Japanese patients with type 2 diabetes mellitus and serum LDL-C ≥ 120 mg/dL, TG < 400 mg/dL and HbA_{1c} < 9.0% between March, 2004 and September, 2006. These patients met the following inclusion criteria: more than 20 years old, no hypolipidemic drug administration for at least the preceding 4 weeks, no chronic or acute inflammatory diseases diagnosed by clinical symptoms and/or laboratory data, no corticosteroid administration, serum creatinine concentrations < 2.0 mg/dL, serum transaminase concentrations less than twice the upper limit of control ranges, and no viral hepatitis. The study was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association, and was approved by the Ethics Committees of all institutions. Written informed consent was obtained from each patient after full explanation of the purpose, nature and risk of all procedures used.

Study Protocol

The recruited patients received 2 mg per day of pitavastatin. Before and after treatment for 1, 3 and 6 months, the patients were scheduled to undergo a complete physical examination, laboratory analyses, and assessment of medication compliance. The patients were not given any medical advice on exercise and/or any instructions about smoking cessation during the treatment periods. The findings from the 65 patients who completed the 6-month follow-up were analyzed in this study and their baseline clinical characteristics are shown in **Table 1**. The diabetes treatment consisted of diet therapy alone for 14 patients, one or a combination of oral hypoglycemic agents (OHA) for 42 patients (sulfonylureas for 30, thiazolidinediones for 8, biguanides for 9, glinides for 2, α -glucosidase inhibitors for 16), insulin administration for 8 patients,

Table 2. Changes in serum lipids and plasma CRP levels before and after treatment with pitavastatin

	Baseline	Months of treatment		
		1 month	3 months	6 months
FPG (mg/dL)	130 ± 24	132 ± 24	135 ± 28	132 ± 29
HbA _{1c} (%)	6.8 ± 0.7	6.9 ± 0.7	7.0 ± 0.9*	7.1 ± 1.0*
TC (mg/dL)	250 ± 31	175 ± 25***	179 ± 28***	182 ± 29***
TG (mg/dL)	121 (98–168)	107 (76–146)***	103 (78–136)***	107 (80–140)*
HDL-C (mg/dL)	59 ± 20	58 ± 15*	61 ± 20***	61 ± 20*
LDL-C (mg/dL)	165 ± 23	96 ± 20***	96 ± 23***	96 ± 22***
hsCRP (mg/L)	0.49 (0.26–0.87)	0.48 (0.23–1.09)	0.43 (0.24–0.73)	0.37 (0.23–0.79)*

Figures show the means ± SD or median (interquartile range).

* $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ vs. baseline.

and insulin plus oral hypoglycemic agents for 2 patients. Twenty-nine patients had been diagnosed with hypertension and given anti-hypertensive drugs.

Data for serum hsCRP levels that were over 10 mg/L at baseline or at follow-up, or that showed either a five-fold or more increase or a five-fold or more decrease during the study period, were excluded from the analysis of hsCRP. The hsCRP findings for patients who were diagnosed as having acute infectious and inflammatory disorders were also excluded from the analysis.

Laboratory Methods

Plasma glucose, HbA_{1c}, total cholesterol (TC), HDL-C and TG were determined by standard laboratory assays. Serum LDL-C levels were calculated with the equation of Friedewald *et al.*³¹⁾. Serum hsCRP was determined by latex-enhanced immunonephelometry on a BN II Analyzer (Dade Behring, Marburg, Germany). The range of determinants was 0.05–10 mg/L. Intra- and inter-assay coefficients of variation were 4.7 and 2.9%, respectively³²⁾.

Statistical Analyses

Continuous variables are shown as the means ± SD when distribution was normal and as medians with interquartile range when distribution was skewed. Effects of treatment were analyzed by paired Student's *t*-test for normally distributed variables and with the Wilcoxon matched-pairs signed-ranks test for skewed distributed variables (triglycerides and hsCRP). The StatView computer program (Version 5.0 for Windows; Abacus Concepts, Berkeley, CA) was used for all statistical analyses. A *p* value of < 0.05 was considered significant.

