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[Original Article]

FLUVASTATIN INCREASES BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN

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Abstract : Although several studies have reported a lower risk of osteoporotic fracture in hypercholesterolemic patients (WHO IIa) treated with statin, longitudinal studies on the effects of statins on bone are lacking. The aim of the present study was to evaluate bone mineral density (BMD) and bone turnover changes induced by 3-year fluvastatin treatment in postmenopausal women. Twenty-eight consecutive postmenopausal non-diabetic, normotensive hypercholesterolemic women (64.0±3.6 years) were treated for 36 months with 30 mg/day fluvastatin and 28 non-diabetic, normotensive normocholesterolemic age- and body mass index-matched postmenopausal women served as the control subjects. The result revealed a significant increase of the BMD as compared with the level at the base line ($p < 0.001$) in the fluvastatin-treated group, from 6 months onward after the start treatment. Significant differences of the BMD were found between the controls and fluvastatin-treated group ($p < 0.001$) were at 6, 12, 24 and 36 months after the start of the study. In conclusion our results, although obtained small sample of postmenopausal hypercholesterolemic women, suggest a probable favorable effect of fluvastatin on bone formation and BMD.

Key words : fluvastatin, bone mineral density, osteocalcin, deoxypyridinone, postmenopausal women

INTRODUCTION

Hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor, known as statins, which are well-established cholesterol-lowering agents, have also been shown to have pleiotropic effects, such as anti-inflammatory, antithrombotic, and immunoregulatory actions¹⁾. In fact, since Mundy *et al.* reported favorable effects of statins on bone tissue in rats²⁾, numerous other studies have confirmed such effects *in vitro*³⁻⁵⁾. These studies have also demonstrated that the favorable statin effects on bone are mediated by the enhanced expression of the bone morphogenic proteins (BMPs), in particular, of BMP2, induced by this class of drugs, which, in turn, leads to osteoblastic differentiation and bone

formation²⁾. In addition, statins also seem to interfere with osteoclastic activity⁶⁾. In fact, HMG-CoA reductase inhibitors have been demonstrated to induce apoptosis of osteoclasts, similar to the actions reported for bisphosphonates⁷⁻⁹⁾.

The reported actions of bisphosphonate and statins inhibiting different steps of the mevalonate pathway⁹⁾ lend support to the hypothesis that the statins may have significant effects on the bone metabolism in humans.

In recent years, there has been growing evidence to suggest that statins interfere with exert effort on the bone metabolism. Although some controversial data have been reported¹¹⁻¹²⁾, numerous experimental and epidemiological studies have shown that statins decrease the risk of fractures in

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the elderly¹³⁻¹⁷. In addition to these observational studies on the risk of fracture, the effects of statins on the bone mineral density (BMD)¹⁸⁻²⁴ and bone turnover parameters²⁵⁻²⁸ have also been investigated in some previous studies, and some contradictory results have been reported. At present, because of the limited data and lack of prospective studies conducted to evaluate the effects of the statins on bone remodeling, there is no consensus on the effects of statins on the makers of bone turnover and the BMD²⁹⁻³¹.

Although type 1 diabetes mellitus has been reported to be associated with a decrease of BMD³², reports on the status of the BMD in type 2 diabetes mellitus are conflicting³³. We observed that hypertension might be associated with reduced BMD in female essential hypertension³⁴.

The present prospective study was aimed of evaluating the effect of 3-year treatment with fluvastatin at 30 mg/day on the BMD and bone turnover in non-diabetic, normotensive and postmenopausal hypercholesterolemic women.

SUBJECTS AND METHODS

Subjects

Twenty-eight non-diabetic, normotensive and consecutive postmenopausal hypercholesterolemic women (mean±SD, age: 64.0±3.6 years; range 57-71 years) and 28 healthy postmenopausal women of complete physical examination matched for age, body mass index (BMI) and spine BMD with a T-score of -1 to -2.5 SD in any region (mean±SD, age: 64.0±3.6; range 57-70 years) were recruited. Only subjects with hypercholesterolemia, (≥ 220 mg/dl, WHO IIa) who had not been treated previously for dyslipidemia were included in the study. In addition, patients were not included in the study if they had receiving any lipid-lowering drugs (estrogens, calcitonin, bisphosphonates, anabolic steroids, vitamin D, or drugs known to interfere with bone metabolism) during the previous 6 months or who had amenorrhea for less than 12 months were excluded from the study. Patients with other health problems which could interfere with the conduct of the study were also excluded.

