Effects of Pitavastatin on Lipid Profiles and High-Sensitivity CRP in Japanese Subjects with Hypercholesterolemia: Kansai Investigation of Statin for Hyperlipidemic Intervention in Metabolism and Endocrinology (KISHIMEN) Investigators

Hiroyuki Koshiyama¹, ², Ataru Taniguchi², Kiyoshi Tanaka³, Shinji Kagimoto⁴, Yoshio Fujioka⁵, Kenichi Hirata⁵, Yoshiho Nakamura⁶, Akane Iwakura⁶, Kyoko Hara⁶, Taizo Yamamoto⁷, Akira Kuroe², Michihiro Ohya⁶, Shimpei Fujimoto², Yoshiuki Hamamoto¹, ², Sachiko Honjo¹, Hiroki Ikeda¹, Koichiro Nabe¹, Kinsuke Tsuda⁹, Nobuya Inagaki⁸, Yutaka Seino², ⁸, and Noriaki Kume¹⁰

¹Center for Diabetes & Endocrinology, The Tazuke Kofukai Foundation Medical Research Institute Kitano Hospital, Osaka, Japan
²Division of Diabetes and Clinical Nutrition, Kansai Electric Power Hospital, Osaka, Japan
³Department of Nutrition, Kyoto Women’s University, Kyoto, Japan
⁴Department of Endocrinology and Metabolism, Kamo Hospital, Kyoto, Japan
⁵Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
⁶Division of Diabetes & Endocrinology, Department of Internal Medicine, Hyogo Prefectural Amagasaki Hospital, Hyogo, Japan
⁷Department of Endocrinology and Diabetes, Kyoto-Katsura Hospital, Kyoto, Japan
⁸Department of Diabetes & Clinical Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, Japan
⁹Graduate School of Human Science, Kyoto University, Kyoto, Japan
¹⁰Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Aim: The effect of pitavastatin on high-sensitivity C-reactive protein (hs-CRP) has not been reported, yet, in humans. We, therefore, investigated the effects of pitavastatin on lipid profiles and hs-CRP in Japanese subjects with hypercholesterolemia.

Methods: The subjects were 178 Japanese with hypercholesterolemia, including 103 (58%) with type 2 diabetes. Pitavastatin (1–2 mg/day) was administered for 12 months. Serum low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), remnant-like particle cholesterol (RLP-C), triglycerides (TG) and hs-CRP levels were measured for 12 months.

Results: Serum LDL-C and RLP-C levels were significantly decreased by 30.3% and 22.8%, respectively. Serum TG levels were decreased by 15.9% in subjects with basal TG levels above 150 mg/dl. Serum HDL-C levels were significantly increased. The administration of pitavastatin reduced serum hs-CRP levels by 34.8%. No serious adverse events were observed, including changes in glycosylated hemoglobin levels of diabetic patients.

Conclusion: These results suggest that pitavastatin significantly improves lipid profiles and reduces proinflammatory responses, without adverse effects, in Japanese subjects with hypercholesterolemia, including those with diabetes mellitus.


Key words: Inflammation, Diabetes, LDL-C, HDL-C

Introduction

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are well known to reduce circulating low-density lipoprotein cholesterol (LDL-C) levels by inhibiting de novo cholesterol synthesis in the liver and thereby inducing the
bexpression of hepatic LDL receptors\textsuperscript{1, 2}. However, in clinical trials, the overall reductions in cardiovascular events following statins appear to occur much earlier and to a greater extent than expected from the levels of LDL-C lowering alone\textsuperscript{3, 4}; therefore, it has been considered that statins have pleiotropic effects independent of the reduction in circulating LDL-C levels\textsuperscript{3, 4}, including anti-inflammatory effects\textsuperscript{5-8}.

