Fluvastatin prevents development of arterial stiffness in haemodialysis patients with type 2 diabetes mellitus

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Abstract

Background. Arterial stiffness assessed by pulse wave velocity (PWV) predicts all-cause and cardiovascular mortality in diabetic patients with end-stage renal disease. We studied the preventive effects of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, fluvastatin, on arterial PWV values in this population.

Methods. Twenty-two patients with normal serum lipid levels received fluvastatin (20 mg/day p.o.) or a placebo for 6 months. Their serum lipid levels, serum levels of C-reactive protein (CRP), arterial PWV, and ankle brachial indexes (ABI) were determined before, and 3 and 6 months after taking the medication to evaluate arterial stiffness.

Results. At the beginning of the follow-up, there were no differences in age, blood pressure, body mass index, serum haemoglobin A1c level, serum CRP level, serum lipid levels, PWV or ABI between the placebo- (n=10) and the fluvastatin-treated patients (n=12). After 6 months, the PWV and the serum oxidized low-density lipoprotein cholesterol (LDL-C) level increased significantly (from 1969±140 to 2326±190 cm/s and 70.4±13.8 to 91.8±15.5 U/l, respectively) in the placebo-treated patients. However, the fluvastatin group had a significantly reduced PWV (from 1991±162 to 1709±134 cm/s), oxidized LDL-C serum levels (from 89.0±9.6 to 73.0±5.8 U/l) and CRP serum levels (from 0.97±0.32 to 0.26±0.16 mg/dl) compared with those in the placebo group.

Conclusions. Long-term administration of fluvastatin prevents further worsening of arterial biomechanics in haemodialysis patients with type 2 diabetes mellitus, even in the presence of serum lipid levels in the normal range.

Keywords: ankle brachial index; end-stage renal disease; HMG-CoA reductase inhibitor; oxidized low-density lipoprotein; pulse wave velocity

Introduction

While the cardiovascular mortality rate is elevated in patients with end-stage renal disease (ESRD) [1] or diabetes mellitus [2,3], the cardiovascular mortality rate is even higher in patients with both ESRD and diabetes mellitus [4-6]. Recent studies demonstrated that arterial wall stiffness predicts all-cause and cardiovascular mortality in patients with ESRD [7] and in those with both ESRD and diabetes mellitus [8]. In these patients, arterial wall stiffness can be non-invasively assessed by measuring the pulse wave velocity (PWV) along the aortoiliac pathway [9-11]. PWV is positively related to wall stiffness, so a larger arterial PWV indicates a greater degree of arterial wall stiffness, which is a feature of atherosclerosis. Therefore, monitoring the PWV along the aortoiliac pathway is a useful method of predicting all-cause and cardiovascular mortality in these patients.

Dyslipidaemia and elevated oxidative stress, which have been implicated in the pathogenesis of atherosclerosis, are common in patients with ESRD and diabetes mellitus. Studies have demonstrated that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors with antioxidant activity have beneficial effects on dyslipidaemia in patients with chronic renal insufficiency [12] and diabetes mellitus [13], and significantly reduce the rates of cardiovascular morbidity and mortality in the patients with ESRD [14]. To our knowledge, however, the effects of HMG-CoA reductase inhibitors with antioxidant activity on arterial stiffness, and the subsequent effects on all-cause and cardiovascular mortality, have not been examined in patients with both ESRD and diabetes mellitus.
The present study examined the preventive effects of fluvastatin, an HMG-CoA reductase inhibitor with antioxidant activity, on arterial stiffness in haemodialysis patients with type 2 diabetes mellitus and normal serum lipid levels. To evaluate arterial stiffness, the PWV along the aortoiliac pathway between the heart and posterior tibial arteries was measured. In addition, recent studies have demonstrated that a HMG-CoA reductase inhibitor has anti-inflammatory effects independent of lipid-lowering effects [15,16]. Since chronic inflammation is suggested to play a key role in the formation and progression of atherosclerosis in ESRD patients [17], we also assessed serum levels of C-reactive protein (CRP), a sensitive marker of underlying systemic inflammation, during the 6-month follow-up.

Subjects and methods

Patients

Twenty-two haemodialysis patients with type 2 diabetes mellitus were recruited for a double-blind trial of a placebo vs fluvastatin. Patients were eligible for inclusion if (i) they had been on haemodialysis for 6–60 months; (ii) they had had no clinical cardiovascular disease, secondary hyper-parathyroidism or adynamic bone disease during the 6-months preceding their inclusion into the study; (iii) they had had a fasting plasma glucose level of >110 mg/dl on two mornings, 1–3 weeks apart; and (iv) they were fully informed and had agreed to participate in the follow-up study, which was approved by our Institutional Ethics Committee. Exclusion criteria included pre-menopausal women, patients having hormone replacement therapy, dietary supplements, endocrine-metabolic disorders other than diabetes or drugs that may affect lipid metabolism, smokers, and a daily ethanol consumption of >40 g for men and >20 g for women. All subjects followed a stringent cholesterol-reducing diet and received dialysis by the same methods throughout the follow-up study.