Standard renal, liver, and thyroid function tests were performed before the start of statin therapy, to exclude secondary hypercholesterolemia. Serum creatine kinase was measured to detect any possible side effects of the statin on the muscle tissue.

Hypertension was defined as a systolic blood

pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg³⁵ in the sitting position on at least three different occasions. The diagnosis of diabetes mellitus was based on a 75-g oral glucose tolerance test³⁶; individuals were labeled as having diabetes mellitus if the fasting plasma glucose level was 126 mg/dl or the plasma glucose level at 2 h after glucose administration was 200 mg/dl or greater. Patients with hypertension and diabetes mellitus were excluded from the study.

A detail medical history was obtained from all the subjects and the dietary calcium intake was assessed using a validated questionnaire to detect the amount of intake of foods that are known to account for the majority of the calcium in the diet.

During the study period, none of the patients received any treatment that could potentially affect bone metabolism, such as estrogen, calcitonin, bisphosphonates, or calcium and vitamin D supplements.

Study design

The 28 non-diabetic, normotensive hypercholesterolemic women selected according to the above-mentioned criteria were administered fluvastatin at the dosage of 30 mg/day for 36 months and 28 healthy age-, body mass index-matched postmenopausal women served as the control group. It was ensured that the daily dietary calcium intake was about 700 mg the study period in all the study subjects (both hypercholesterolemic patients and control subjects).

In all subjects, fasting venous blood samples were drawn at baseline and at 3-month intervals up to 36 months of fluvastatin treatment in order to determine the serum levels of total cholesterol (TC), high-, low-density and non-high-density lipoprotein cholesterol (HDL-C, LDL-C and non-HDL-C, respectively), triglycerides (TG), serum calcium (Ca), serum inorganic phosphate (iP).

Measurements

The lipid parameters, Ca and iP were measured with a Model 7250 autoanalyzer (Hitachi Co., Ltd., Tokyo, Japan). The LDL-C were calculated from TC, TG and HDL-C by using the formula proposed by Friedwald: $LDL-C = TC - [HDL-C + TG/5]$. The non-HDL-C were calculated from TC and HDL-C: $TC - HDL-C$. The serum levels of intact PTH and osteocalcin were measured by chemiluminescent immunoassay (Nichols Institute Diagnosis SanClement, USA). Serum osteocalcin (OC) was assayed by an immunoradiometric assay (Mitsubishi

Kagaku Iatron, Inc., Tokyo, Japan). Urinary deoxyypyridinoline (u-DPD) was determined by an enzyme immunoassay (Quidel Corporation, San Diego, USA).

In all subjects, the BMD was assessed in the lumbar supine (using the central portion of the lateral scout view of the L2-4 vertebrae) by dual energy X-ray absorptiometry (DXA) using a Hologic QDR 2000 (Bedford, USA, at baseline and at 6, 12, 24 and 36 months after the start of the study).

The study was approved by the Ethics Committee of Fukushima Rosai Hospital. All patients and control subjects provided informed written consent to participate in the study.

All of the 28 patients treated with 30 mg of fluvastatin and 28 subjects of the control group completed the 3-year study period.

Statistical analysis

Values are expressed as the mean \pm SD, unless otherwise specified. Statistical analyses were performed by unpaired two-tailed Student's t-test, one-way analysis of variance (ANOVA) followed by Fisher's PSLD post-hoc test and Pearson's correlation method using Stat View for Macintosh version 5.0 software (Abacus Concepts, Inc., Berkeley, USA). The null hypothesis was rejected at $p < 0.05$.

RESULTS

Table 1 shows the clinical characteristics and baseline values of the BMD, bone markers, and serum lipids in the hypercholesterolemic patients and the control group. There were no significant differences in the age, years after menopause, BMI, systolic and diastolic blood pressure, fasting blood glucose, lumbar BMD, serum OC, urinary DPD, intact PTH, Ca or iP between the two groups.