Numerous studies have suggested that low-grade inflammation has a pivotal role in atherosclerosis\textsuperscript{5-9, 10}. Prospective studies have indicated that high-sensitivity C-reactive protein (hs-CRP) is an important risk factor for atherosclerotic cardiovascular disease\textsuperscript{5, 9}. Ridker\textit{et al.} demonstrated that slight elevation in hs-CRP could lead to the evolution of atherosclerosis in humans\textsuperscript{5, 9}. We previously demonstrated that hs-CRP is associated with insulin resistance and fibrinogen levels in non-obese Japanese type 2 diabetic patients\textsuperscript{11}. Although few studies have investigated the effect of statins on hs-CRP in humans, some conflicting reports exist. Several studies indicated that statins reduce hs-CRP levels\textsuperscript{5, 10, 12, 13}; however, one study failed to demonstrate the inhibitory effect of a statin on hs-CRP levels in diabetic subjects\textsuperscript{14}.

Pitavastatin is a synthetic strong statin, whose molecular structure is similar to atorvastatin and rosuvastatin\textsuperscript{15}. There has been a single report about the effect of pitavastatin on lipid profiles in humans\textsuperscript{10}. Although several studies demonstrated that pitavastatin, as well as other lipophilic statins, has anti-inflammatory effects \textit{in vitro}\textsuperscript{6-8, 17}, the effects of pitavastatin on inflammatory markers, including hs-CRP, have not been reported in humans \textit{in vivo} to the best of our knowledge.

In the present study, therefore, we explored the effects of pitavastatin on lipid profiles as well as hs-CRP levels in Japanese subjects with hypercholesterolemia, including those with diabetes mellitus.

**Patients and Methods**

This study was a 12-month, multi-center, prospective, open-label study. Japanese patients, who met the following inclusion criteria: serum total-cholesterol (TC) $\geq 220$ mg/dL, and triglycerides (TG) $< 400$ mg/dL, were recruited. A total of 209 Japanese subjects were enrolled, of which 31 were excluded because they did not follow the protocol. As a result, 178 cases were investigated. Pitavastatin in a dose of 1–2 mg/day was administered [1 mg/day in 44 cases (25%) and 2 mg/day in 134 cases (75%)]. Before the administration of pitavastatin, no lipid-lowering medications had been administered in 111 cases (62%), whereas other lipid-lowering drugs had been prescribed in 67 cases (38%); 27 pravastatin, 18 atorvastatin, 10 simvastatin, 8 fluvastatin, 1 rosuvastatin, 2 bezafibrate and 1 fenofibrate cases), all of which were withdrawn at least one week before the administration of pitavastatin.

Blood samples were obtained at the beginning and 3, 6 and 12 months after the administration of pitavastatin. Serum TC, LDL-C, TG, HDL-C, glucose, glycosylated hemoglobin (A1C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and creatinine phosphokinase (CK) were measured by standard techniques. Remnant-like particle-cholesterol (RLP-C) and hs-CRP were measured by immunofinity gel (JIMRO, Japan) and N Latex CRP II (Dade Behring Marburg GmbH, Marburg, Germany), respectively.

Continuous variables are shown as the mean $\pm$ S.E.M. when the distribution was normal. Statistically significant differences among groups were analyzed by paired $t$ test. When the distribution was skewed, statistically significant differences among groups were analyzed by Wilcoxon signed-rank test. The JMP Software computer program (Version 5.0 for Windows; SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. $P$ values 0.05 were considered significant.

This study was approved by the local ethics committee, and informed consent was obtained from all participants before the study.

**Results**

Basal characteristics of the 178 patients are shown in Table 1 [age: $62.0 \pm 0.9$ years, 83 men (47%) and 95 women (53%)]. The mean body mass index (BMI) and fasting glucose levels of the subjects were 24.5 kg/m$^2$ and 126.0 mg/dL, respectively. The participants in this study included 103 cases (58%) of type 2 diabetes, 62 cases (35%) of hypertension, 7 cases (4%) of peripheral arterial disease, 12 cases (7%) of cerebral infarction, and 32 cases (18%) of coronary heart disease. Serum LDL-C levels were significantly decreased by 32.6%, 31.0% and 30.3% after 3, 6 and 12 months, respectively (Fig. 1A). Serum TG levels were significantly decreased by 17.7% and 15.9% after 3 and 12 months, respectively, in subjects whose basal TG levels were more than 150 mg/dL, although serum TG levels were not significantly changed in overall subjects (Fig. 1B). Serum HDL-C levels were significantly increased by 3.1%, 5.9% and 2.6% after 3, 6 and 12 months, respectively (Fig. 1C). In subjects whose basal HDL-C levels were below 40 mg/dL, HDL-C levels were increased by 16.2%, 22.4% and 19.0% after 3, 6
**Table 1.** Basal characteristics of subjects.

