Rosuvastatin Increased Serum Osteocalcin Levels Independent of Its Serum Cholesterol-Lowering Effect in Patients with Type 2 Diabetes and Hypercholesterolemia

Ippei Kanazawa, Toru Yamaguchi, Mika Yamauchi and Toshitsugu Sugimoto

Abstract

Objective  Accumulating evidence suggests that statins might positively affect bone metabolism. In the present study, we compared the effect of rosuvastatin with that of ezetimibe on bone turnover markers in patients with type 2 diabetes mellitus as well as hypercholesterolemia.

Design and Methods  A total of 36 Japanese patients were enrolled in this open-label study and randomized to either rosuvastatin (2.5 mg/day) or ezetimibe (10 mg/day) groups at Shimane University Hospital. Bone turnover markers, such as bone-specific alkaline phosphatase, serum osteocalcin, urinary N-terminal telopeptide of type 1 collagen, and urinary deoxypyridinoline, were collected and compared between at baseline and at 3 months of treatment in each group.

Results  Background data was not significantly different between the two groups. Total cholesterol and LDL cholesterol levels were significantly decreased at 3 months in both groups. Serum osteocalcin levels in the rosuvastatin group were significantly increased with mean changes of 0.48 (95% confidence interval; 0.05 to 0.91, p=0.03), while no other bone marker in the ezetimibe group was changed. Changes in total cholesterol or LDL cholesterol levels were not significantly correlated with the changes in bone turnover markers.

Conclusion  Rosuvastatin may have a beneficial effect on bone metabolism in patients with type 2 diabetes and hypercholesterolemia by stimulating osteoblast function and bone formation, which seems to be independent of its cholesterol-lowering effect.

Key words: rosuvastatin, osteocalcin, ezetimibe, hypercholesterolemia, type 2 diabetes mellitus

Introduction

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are widely used as cholesterol-lowering medicines for the prevention of cardiovascular disease. Moreover, statins have recently been shown to exert pleiotropic effects on various cells, which may not be directly related to cholesterol synthesis. Basic studies have shown that statins affect bone, by inducing bone morphogenetic protein-2 (BMP-2) and endothelial nitric oxide synthase (eNOS) expression in osteoblasts and by stimulating bone formation (1, 2). In addition, some studies have demonstrated that statins inhibit bone resorption by directly inhibiting the mevalonate pathway in osteoclasts (3). In contrast, several clinical studies investigating the effects of statins on bone present controversial results (4-10). Rosuvastatin is a relatively new product with powerful lipid-lowering potency. Previous in vitro and in vivo studies have shown that rosuvastatin inhibited bone resorption and recovered ovariectomy-induced bone loss (11). However, to our knowledge, there is no report which examined the effects of rosuvastatin on bone metabolism in humans.

Ezetimibe, a specific inhibitor of cholesterol absorption, is widely used for the treatment of dyslipidemia as monotherapy or given with a statin (12). However, no study have
demonstrated the effects of ezetimibe on bone metabolism. The purpose of the present study was thus to investigate the
effects of rosuvastatin and ezetimibe on bone turnover mark-
ers and determine whether the action is independent of their
cholesterol-lowering effects.

Methods

Subjects

Thirty-six patients with newly diagnosed hypercholes-
terolemia, who visited our outpatient clinic for education,
evaluation, or treatment of type 2 diabetes, were enrolled if
informed consent was obtained after a detailed explanation
of the study purpose and methods. Hypercholesterolemia
was defined as LDL cholesterol ≥120, or LDL cholesterol
≥100 with a history of cardiovascular disease. Nobody had
hepatic or renal dysfunction or nutritional derangement. Pa-
tients who had taken statins or ezetimibe in the past were
excluded from this study. All patients were free of drugs
known to influence bone and calcium metabolism, such as
vitamin D, bisphosphonate, or estrogen, up until the time of
the study. Nobody had treatments with any cholesterol-
lowering agent. In this 3-month prospective study, rosuva-
statin (2.5 mg) or ezetimibe (10 mg) was orally administered
to each group once a day throughout the 3-month treatment
period. No patient suffered from a new fracture during this
study. This study was approved by the ethical review board
of our institution, and complied with the Helsinki Declara-
tion.

Biochemical measurements

After overnight fasting, serum and urine were collected.
Biochemical markers were measured by standard biochemi-
cal methods, as previously described (13, 14). Hemoglobin
A1c (HbA1c) was determined by high performance liquid
chromatography (HPLC). Bone-specific alkaline phosphatase
(BAP) and osteocalcin (OC), bone formation markers, were
measured by radioimmunoassay (RIA) and enzyme immu-
noassay (EIA), respectively. Urinary N-terminal cross-linked
telopeptide of type-I collagen (uNTX) and urinary de-
oxypyridinoline (uDPD), bone resorption markers, were
measured by enzyme-linked immunosorbent assay (ELISA)
and EIA, respectively.