The hypercholesterolemic patients who were on treatment with fluvastatin at 30 mg/day showed significant ($p < 0.001$) reduction of the serum levels of TC and LDL-C from 251.9 ± 14.7 and 163.2 ± 15.8 mg/dl at baseline, respectively, to 196.0 ± 14.9 mg/dl and to 113.9 ± 13.6 mg/dl (-22.2% and -30.2% , respectively) at the end of the 36-month study period (Fig. 1). The serum HDL-C increased significantly ($p < 0.001$) from 50.8 ± 11.9 at base line to 65.0 ± 11.5 mg/dl (27.9%) at the end of the 36-month study period in the fluvastatin-treated patients (Fig. 1). The serum non-HDL-C decreased significantly ($p < 0.001$) from 201.1 ± 12.6 at base line to 131.0 ± 13.2 mg/dl (-34.8%) at the end of the 36-month study period.

No significant changes of the lipid profile were observed at any time-point during the study period

Table 1. Baseline characteristics of the study population

Characteristics	Hypercholesterolemic patients ($n=28$)	Control subjects ($n=28$)	p value
Age (years)	64.0 ± 3.6	63.9 ± 3.8	n.s.
Years after menopause	14.2 ± 4.5	14.4 ± 4.2	n.s.
Body mass index (kg/m^2)	22.4 ± 1.9	22.5 ± 1.7	n.s.
Systolic blood pressure (mmHg)	125.3 ± 13.6	123.5 ± 14.8	n.s.
Diastolic blood pressure (mmHg)	70.7 ± 9.6	73.0 ± 10.8	n.s.
Total cholesterol (mg/dl)	251.9 ± 14.7	170.1 ± 12.5	< 0.001
Triglycerides (mg/dl)	88.4 ± 13.6	90.4 ± 15.2	n.s.
LDL-cholesterol (mg/dl)	163.2 ± 15.8	106.0 ± 12.3	< 0.001
HDL-cholesterol (mg/dl)	50.8 ± 11.9	51.6 ± 6.3	n.s.
Fasting blood glucose (mg/dl)	89.2 ± 14.3	87.3 ± 16.5	n.s.
Lumbar BMD (g/cm^2)	0.589 ± 0.078	0.592 ± 0.070	n.s.
Osteocalcin (ng/ml)	10.8 ± 3.2	10.8 ± 3.1	n.s.
Urinary DPD (nM/mMcr)	10.0 ± 3.1	10.6 ± 2.9	n.s.
intact PTH (pg/ml)	46.6 ± 9.8	46.8 ± 9.9	n.s.
serum calcium (mg/dl)	9.2 ± 0.5	9.3 ± 0.6	n.s.
serum iP (mg/dl)	3.5 ± 0.5	3.5 ± 0.4	n.s.

Values are expressed as mean \pm SD. LDL, serum low-density lipoprotein; HDL, serum high-density lipoprotein; BMD, bone mineral density; DPD, deoxyypyridinoline; iP, inorganic phosphate; n.s., not significant