Study design

Before, and 3 and 6 months after the initiation of the follow-up study, the PWV, ankle brachial index (ABI) and blood pressure were determined using a pulse pressure analyser (model BP-203RPE; Nihon Colin, Tokyo, Japan) once a stable condition with dry weight was achieved after a dialysis session. Pulse waves were recorded using sensors placed on both posterior tibial arteries. Electrocardiograms were obtained with electrodes placed at two points on the left arm and one point on the right arm. The time intervals required for the pulse waves to travel from the heart to both posterior tibial arteries were measured, and the distances between the heart and both posterior tibial arteries were estimated from the patient’s height. The best 10 consecutive pulses were analysed, and the average PWV from the heart to the posterior tibial artery was calculated by dividing the distance by the time interval. Two measurements were performed in each leg and the average value was used for the analysis. Since the PWV is independent of blood pressure in patients with ESRD [18], the PWV data were not standardized by blood pressure in the present study. PWV was expressed in centimetres per second. The coefficient of variation of the PWV was <5%.

Biochemical analysis

On the same days as the PWV measurements, blood was drawn in the morning immediately before the dialysis sessions. Haemoglobin A1c was measured using high-performance liquid chromatography. Total cholesterol (TC), triglyceride (TG), phospholipids (PL) and free fatty acid (FFA) concentrations were determined using routine enzymatic methods. High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were measured using commercially available kits (Wako Pure Chemical, Osaka, Japan). For the analysis of oxidized LDL-C, malondialdehyde LDL-C was assayed by enzyme-linked immunosorbent assay methods (SRL Inc., Tokyo, Japan). CRP was determined by enzyme-linked immunosassay.

Statistical analysis

Changes in the values were analysed using a paired t-test. Differences between the placebo and fluvastatin groups were assessed using a two-way analysis of variance (ANOVA) for repeated measures combined with a Newman–Keuls post hoc test. A value of P < 0.05 was considered significant. Data are presented as means ± SEM (standard error of the mean).

Results

Serum lipid concentrations

Patient characteristics, such as age, gender distribution, duration of haemodialysis, body mass index, blood pressure and serum levels of haemoglobin A1c, were similar for both groups at the onset of the study, as shown in Table 1. During the 6-month follow-up, there were no significant changes in body mass index, blood pressure or serum haemoglobin A1c level in either group.

Table 2 and Figure 1 show the similar TC, HDL-C, TG, PL, FFA, LDL-C and oxidized LDL-C serum concentrations of the placebo and fluvastatin groups.

Table 1. Characteristics of subjects studied at the beginning of follow-up

<table>
<thead>
<tr>
<th>Medication</th>
<th>Placebo</th>
<th>Fluvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.3 ± 3.7</td>
<td>65.8 ± 3.0</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>6/4</td>
<td>8/4</td>
</tr>
<tr>
<td>Duration of dialysis (months)</td>
<td>35.4 ± 5.7</td>
<td>34.5 ± 5.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.4 ± 0.9</td>
<td>20.9 ± 0.6</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>151 ± 10</td>
<td>157 ± 7</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82 ± 7</td>
<td>83 ± 3</td>
</tr>
<tr>
<td>Serum haemoglobin A1c (%)</td>
<td>6.1 ± 0.4</td>
<td>6.0 ± 0.4</td>
</tr>
</tbody>
</table>

Data are represented as mean ± SEM. No significant difference was observed between the placebo and fluvastatin groups.
Fluvastatin improves PWV in diabetic ESRD patients

Table 2. Changes in serum lipid concentrations

<table>
<thead>
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<th>Month</th>
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</thead>
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<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>150 ± 16</td>
</tr>
<tr>
<td>Placebo (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin (n = 12)</td>
<td>168 ± 13</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dl)</td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 10)</td>
<td>45 ± 5</td>
</tr>
<tr>
<td>Fluvastatin (n = 12)</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>93 ± 11a</td>
</tr>
<tr>
<td>Placebo (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin (n = 12)</td>
<td>94 ± 12</td>
</tr>
<tr>
<td>Phospholipid (mg/dl)</td>
<td>178 ± 12</td>
</tr>
<tr>
<td>Placebo (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin (n = 12)</td>
<td>196 ± 12</td>
</tr>
<tr>
<td>Free fatty acid (mEq/l)</td>
<td>0.17 ± 0.02</td>
</tr>
<tr>
<td>Placebo (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin (n = 12)</td>
<td>0.19 ± 0.02</td>
</tr>
</tbody>
</table>

Data are represented as mean ± SEM. *P < 0.05 vs 0 month; †P < 0.05 vs 3 months. No significant difference was observed between the placebo and fluvastatin groups.