Statistical analysis

Data were expressed as mean ± SD. Student’s t tests were
used for comparison between two groups, paired t tests for
comparison of mean values within groups, and correlation
analysis for the relationships between two parameters. All
analyses were carried out using the statistical computer pro-
gram StatView (Abacus Concepts, Berkeley, CA). p<0.05
was considered to be significant.

Results

Baseline characteristics of patients and comparison
of values of bone turnover markers before and after
treatments in the rosuvastatin group and the
ezetimibe group

The baseline characteristics of the patients and chrono-
logical changes in the levels of serum lipids and bone turn-
over markers are shown in Table 1. First, we compared
these baseline parameters between the two groups. The pa-
rameters did not significantly differ (p values not shown). In
each group, total cholesterol and LDL cholesterol were sig-
ificantly decreased at 3 months (p<0.001). In the rosuva-
statin group, serum osteocalcin levels were significantly in-
creased at 3 months (p=0.027), but other bone turnover
markers were not significantly changed. On the other hand,
no bone turnover marker was significantly changed at 3
months in the ezetimibe group.

Correlations between changes in bone markers versus baseline characteristics

Correlations between the changes in bone turnover mark-
ers versus baseline characteristics including serum lipids lev-
els were analyzed in all subjects (Table 2), however, no sig-
nificant correlation was found. We also found no significant
correlation when each group was analyzed separately (data
not shown).

Correlations between the changes in bone markers versus changes in serum cholesterol levels

Next, we analyzed correlations between the changes in
bone turnover markers versus changes in levels of total cho-
lesterol and LDL cholesterol in all subjects (Table 3), al-
though no significant correlation was found between them.
We also found no significant correlation when each group
was analyzed separately (data not shown).

Discussion

In this study, serum osteocalcin levels were significantly
increased at 3 months in the rosuvastatin group. On the
other hand, no bone turnover marker was changed in the
ezetimibe group. Changes in bone turnover markers were
not associated with baseline serum lipids levels or with
changes in serum lipids levels. These findings suggest that
rosuvastatin stimulated osteoblast function independent of its
cholesterol-lowering effect in patients with type 2 diabetes
as well as hypercholesterolemia.

Accumulating experimental evidence has recently revealed
the importance of the mevalonate pathway in bone metabo-
lism. Inhibition of the mevalonate pathway stimulates the
differentiation and mineralization of osteoblasts (1, 2, 15, 16)
and suppresses osteoclastic activity (17), resulting in bone
mass increase. However, in humans the effects of statins on
bone metabolism are still controversial. Some studies have shown that bone formation markers increase (4, 5) and bone resorption markers decrease (5, 6), while others showed negative results (7, 8). Moreover, higher bone mineral density (5) and lower fracture rates (5, 9) in patients treated with statins have been shown in some studies, but not in others (10). The differences in the background of patients and statin use might be the reason for these discrepancies.

To our knowledge, there is no clinical trial investigating the effects of treatment with rosuvastatin on bone metabolism. In this study, we showed for the first time that treatment with rosuvastatin increased serum osteocalcin levels in type 2 diabetes patients associated with hyperlipidemia. Thus, in the future prospective studies on larger populations would be necessary to investigate the effects of rosuvastatin on bone mineral density and the fracture rate.

Several in vitro studies showed that LDL inhibited the differentiation of osteoblastic cells (18) and induced apoptosis of the cells (19). Parhami et al showed that minimally oxidized LDL and native LDL inhibited the alkaline phosphatase activity and calcium uptake in osteoblastic MC3T3-E1 cells (18). Klein et al showed that native LDL induced apoptosis in osteoblastic Saos2 cells via the Akt signaling pathway (19). Our previous clinical study indicated that serum LDL cholesterol levels are significantly and negatively associated with bone mineral density in postmenopausal women adjusted for age, years of menopause, body mass index, and percent fat mass (20). These findings suggest that LDL cholesterol might directly and negatively modulate bone metabolism. However, in this study, we found that bone turnover markers were not changed in the ezetimibe group at 3 months and changes in LDL cholesterol were not associated with changes in bone turnover markers. These findings suggest that short period cholesterol-lowering effects dose not affect bone metabolism.

Previous studies including ours indicated that hyperglycemia induces a low turnover of bone with osteoblast dysfunction and suppresses serum osteocalcin levels (14, 21-23). On the other hand, recent animal studies have shown that osteocalcin functions as a hormone that regulates glucose metabolism and fat mass (24, 25). Fernandez-Real et al have demonstrated that serum osteocalcin levels are associated with insulin sensitivity and insulin secretion in non-diabetic subjects (26). We have recently shown that the serum osteocalcin level is associated with serum levels of HbA1c and LDL cholesterol might directly and negatively modulate bone metabolism. However, in this study, we found that bone turnover markers were not changed in the ezetimibe group at 3 months and changes in LDL cholesterol were not associated with changes in bone turnover markers. These findings suggest that short period cholesterol-lowering effects dose not affect bone metabolism.