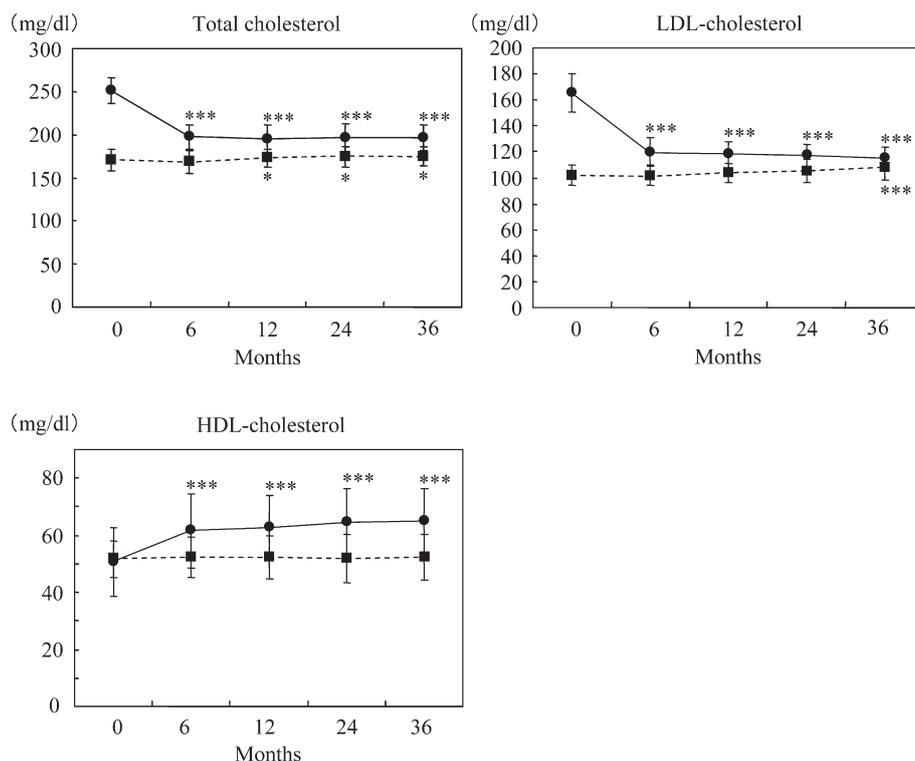


Fig. 1. Changes in the serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol. Each value is expressed as mean \pm SD; fluvastatin treated group (●-●), $n=28$; controls (■-■) $n=28$; *** $p<0.001$ vs. baseline (paired t-test); * $p<0.05$ vs. baseline (paired t-test);

in the control group. Also, the serum levels of Ca, iP and intact PTH remained within their respective normal ranges in both the treated patients and the control group.

The mean BMD changes over the 3-year study period relative to the values at the baseline are shown in Fig. 2. In the fluvastatin-treated group BMD significant ($p<0.001$) increase of the BMD began to be noted from 6 months onward after the start of the study. On the other hand, significant decrease of the BMD ($p<0.001$) as compared with the value at baseline was observed in the control group at the time-points examined. The differences between the two groups remained statistically significant ($p<0.001$) throughout the study period (Fig. 2).

In patients treated with fluvastatin, no significant changes of the serum OC or u-DPD were observed at any time-point of examinations during the study period (Fig. 3). In control group, the serum OC began to decrease significantly ($p<0.001$) as compared with the values at baseline from 12 months onward, and the values continued to decrease thereafter until 36 months, or the end of the study periods (Fig. 3). In the same group, the u-DPD level remained significantly higher ($p<0.001$)

as compared with the value at baseline throughout the study period. The difference between the treated patients and control subjects were statistically significant ($p<0.001$) at 12, 24 and 36 months for the serum OC, and at 6, 12, 24 and 36 month for the u-DPD (Fig. 3).

A significant negative correlation was found at 24 months between the changes in the spine BMD and the u-DPD in fluvastatin-treated group ($r=-0.405$, $p<0.05$) (Fig. 4).

DISCUSSION

According to the results of the present study, 3-year treatment with fluvastatin at 30 mg/day moderately increase bone formation and stability and thereby the BMD in postmenopausal hypercholesterolemic women. Although caution must be exercised in comparing the results obtained using different experimental models, these findings are consistent with the results of previous *in vitro* and animals studies that examined the influence of statins on the osteoblastic activity²⁻⁵. Namely, Mundy *et al.* conducted an in-depth study of the effects of statins on prenylation of GTPase proteins blocking the mevalonate pathway in osteoblast

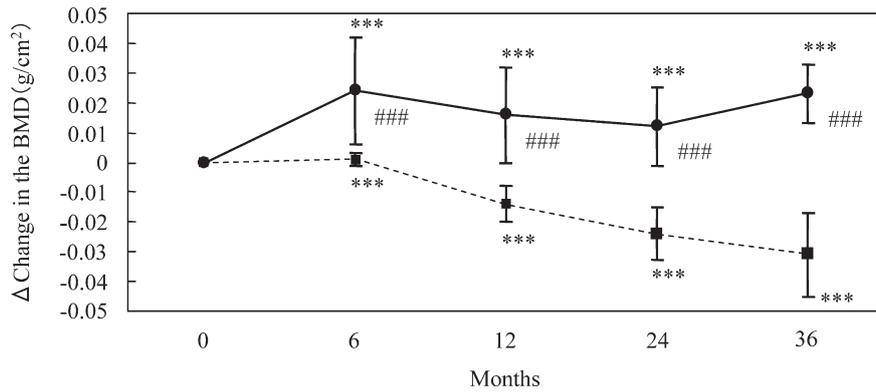


Fig. 2. Effect of fluvastatin on bone mineral density (BMD) in the lumbar spine of the central portion of lateral scout view of lumbar 2 to 4 vertebrae. Each value is expressed as mean±SD; fluvastatin treated group (●-●), n=28; controls (■-■) n=28; ***p<0.001 vs. baseline (paired t-test); ###p<0.001 vs. controls (ANOVA).