<table>
<thead>
<tr>
<th>Age</th>
<th>62.0 ± 0.9 (178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male %</td>
<td>47% (83)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5 ± 0.3 (174)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>153.4 ± 3.3 (174)</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>154.7 ± 5.5 (175)</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>242.2 ± 3.6 (174)</td>
</tr>
<tr>
<td>RLP-C (mg/dL)</td>
<td>7.9 ± 0.5 (63)</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>7.2 ± 0.2 (139)</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>126.0 ± 3.9 (116)</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>0.69 (0.33–1.36) (31)</td>
</tr>
<tr>
<td>Diabetes mellitus %</td>
<td>58% (103)</td>
</tr>
<tr>
<td>Hypertension %</td>
<td>35% (62)</td>
</tr>
<tr>
<td>Peripheral arterial disease %</td>
<td>4% (7)</td>
</tr>
<tr>
<td>Cerebral infarction %</td>
<td>7% (12)</td>
</tr>
<tr>
<td>Coronary heart disease %</td>
<td>18% (32)</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± S.E.M. Numbers of subjects are shown in parentheses. Abbreviations: TC: total cholesterol, FPG: fasting plasma glucose.

and 12 months, respectively (Fig. 1C). Furthermore, serum RLP-C levels were significantly decreased by 14.0%, 20.2% and 22.8% after 3, 6 and 12 months, respectively (Fig. 1D).

Serum hs-CRP levels were significantly decreased in 31 subjects after 12 months (median: 0.69 mg/L to 0.45 mg/L, −34.8%, p < 0.01, Fig. 2A). Pitavastatin similarly decreased hs-CRP levels in subjects with diabetes mellitus (median: 0.59 mg/L to 0.36 mg/L, −39.0%, p < 0.05, Fig. 2B).

There was no significant correlation between changes in LDL-C and hs-CRP levels even after transformation of hs-CRP values into a logarithm after 12 months (r = 0.124, p = 0.39). We also found no significant correlation between changes in hs-CRP and changes in serum TG or serum RLP-C levels during the study (data not shown) and there were no serious adverse events. In a subgroup of diabetic patients, there was a slight and statistically insignificant decrease in A1C after pitavastatin treatment for 12 months (7.0% to 6.9%, n = 80, p = 0.07).

![Fig. 1. Effect of pitavastatin on lipid levels in all subjects.](image)

A: Effect of pitavastatin on total cholesterol (TC) and LDL cholesterol (LDL-C) levels. B: Effect of pitavastatin on triglyceride (TG) levels in all subjects and in subjects with basal TG levels of more than 150 mg/dL. C: Effect of pitavastatin on HDL cholesterol (HDL-C) levels. Data in subjects with basal HDL-C levels less than 40 mg/dL are indicated separately. D: Effect of pitavastatin on remnant-like particle cholesterol (RLP-C) levels.
A recent study in Korea has shown that pitavastatin reduced mean hs-CRP levels from 24.6 to 16.5 mg/L by 8-week treatment. In the present study, pitavastatin, at similar doses, significantly reduced hs-CRP levels in hypercholesterolemic subjects, including type 2 diabetes, with lower basal hs-CRP levels. These findings have been supported by previous reports which indicated anti-inflammatory effects of pitavastatin in vitro. There have been conflicting reports about the effects of statins on hs-CRP in vivo in diabetic subjects; one report did not show a significantly decrease in hs-CRP after atorvastatin. Therefore, it is possible that diabetic patients are resistant to the inhibitory effects of statins on hs-CRP, although diabetic patients showed a significant decrease in hs-CRP after atorvastatin. There was no significant correlation between pitavastatin-induced decrements in hs-CRP and LDL-C, in the present study with pitavastatin, as previously reported with other statins. Pitavastatin, a new synthetic lipophilic strong statin, lowered hs-CRP levels in hypercholesterolemic subjects, including type 2 diabetes, with lower basal hs-CRP levels. These findings have been supported by previous reports which indicated anti-inflammatory effects of pitavastatin in vitro. There have been conflicting reports about the effects of statins on hs-CRP in vivo in diabetic subjects; one report did not show a significantly decrease in hs-CRP after atorvastatin. Therefore, it is possible that diabetic patients are resistant to the inhibitory effects of statins on hs-CRP, although diabetic patients showed a significant decrease in hs-CRP after atorvastatin in a recent paper. The present as well as the previous study, also demonstrated that pitavastatin, a new synthetic lipophilic strong statin, lowered hs-CRP levels in hypercholesterolemic subjects, including type 2 diabetes. There was no significant correlation between pitavastatin-induced decrements in hs-CRP and LDL-C, in the present study with pitavastatin, as previously reported with other statins. We also found no significant correlation between pitavastatin-induced decrement in hs-CRP and those in RLP-C in this study cohort. Thus, it is suggested that pitavastatin may have direct anti-inflammatory effects which are independent of improved lipid profiles. A previous study showed that non-responders,