Table 1. Baseline Characteristics and Chronological Changes in Markers for Lipid and Bone Metabolism

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before</th>
<th>After</th>
<th>mean change</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (Male/Female)</td>
<td>18 (9/10)</td>
<td>18 (8/10)</td>
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<td></td>
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<tr>
<td>Age (years)</td>
<td>64.7 ± 2.7</td>
<td>64.7 ± 2.7</td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>14.7 ± 10.6</td>
<td>14.7 ± 10.6</td>
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<tr>
<td>Body height (cm)</td>
<td>158.6 ± 6.9</td>
<td>158.6 ± 6.9</td>
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<tr>
<td>Body weight (kg)</td>
<td>64.1 ± 14.5</td>
<td>64.1 ± 14.5</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>25.3 ± 4.4</td>
<td>25.3 ± 4.4</td>
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<tr>
<td>Total cholesterol (mg/dL)</td>
<td>240 ± 59</td>
<td>240 ± 59</td>
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<tr>
<td>Triglyceride (mg/dL)</td>
<td>209 ± 183</td>
<td>209 ± 183</td>
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<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>57 ± 15</td>
<td>57 ± 15</td>
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<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>153 ± 48</td>
<td>153 ± 48</td>
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<tr>
<td>HbA1c (%)</td>
<td>6.5 ± 1.0</td>
<td>6.5 ± 1.0</td>
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<tr>
<td>BAP (U/L)</td>
<td>34 ± 7.7</td>
<td>34 ± 7.7</td>
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<tr>
<td>OC (ng/mL)</td>
<td>2.4 ± 6.6</td>
<td>2.4 ± 6.6</td>
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<tr>
<td>uNTX (nMBCE/mM-Cr)</td>
<td>29 ± 7.1</td>
<td>29 ± 7.1</td>
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<tr>
<td>uDPD (nM/mM-Cr)</td>
<td>14 ± 11.4</td>
<td>14 ± 11.4</td>
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</tr>
</tbody>
</table>

Ezetimibe

| Subjects (Male/Female) | 18 (9/10) | 18 (8/10) | | | |
| Age (years) | 64.7 ± 2.7 | 64.7 ± 2.7 | | | |
| Duration of diabetes (years) | 14.7 ± 10.6 | 14.7 ± 10.6 | | | |
| Body height (cm) | 158.6 ± 6.9 | 158.6 ± 6.9 | | | |
| Body weight (kg) | 64.1 ± 14.5 | 64.1 ± 14.5 | | | |
| BMI (kg/m²) | 25.3 ± 4.4 | 25.3 ± 4.4 | | | |
| Total cholesterol (mg/dL) | 240 ± 59 | 240 ± 59 | | | |
| Triglyceride (mg/dL) | 209 ± 183 | 209 ± 183 | | | |
| HDL cholesterol (mg/dL) | 57 ± 15 | 57 ± 15 | | | |
| LDL cholesterol (mg/dL) | 153 ± 48 | 153 ± 48 | | | |
| HbA1c (%) | 6.5 ± 1.0 | 6.5 ± 1.0 | | | |
| BAP (U/L) | 34 ± 7.7 | 34 ± 7.7 | | | |
| OC (ng/mL) | 2.4 ± 6.6 | 2.4 ± 6.6 | | | |
| uNTX (nMBCE/mM-Cr) | 29 ± 7.1 | 29 ± 7.1 | | | |
| uDPD (nM/mM-Cr) | 14 ± 11.4 | 14 ± 11.4 | | | |

BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; HbA1c, hemoglobin A1c; BAP, bone specific alkaline phosphatase; OC, osteocalcin; uNTX, urinary N-terminal cross-linked telopeptide of type-I collagen; uDPD, urinary deoxypyridinoline; CI, confidential interval. Statistical significance was determined using the paired t tests.

* Normal range: BAP; 9.6-35.4, OC; 2.5-13.0, uNTX; male 13.0-66.2, female 14.3-89.0, uDPD; male 2.1-5.4, female 2.8-7.6

This study has some limitations. First, the sample size...
was small in order to make definite conclusions. Second, the present study lacks a parallel placebo or treatment control. Therefore, it is not possible to neutralize the effects of additional factors on outcome. In conclusion, we found that treatment with rosuvastatin, but not ezetimibe, increased serum osteocalcin levels. This result suggests that rosuvastatin might exert beneficial effects on bone metabolism by stimulating osteoblast function in patients with type 2 diabetes as well as hypercholesterolemia.

References

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