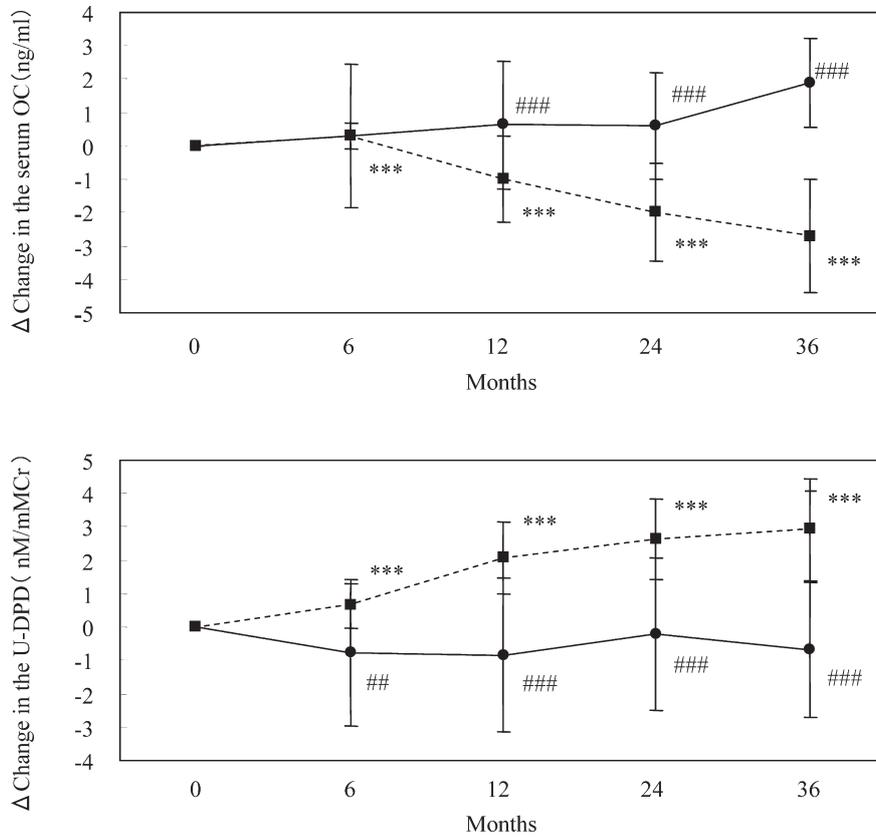


Fig. 3. Changes in the serum osteocalcin (OC) and urinary deoxypyridinoline (U-DPD) levels. mean±SD; fluvastatin treated group (●-●), n=28; controls (■-■) n=28; ***p<0.001 vs. baseline (paired t-test); ##p<0.01 vs. controls (ANOVA); ###p<0.001 vs. controls (ANOVA).

recruitment and proliferation. In addition, Hanayama *et al.*³⁷⁾ demonstrated that fluvastatin significantly attenuated osteoclast differentiation and activation through blockade of the classical mevalonate pathway and an antioxidant action, leading to prevention of osteoporosis. To the best of our knowledge, this is the first prospective study to investigate the changes in both bone remodeling

parameters and BMD in postmenopausal women treated with the usual clinical dose of fluvastatin.

Although the 3-year treatment period used in this study might have been too short for precise evaluation of the longitudinal changes of the BMD by DXA, the favorable effects of statins on the BMD and bone formation observed in the fluvastatin-treated subjects as compared with the changes in

