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Short-term Effects of Atorvastatin on Bone Turnover in Male Patients with Hypercholesterolemia

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Abstract. No consensus has been reached on whether the 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, known as statins, have beneficial effects on bone health. The purpose of our study was to evaluate the effects of atorvastatin on bone metabolism by means of measuring bone turnover markers in male patients with hypercholesterolemia both at diagnosis and prospectively after 3 months of treatment. Twenty-two Japanese male patients (mean age 62.36 ± 10.1 years) with untreated hypercholesterolaemeia were selected for this study. After 3-months treatment of atorvastatin, total cholesterol and low density lipoprotein cholesterol significantly decreased as expected (p<0.001 for both parameters). Bone-specific alkaline phosphatase (BAP) did not change significantly (p = 0.444). However, serum N-terminal telopeptide of type I collagen (NTx) significantly decreased by –19.86 ± 26.4% (p = 0.020). In addition, ΔNTx during the course of this study was negatively correlated with NTx at baseline (r = –0.645, p = 0.0008). Although there was a tendency of positive correlations of ΔNTx with Δtotal cholesterol, Δtriglycerides, and Δlow density lipoprotein cholesterol, and of negative correlations of ΔNTx and ΔBAP with Δhigh density lipoprotein cholesterol, none of them reached statistical significance. Our findings suggest that atorvastatin may have potentially beneficial effects on bone metabolism in patients with hypercholesterolemia mostly by reducing bone resorption rather than by stimulating bone formation. Further studies with more patients and longer duration are warranted to evaluate its effects, if any, on prevention of osteoporosis and subsequent fractures.

Key words: Atorvastatin, Bone turnover, Osteoporosis, Hypercholesterolemia

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IN addition to their cholesterol-lowering properties, statins, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are known to have various so-called pleiotropic effects including improvement of endothelial function, increased nitric oxide (NO) bioavailability, antioxidant properties, stabilization of atherosclerotic plaques, regulation of progenitor cells, inhibition of inflammatory responses and immunomodulatory actions [1]. However, no consensus has been reached yet as to whether statin has beneficial effects on bone health [2]. Experimental studies have shown that statins stimulate osteoblast-derived bone morphogenetic protein 2 (BMP-2) expression and subsequently enhance osteoblastic bone formation [3, 4]. In addition, it has also been suggested that statins directly affect osteoclasts through mechanisms analogous to those of bisphosphonates, because bisphosphonates and statins exert their effects by inhibiting the same mevalonate pathway [5, 6]. These findings raise the hope that statins might have significant bone-formative and antiresorptive effects on bone metabolism in humans.

However, although there have been a growing number of clinical studies examining the effects of statins

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Table 1. Clinical trials examining effects of statins on bone turnover, cited in the discussion

Authors and Year	Patients with Hyperlipidemia		Statins	Duration (month)	Bone Turnover Markers	
	Number	Gender (M/F)			Bone Formation Markers	Bone Resorption Markers
Stein *et al.*[13], 2001	390	170/220	Simvastatin	3	BAP decreased.	s-CTx unchanged
	404	157/247	Atorvastatin		BAP unchanged.	
Watanabe *et al.*[16], 2001	12	0/12	Fluvastatin	1	OC increased. BAP unchanged.	u-NTx decreased.
				6	OC unchanged. BAP unchanged.	u-NTx unchanged.
Bjarnason *et al.*[12], 2001	45	0/45	Fluvastatin	3	OC unchanged. ALP unchanged.	u-CTx decreased. s-CTx decreased.
Rejnmark *et al.*[7], 2002	140	0/140	Simvastatin, Atorvastatin, Lovastatin, Pravastatin, Fluvastatin, Cerivastatin	Cross Sectional	OC was lower. BAP was lower.	s-CTx was lower.
Kajinami *et al.*[8], 2003	35	23/12	Atorvastatin	3	OC unchanged. BAP unchanged.	u-NTx unchanged.
				6	OC unchanged. BAP increased.	
Kuzuya *et al.*[9], 2003	16	3/13	Atorvastatin	3 6	BAP unchanged.	u-NTx decreased.
Braatvedt *et al.*[11], 2004	25	9/16	Atorvastatin	3	OC unchanged. BAP unchanged.	β-CTx unchanged.
Berthold *et al.*[10], 2004	24	0/24	Atorvastatin	2	OC unchanged. BAP unchanged.	s-CTx unchanged.
Rejnmark *et al.*[14], 2004	39	0/39	Simvastatin	12	OC unchanged. BAP unchanged.	s-CTx unchanged.
Rosenson *et al.*[15], 2005	12	not shown	Pravastatin	2	OC unchanged. BAP unchanged.	u-NTx unchanged.
	14		Simvastatin		OC unchanged. BAP unchanged.	
	15		Simvastatin		OC unchanged. BAP decreased.	
Own study, 2006	22	22/0	Atorvastatin	3	BAP unchanged.	s-NTx decreased.