Results

Baseline serum lipid levels and their changes after pitavastatin treatment are shown in **Table 2**. Significant reductions in TC, LDL-C and TG and significant increase in HDL-C were attained after 1 month of treatment with pitavastatin. Changes in these lipid levels continued from 1 month through 6 months after treatment. After 6 months of treatment, the average reductions in TC, LDL-C and TG were −27.1%, −41.1% and −6.2%, respectively, and the average increase in HDL-C was +4.5%. Fasting plasma glucose (FPG) did not significantly change, while HbA_{1c} concentrations had increased slightly at 3 and 6 months of treatment.

Serum hsCRP levels were 0.49 mg/L (median) at baseline and after pitavastatin treatment gradually decreased to 0.43 mg/L at 3 months of treatment, but this change was not statistically significant ($p = 0.057$). After 6 months, however, there was a significant reduction to 0.37 mg/L (**Table 2**). Baseline hsCRP levels were significantly associated with BMI ($r = 0.425$, $p = 0.001$), but not with age ($r = -0.070$, $p = 0.610$) or concentrations of TC ($r = 0.047$, $p = 0.735$), LDL-C ($r = 0.009$, $p = 0.952$), HDL-C ($r = -0.081$, $p = 0.559$), TG ($r = 0.177$, $p = 0.215$), FPG ($r = 0.135$, $p = 0.346$) and HbA_{1c} ($r = 0.117$, $p = 0.394$). Six-month changes in hsCRP levels were not associated with those in BMI ($r = -0.063$, $p = 0.700$) or concentrations of TC ($r = -0.010$, $p = 0.947$), LDL-C ($r = 0.007$, $p = 0.966$), HDL-C ($r = 0.028$, $p = 0.853$) and TG ($r = -0.093$, $p = 0.561$) levels.

Discussion

The results of this study indicate that the new HMG-CoA reductase inhibitor pitavastatin improved

lipid profiles of TC, LDL-C, HDL-C and TG in Japanese patients with type 2 diabetes mellitus. Strict lipid management for diabetic patients to lower LDL-C and TG and to raise HDL-C has been strongly recommended by the National Cholesterol Education Program³³, American Diabetes Association³⁴ and Japan Atherosclerosis Society³⁵. In our study, pitavastatin treatment for 1 month significantly reduced serum LDL-C and TG, and significantly increased HDL-C levels. These effects lasted for 6 months, with a reduction in LDL-C and TG after 6 months of -41.1% and -6.2% , respectively, and an increase in HDL-C of $+4.1\%$. The efficacy of statins to lower serum LDL-C has been established for hyperlipidemic as well as diabetic patients with and without coronary heart diseases^{5-7, 21, 23, 27-30}. By contrast, the effects of statins on serum HDL-C and TG levels seem inconsistent. A large scale study (CARDS) showed that long-term treatment with 10 mg daily of atorvastatin resulted in a net reduction in TG of 19% and a negligible increase in HDL-C (1%) in type 2 diabetic patients⁵. In other studies, atorvastatin treatment resulted in a significant decrease in TG but failed to increase HDL-C levels in type 2 diabetes^{27, 28}. In a sub-analysis of the Heart Protection Study⁶, simvastatin produced a significant increase in HDL-C but failed to significantly reduce TG levels in diabetic patients, while pravastatin failed to increase HDL-C levels in patients with type 2 diabetes²⁹. In a recent study of Japanese patients with type 2 diabetes mellitus, pitavastatin treatment resulted in a significant reduction in TG levels (-10%) and an increase in HDL-C levels ($+3.1\%$) although the latter did not reach statistical significance ($p=0.055$)³⁶. Taken together with our data, these findings indicate that pitavastatin may be more effective than other statins for enhancing HDL-C levels; however, the studies cited here differ in terms of the racial and baseline clinical characteristics of the patients, which may influence the effects of specific statins on TG and HDL-C levels. In order to prove that pitavastatin has a more favorable effect on TG and HDL-C, comparative studies of pitavastatin and other statins will be needed.