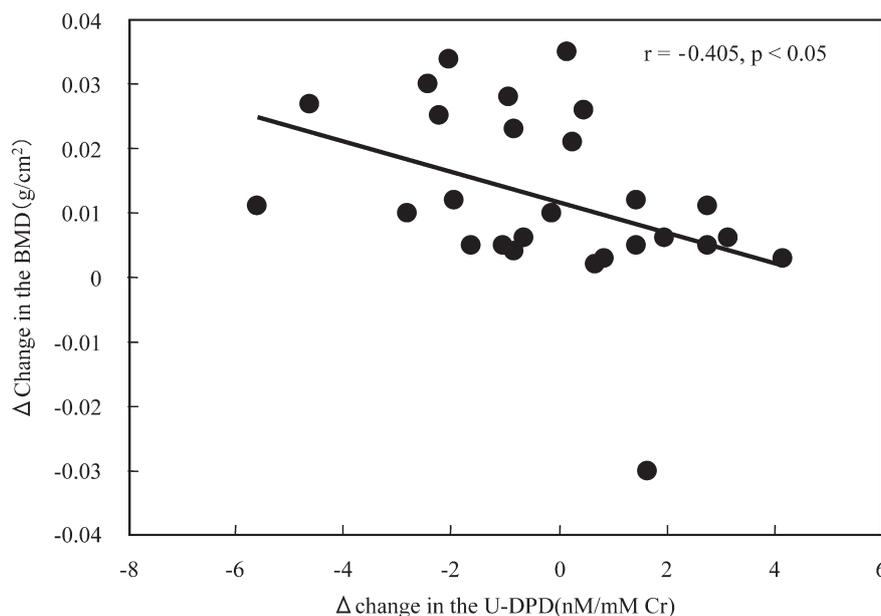


Fig. 4. Correlation between the changes of bone mineral density (BMD) and those of the urinary deoxypyridinoline (U-DPD) levels at month 24 in fluvastatin treated group (●). $n=28$.

the control group could partially explain the fracture risk reduction observed in most retrospective studies^{13,38–41}. Watanabe *et al.*⁴², in a clinical trial comparing the effects of fluvastatin and pravastatin, stated that OC and serum carboxyterminal telopeptide of collagen I and bone-ALP fell 24% after 26 weeks in subjects randomized to fluvastatin 20 mg/day, and fell 44% and 25%, respectively, in those who were randomized to fluvastatin 10 mg/day. Moreover, in our study, the tendency towards increase of the BMD in the fluvastatin-treated group was also accompanied by a decrease of the u-DPD, suggestive of a reduced osteoclastic activity. Our results seem to be inconsistent with those of previous studies, which have reported a reduction or no variation of the bone-ALP in patients treated with fluvastatin or simvastatin^{20,25,43}. It is possible that the difference in the results between these previous studies and our own experience could be explained by the different age group of the subjects and use of different types and dosages of the statins between our studies.

With regard to bone formation, we did not find any change of serum OC levels in the fluvastatin-treated group as compared with that in the control group during the examination period in our study. These results seem in contrast with the data reported by other authors^{2,6,43}, which demonstrated an influence of the statins, *in vitro*, also on the osteoclastic activity. Likewise, longitudinal studies in humans have reported an inhibitory effect

of the statins on the osteoblastic activity^{20,43}. However, most of these data were obtained over shorter treatment periods than the 3-year treatment period employed in our study, and were obtained using different statins at different dosages, which has been reported to have differential effects on the activity of bone cells in rats⁴⁴.

Although the number of patients in our study is limited, the findings of no significant changes of the serum OC or u-DPD in the fluvastatin-treated group as compared with that in the control group during the study period could suggest an imbalance between bone formation and resorption. These variations of the BMD have been reported to occur to lesser extent with simvastatin treatment in postmenopausal women⁴⁵, as compared to those reported for the majority of antiresorptive drugs^{46,47}. However, other drugs used for the treatment of osteoporosis, such as raloxifene⁴⁸ and calcitonin⁴⁹, have been reported to markedly reduce the risk of vertebral fractures in the face of a modest increase of the BMD, comparable to that observed with fluvastatin in the present study. Therefore, our longitudinal data could partially support the findings of previous retrospective studies reporting a reduced risk of fractures in dyslipidemic patients treated with statins. Both the stabilization/slight gain of the BMD and the favorable changes of bone turnover could positively influence the bone structure, enhancing the bone strength; however, this hypothesis needs to be verified by further and larger stud-

ies.

In conclusion, although our study may have been limited by the small size of the study population and the short period of follow-up, statins moderately induce bone formation, with a positive effect on the BMD. This findings could represent a useful step for carrying out further large-scale and randomized studies for evaluation of the possible role of statins in the treatment of osteoporosis.

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