BAP, bone-specific alkaline phosphatase; OC, osteocalcin; ALP, alkaline phosphatase; s-, serum; u-, urinary; CTx, C-terminal telopeptide of type I collagen.; NTx, N-terminal telopeptide of type I collagen.

on bone metabolism [7–16], most of them could not find increase of bone formation markers [7, 9–15] (Table 1). Likewise, reduction of bone resorption markers was found in some studies [7, 9, 12, 16], but not in others [8, 10, 11, 13–15]. Moreover, higher bone mineral density (BMD) [16] and lower fracture rates [16, 17] in patients treated with statins have been demonstrated in some clinical studies, but not in others [7, 12, 18, 19]. One of the possible reasons for these discrepancies among previous clinical studies might be the difference in the statin used [3–5, 13, 20]. Therefore, in the present study, we used the same statin, atorvastatin, which is a relatively new product with powerful lipid-lowering potency. In addition, the pos-

sibility has been suggested that it may have greater ability to affect bone [4, 5, 19, 20].

Another possible reason may be the gender difference in the previous clinical studies, because interpretation of the effects of statins on bone metabolism is hampered by the background of involutional osteoporosis in female patients [21]. In addition, there is ample evidence to indicate that osteoporosis in men is already a public health problem. Therefore, our assessment of the potential effects of atorvastatin on bone metabolism was limited to male patients in an effort to largely eliminate the influence of involutional osteoporosis.

The purpose of our study was thus to examine and assess the effects of atorvastatin on bone turnover in male patients with hypercholesterolemia, both at diagnosis and prospectively after 3 months of treatment.

Subjects and Methods

Subjects

Twenty-two Japanese male patients (mean age 62.36 ± 10.1 years) with untreated hypercholesterolemia, who attended the clinic of Rakuwakai Otowa Hospital between January 2005 and January 2006, were selected for this study. The diagnosis of hypercholesterolemia was established on the basis of laboratory findings, including an elevated serum total cholesterol (TC) level (>220 mg/dl) and an elevated serum low density lipoprotein cholesterol (LDL) level (>140 mg/dl). Hypercholesterolemia in all patients was treated with atorvastatin (10 mg/day) alone. During the course of this study, the dose of atorvastatin remained unchanged. This study involved a 3-month (at baseline, and 3 months after the beginning of the treatment) longitudinal examination of these 22 patients. Their clinical data at baseline are shown in Table 2.

All subjects completed a questionnaire administered by the doctor or nurse prior to entry into the study, and underwent laboratory blood and urinary tests. We excluded subjects who had a history of fractures and/or of other diseases (type 1 diabetes mellitus, liver disease, renal dysfunction, malignancy, hyperthyroidism, hyperparathyroidism, hypercorticoidism, or hypogonadism) and those taking medications (active vitamin D3, bisphosphonates, calcitonin, selective estrogen receptor modulators, estrogens, testosterones, steroids, thyroid hormones, diuretics, heparin or anticonvulsants) that could influence bone metabolism. We also excluded those with triglycerides (TG) level >500 mg/dl, because their LDL cannot be calculated adequately using the Friedewald equation. None of the subjects were smokers or substance abusers.