![Fig. 2. Effect of pitavastatin on hs-CRP levels in all patients (panel A) and patients with type 2 diabetes (panel B) after 12 months.](image)

Data are presented as the mean ± S.E.M. Numbers of subjects are shown in parentheses. *p < 0.05 vs. basal values, **p < 0.01 vs. basal values.
whose LDL-C levels were above 100 mg/dL after atorvastatin treatment, tend to be resistant to hs-CRP reduction by statin treatment\(^{19}\); however, the present study did not show such a tendency but hs-CRP reduction to be independent of LDL-C levels after pitavastatin treatment (data not shown).

There were no serious adverse events in the present study, including A1C changes in subjects with diabetes mellitus. In contrast, atorvastatin has been reported to result in a slight but significant increase of A1C in Caucasian diabetic subjects, as shown by the Collaborative Atorvastatin Diabetes Study (CARDS)\(^{20}\). It has been shown that Japanese subjects with type 2 diabetes are mainly insulin-deficient rather than insulin-resistant\(^{21}\). In addition, Asians have higher plasma levels of statins than Caucasians\(^{22}\). Therefore, it is possible to speculate that Japanese subjects with type 2 diabetes may be more prone to worsening glycemic control due to, if any, adverse effects of statins on insulin secretion; however, the present study indicated that pitavastatin did not significantly worsen glycemic control in Japanese diabetic subjects.

This study is limited by the fact that it was an uncontrolled study with a moderate number of subjects, especially a relatively small number with hs-CRP measurement. It is to be noted, however, that the subjects showed lower basal hs-CRP levels before pitavastatin treatment (median: 0.69 mg/L) than those in previous studies of Caucasians (median: about 3 mg/L)\(^{5,9}\). In the Pravastatin Inflammation/CRP Evaluation (PRINCE) study, baseline hs-CRP levels were the major determinants of the change in hs-CRP levels after pravastatin\(^{12}\), indicating that anti-inflammatory effects of statins would be more pronounced in subjects with higher hs-CRP levels. It is intriguing that pitavastatin was able to reduce hs-CRP even in subjects with lower basal hs-CRP levels in the present study. Previous large scale cardiovascular event outcome studies with other statins have been conducted in Caucasians with high basal hs-CRP levels; therefore, it is of clinical importance to investigate whether pitavastatin can similarly reduce cardiovascular events among Japanese subjects with lower basal hs-CRP values than Caucasians\(^{10,23,24}\).

Conclusions

It is concluded that pitavastatin improves lipid profiles, including the reduction of RLP-C levels, and that it decreases hs-CRP levels independently of improved lipid profiles, without any adverse effects, in Japanese subjects with hypercholesterolemia, including type 2 diabetes.

Acknowledgements

The authors are very grateful to Mr. Kazunobu Kasai for his assistance with data analyses.

References

9) Ridker PM, Rifai N, Rose L, Buring JE, Cook NR: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med, 2002; 347:1557-1565
2 diabetic patients. Metabolism, 2002; 51:1578-1581

12) Albert MA, Danielson E, Rifai N, Ridker PM: PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a roundomized trial and cohort study. JAMA, 2001; 286:64-70