In the study presented here, pitavastatin treatment for 6 months resulted in a significant reduction in serum hsCRP levels in type 2 diabetic patients, although the reduction after 3 months did not reach statistical significance. The inhibitory effect on hsCRP levels was attained later after administration than its effect on serum lipid profiles. Since the changes in hsCRP levels were not associated with those in any serum lipid levels, the effect of pitavastatin on hsCRP is clearly unrelated to its effects on serum lipid pro-

files. The underlying mechanism of the anti-inflammatory properties of statins has not yet been fully identified. As IL-6 is an important inducer of circulating hsCRP³⁷, the statin-induced down-regulation of IL-6 may be a possible cause of the negative effect of statins on serum hsCRP levels. It has been shown that some statins can decrease the expression of IL-6 in vascular endothelial cells³⁸. Pitavastatin has also been reported to inhibit IL-6 production in adipose tissues as well as in macrophage cell RAW264³⁹; however, to date, we have not found any reports demonstrating the significant reduction of plasma IL-6 levels by statins. Rather, several reports have shown that atorvastatin failed to reduce plasma IL-6 levels^{40, 41}. In our study, we could not measure plasma IL-6 levels before and after treatment with pitavastatin; however, taken together with previous reports concerning the effects of other statins on plasma IL-6 levels, the hsCRP reduction after pitavastatin treatment may occur via other mechanisms than down-regulation of IL-6.

Studies of the effects of statins on circulating hsCRP in type 2 diabetes have not shown consistent results²⁷⁻³⁰. BMI is known as a major independent determinant of hsCRP^{11-16, 32} and our study also showed that BMI was closely related to serum hsCRP levels in Japanese type 2 diabetic patients, although the mean BMI of our patients was 24.4 kg/m^2 , much lower than that in most studies conducted in western countries^{27, 29, 30}. This may be attributable to lower serum levels of hsCRP (median, 0.49 mg/L) in our patients than in the subjects of previous studies^{27, 29, 30}. Thus, the discrepant results of studies examining the effects of statins on hsCRP levels may be result of differences in baseline hsCRP levels that are probably influenced by BMI and concomitant atherosclerotic vascular diseases.

In our study patients, baseline hsCRP levels were not significantly associated with HbA_{1c}. These results are inconsistent with the previous report showing the association of these parameters in a large national sample of individuals with diabetes⁴². By contrast, it has been shown that hsCRP levels were associated with HbA_{1c} in non-diabetic patients but not in diabetic patients⁴³. In this relation, it has been demonstrated that HbA_{1c} was not an important determinant of hsCRP in recently diagnosed, drug-naïve type 2 diabetic patients⁴⁴. Thus, there are still controversial results about the relation of the glycemic control marker with hsCRP levels. Differences in the severity of diabetes and pharmacological therapy may be attributed to such discrepancies.

HbA_{1c} concentrations in our study showed a slight but significant increase 3 months and later after

pitavastatin treatment. By contrast, FPG levels did not change during the study period. The diabetes treatment was permitted to be changed during the study period. In addition, our study did not include control groups without pitavastatin treatment, so we cannot draw conclusions concerning the effect of pitavastatin on HbA_{1c} levels. In most clinical studies of diabetes treatment lasting several months, HbA_{1c} levels have been shown to increase in placebo groups, but this increase is thought to be not due to pitavastatin treatment but to be a naturally occurring phenomenon.

In conclusion, we analyzed the effects of pitavastatin on serum lipid profiles and hsCRP levels in Japanese patients with type 2 diabetes. Pitavastatin significantly reduced LDL-C and TG, and significantly increased HDL-C levels after 1 month. In addition, pitavastatin significantly reduced serum CRP levels after 6 months in patients with relatively low inflammation. Since submission of this manuscript, it has been shown that pitavastatin improves lipid profiles and reduces hsCRP in subjects with hypercholesterolemia, including those with type 2 diabetes⁴⁵. Taken together, pitavastatin may be more effective than other statins for reducing TG and CRP as well as increasing HDL-C. Treatment with pitavastatin may thus be useful for the prevention and inhibition of atherosclerotic vascular diseases in type 2 diabetes with dyslipidemia. Further clinical studies are necessary to prove this issue.

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