Table 2. Means ± SD of the variables assessed in patients with hypercholesterolemia

	Patients with hypercholesterolemia (n = 22)		*P*-value
	Baseline	3 months later	
Age (years)	62.36 ± 10.1	—	—
Height (cm)	163.44 ± 7.6	—	—
Weight (kg)	66.17 ± 12.9	—	—
BMI (kg/m^2)	24.63 ± 3.6	—	—
TC (mg/dL)	247.68 ± 25.1	179.23 ± 32.3**	<0.001
TG (mg/dL)	165.59 ± 77.7	126.23 ± 61.4*	0.033
HDL (mg/dL)	51.59 ± 11.4	52.96 ± 10.9^{NS}	0.337
LDL (mg/dL)	162.97 ± 23.3	101.03 ± 25.9**	<0.001
Ca (mg/dL)	9.58 ± 0.5	9.44 ± 0.4^{NS}	0.113
ALP (IU/L)	249.05 ± 75.3	238.68 ± 59.8^{NS}	0.31
BAP (IU/L)	22.42 ± 5.6	21.76 ± 5.7^{NS}	0.444
NTx (nmolBCE/L)	15.84 ± 4.0	12.20 ± 3.7*	0.013

Data represent mean ± SD.
BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; Ca, calcium; ALP, alkaline phosphatase; NTx, N-terminal telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase.
P-values for comparisons of the parameters between at baseline and 3 months: $^{NS}P>0.05$; *$P<0.05$; **$P<0.01$.

This study was performed in accordance with the recommendations of the Declaration of Helsinki, and the protocol was approved by the Ethical Committee of Rakuwakai Otowa Hospital. All the subjects gave their informed consent before they were enrolled.

Biochemical measurements

All subjects underwent laboratory blood tests at baseline, and at 3 months. Serum samples were obtained before 8:00 AM after an overnight fast, and were immediately processed and kept frozen at –20°C until the assays were carried out. Serum TC, TG, high density lipoprotein cholesterol (HDL), calcium (Ca), and alkaline phosphatase (ALP) were measured with standard laboratory methods. LDL was calculated by Friedewald equation (LDL = TC – [HDL + TG/5]). Se-

rum bone-specific alkaline phosphatase (BAP) was measured with an enzyme immunoassay kit (Osteolinks-BAP; Sumitomo Pharmaceuticals Inc., Tokyo, Japan; reference range: 13.0–33.9 U/L) as a marker of bone formation. Serum N-terminal telopeptide of type I collagen (NTx) was measured by means of an enzyme-linked immunosorbent assay (OSTEOMARK; Mochida Pharmaceutical Co., Tokyo, Japan; reference range: 9.5–17.7 nmolBCE/L) as a marker of bone resorption. The intra-assay coefficient of variation for BAP and NTx is 3.8% and 7.8% respectively, while the inter-assay coefficient of variation is 1.6% and 3.7%, respectively.

Statistical analysis

Data were analyzed by paired t-test for longitudinal differences between at baseline and at 3 months, and by Pearson's correlation test for determining correlations. Statistics were calculated with StatView version 5.0 (Abacus Concepts, Inc., Berkeley, CA, USA). A P value <0.05 was considered statistically significant.

Results

Fortunately, the atorvastatin treatment was well tolerated by our patients, and none of them dropped out during the course of this study. Table 2 shows the longitudinal characteristics of the patients. NTx, but not BAP, was significantly decreased after 3-months treatment of atorvastatin ($p = 0.013$) (Fig. 1). NTx was decreased in as many as 18 (81.8%) of the patients, while BAP only in 11 (50.0%) of them. The percentage change of the reduction of NTx was significant compared with the baseline (–19.86 ± 26.4%, $p = 0.020$), while that of BAP was not significant (–1.32 ± 19.1%, $p = 0.749$). The change of NTx and BAP was over the so-called minimum significant change (14.2% and 23.1%, respectively) in 14 and 3 patients, respectively. TC and LDL were also significantly decreased after 3-months treatment, as expected. The other biochemical parameters (TG, HDL, Ca, and ALP) were unaltered after 3-months treatment of atorvastatin.

Table 3 shows correlations of ΔNTx and ΔBAP with age, height, weight, BMI and the biochemical parameters at baseline. ΔBAP was positively correlated with HDL at baseline (r = 0.543, $p = 0.0079$). ΔNTx was negatively correlated with NTx at baseline (r = –0.645, $p = 0.0008$) (Fig. 2).