Fig. 1. Changes in low-density lipoprotein cholesterol (LDL-C) and oxidized low-density lipoprotein cholesterol (Ox-LDL-C) for 6 months in patients treated with placebo (open circles) and fluvastatin (closed circles). Values are mean ± SEM. *P < 0.05 vs 0 month; †P < 0.05 vs 3 months; §P < 0.05 for the fluvastatin vs placebo groups.

at the start of the follow-up period. For both groups, the serum LDL-C levels averaged 80 ± 12 and 92 ± 8 mg/dl, respectively, and the oxidized LDL-C levels averaged 70.5 ± 13.8 and 89.0 ± 9.6 U/l, respectively. As shown in Table 2, TC and PL levels decreased after 6 months of fluvastatin administration, and the placebo did not cause any changes in serum lipid levels except for a minimal decrease in TG and a transient increase in PL. However, the decrease in TC or PL at 6 months determined in the fluvastatin group was not different from those insignificant changes determined in the placebo group. More importantly, as shown in Figure 1, the serum levels of LDL-C and oxidized LDL-C decreased after 3 months of fluvastatin administration, and this reduction was maintained until the end of the follow-up period. After 3 and 6 months of fluvastatin administration, the serum LDL-C levels decreased to 77 ± 7 and 78 ± 6 mg/dl, respectively, and the serum oxidized LDL-C levels decreased to 78.6 ± 9.1 and 73.0 ± 5.8 U/l, respectively. During the 6 months of placebo administration, the serum LDL-C levels did not change, but the serum oxidized LDL-C levels increased. Three and 6 months after the initiation of placebo administration, the serum oxidized LDL-C levels increased to 78.1 ± 13.1 and 91.8 ± 15.5 U/l, respectively. At 6 months, the decreases in serum oxidized LDL-C levels observed in the fluvastatin group were significantly different from the increases observed in the placebo group. However, the decreases in serum LDL-C levels observed in the fluvastatin group were not different from the non-significant changes in the placebo group.

Pulse wave velocity

Figure 2 shows the changes in PWV and ABI during the 6-month administration of placebo or fluvastatin. At the beginning of the follow-up period, the PWVs of the placebo- and fluvastatin-treated patients were similar and averaged 1969 ± 140 and 1991 ± 162 cm/s, respectively. Six months of fluvastatin administration decreased the PWV to 1709 ± 134 cm/s, while the PWV of the placebo-treated patients increased to 2326 ± 190 cm/s after the same period. These changes in PWV at 6 months were significantly different between the placebo- and fluvastatin-treated patients. At the beginning of the follow-up study, the ABI of the placebo- and fluvastatin-treated patients were similar and averaged 1.16 ± 0.04 and 1.07 ± 0.07, respectively. The ABI did not change significantly in either group during the 6-month follow-up period.

Serum concentration of C-reactive protein

Figure 3 illustrates the changes in serum CRP levels during the 6-month administration of placebo or fluvastatin. At the beginning of the follow-up period, serum CRP levels of the placebo- and fluvastatin-treated patients were similar and averaged 0.98 ± 0.29 and 0.97 ± 0.32 mg/dl, respectively. Serum CRP levels were not changed during 6 months of placebo administration, and averaged 1.01 ± 0.35 and 0.97 ± 0.26 mg/dl at 3 and 6 months, respectively. However, fluvastatin administration decreased serum CRP levels to 0.23 ± 0.17 and 0.26 ± 0.16 mg/dl at 3 and 6 months, respectively. The decreases at 6 months were significantly different from the constant values of serum CRP observed in the placebo-treated patients.
Discussion

The present randomized, double-blind, placebo vs fluvastatin study showed that 6 months of medication with fluvastatin, an HMG-CoA reductase inhibitor with antioxidant activity, significantly reduced the PWV in type 2 diabetic haemodialysis patients with normal serum lipid levels. Theoretically, both blood pressure and ABI influence the PWV values. A reduction in blood pressure or a decrease in the ABI value, such as in severe arterial stenosis and/or obstruction, retards the transmission of the pulse wave along the arterial wall, reducing the PWV. In the present study, however, the changes in PWV were not associated with any changes in blood pressure or ABI. Therefore, the decrease in PWV after fluvastatin therapy may be related to a decrease in arterial stiffness.

While previous studies suggested a gradual increase in the PWV of normal subjects at the rate of 18–19 cm/s per year [19,20], the present study demonstrated a much greater increase in PWV of diabetic ESRD patients after 6 months of placebo treatment. The PWV of placebo-treated patients increased by 357 cm/s over 6 months, and its progression rate was ~40 times higher than that observed previously in normal subjects [19,20]. Increased arterial stiffness, as assessed by PWV measurement, predicts all-cause and cardiovascular mortality in ESRD patients [7,8,18]. Studies have demonstrated that cardiovascular mortality in ESRD patients is 10–20 times higher than that in the general population [21], and that the incidence rate of cardiovascular events in diabetic ESRD patients is a further two or three times higher compared with that in non-diabetic ESRD patients [8]. Therefore, the rapid progression of PWV observed in the present study may represent the accelerated atherosclerosis of diabetic ESRD patients. Since a non-medicated state may cause the progressive stiffening of arterial walls, some strategies against atherogenesis are needed for this patient population. Guerin et al. demonstrated that in ESRD patients, angiotensin-converting enzyme inhibitors improve the survival rate and arterial stiffness, as assessed by PWV, independently of changes in blood pressure [18]. The present study, which observed 22 patients for 6 months, showed that fluvastatin improves the arterial stiffness of diabetic ESRD patients even if their serum lipid levels are within the normal ranges. Further studies with a larger number of patients and a longer observation period are needed to confirm the beneficial effects of fluvastatin on arterial wall stiffness, contributing to the cardiovascular morbidity and mortality rates.

Six months of fluvastatin medication decreased the serum concentrations of TC, LDL-C and oxidized LDL-C, despite the normal levels at the beginning of the follow-up study. Since serum oxidized LDL-C levels only elicited a significant decrease compared with the changes observed in the placebo-treated patients, a reduction in arterial stiffness by fluvastatin therapy may be achieved by lowering the oxidized LDL-C concentration, but not the LDL-C concentration. Haemodialysis patients are chronically exposed to oxidative stress, which plays an important role in atherogenesis via the generation of oxidized LDL-C [22]. Therefore, the inhibition of LDL-C oxidation produced by fluvastatin therapy, rather than the reduction in LDL-C levels, may have a larger contribution to the softening of the arterial wall.

Although a significant decrease in the oxidized LDL-C level was observed during the 6-month follow-up study, it is unlikely that structural changes in the arterial wall can occur so rapidly. A recent study demonstrated that fluvastatin improves endothelial function and arterial distensibility in ESRD patients [23]. These beneficial effects of fluvastatin may result from a statin-induced upregulation of endothelial nitric oxide synthase expression and/or activity [24], since oxidized LDL-C has an inhibiting effect on the
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expression of endothelial nitric oxide synthase [25]. In addition, another recent study has shown that antioxidant supplementation preserves endothelium-dependent arterial vasodilation by increasing the bioavailability of nitric oxide in pigs fed a high-cholesterol diet [26]. The antioxidant activity of fluvastatin may also contribute to an improvement in endothelial function, leading to increased arterial distensibility.

Haemodialysis patients are also exposed to chronic inflammation [22]. Studies have suggested that elevated concentrations of CRP, a marker of inflammation, may be involved in the initiation and progression of accelerated atherosclerosis in ESRD patients [17]. The present study also showed a significant reduction in serum CRP levels by 6 months of fluvastatin administration, consistent with previous studies demonstrating anti-inflammatory effects of an HMG-CoA reductase inhibitor [15,16]. These results suggest that anti-inflammatory effects of fluvastatin may cause the reduction of arterial stiffness assessed by decreased PWV. It is, however, possible that an elevated CRP level is a reflection of the inflammatory nature of atherogenesis. Thus, the decreased serum CRP levels may result from improvement of accelerated atherosclerosis by fluvastatin therapy.

In conclusion, the present study shows that fluvastatin therapy significantly decreases serum concentrations of oxidized LDL-C and CRP, and reduces arterial stiffness, as measured by PWV, in haemodialysis patients with type 2 diabetes mellitus, even if their serum lipid levels are within the normal ranges. Antioxidant actions and anti-inflammatory effects of fluvastatin may make a large contribution to the reduction in arterial wall stiffness. Since the present study is based on a relatively small number of patients and a relatively short observation period, the present findings need to be confirmed in a larger group of patients and over a longer period of observation.

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References

12. Lintott CJ, Scott RS, Bremer JM, Shand BI. Fluvastatin for dyslipoproteinemia, with or without concomitant chronic renal insufficiency. Am J Cardiol 1995; 76: 97A–101A

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