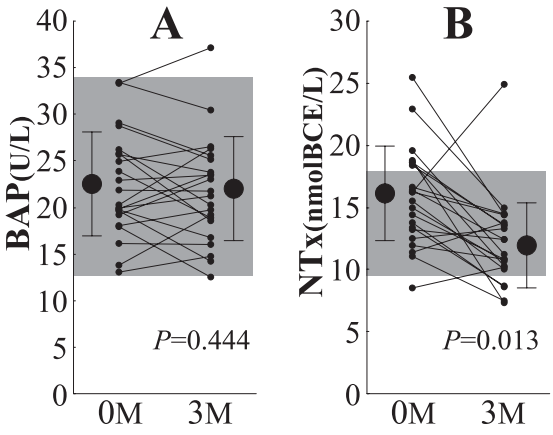

Fig. 1. Comparison of bone turnover markers between at baseline and at 3 months. BAP (A) and NTx (B) levels at baseline (0 M) and at 3 months (3 M) in patients with hypercholesterolemia are plotted. The bold circles represent the mean, and the vertical lines represent the SD for each marker. The shaded areas represent reference range. *P*-values for comparison of the parameters between at baseline and the 3 months.

Table 4 shows correlations of ΔNTx and ΔBAP with Δage, Δheight, Δweight, ΔBMI and the Δbiochemical parameters. Although there was a tendency of positive correlations of ΔNTx with ΔTC, ΔTG, and ΔLDL, and of negative correlations of ΔNTx and ΔBAP with ΔHDL, none of these trends reached statistical significance.

Discussion

Concerning the biological effects of statins on bone metabolism, Mundy *et al.* [3] first reported that statins stimulated osteoblast-derived BMP-2 expression and subsequently enhanced osteoblastic bone formation. Since then, this enhancing effect of statins on bone formation has been repeatedly confirmed by numerous *in vitro* studies [4]. In addition, animal model studies also showed that bone formation rate was increased in rats given statins [22]. These findings strongly suggest the possibility that statins could potentially be useful as an anabolic therapeutic agent for osteoporosis.

However, clinical studies in humans have not always succeeded in demonstrating this stimulating effect of statins on bone formation [7, 9–15]. One of the possible reasons for this discrepancy between *in vivo* and *in vitro* studies may be the differences in the dosage of

Table 3. Correlations of ΔBAP and ΔNTx with age, height, weight, BMI and the biochemical parameters at baseline in patients with hypercholesterolemia

	Age	Height	Weight	BMI	TC	TG	HDL	LDL	Ca	ALP	BAP	NTx
ΔBAP	0.196	0.156	–0.185	–0.347	0.072	–0.138	0.543**	–0.097	0.083	0.218	–0.332	0.224
ΔNTx	–0.021	0.063	0.135	0.171	–0.030	–0.039	0.251	–0.094	0.017	0.094	0.249	–0.645**

Values are correlation coefficients.
BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; Ca, calcium; ALP, alkaline phosphatase; NTx, N-terminal telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase.
P-values for correlations of BAP and NTx with age, height, weight, BMI and the biochemical parameters in patients with hypercholesterolemia: $^{**}P<0.01$.

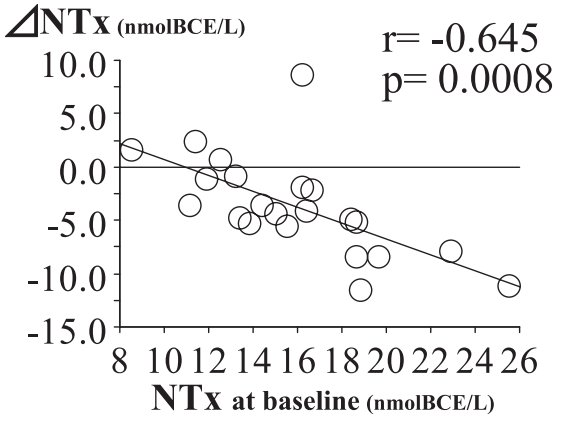

Fig. 2. Correlation of ΔNTx with NTx at baseline. ΔNTx are plotted against NTx at baseline. The line reflects the regression and r means the correlation coefficient. *P*-value for correlation between ΔNTx with NTx at baseline.

Table 4. Correlations of ΔBAP and ΔNTx with Δbiochemical parameters in patients with hypercholesterolemia

	ΔTC	ΔTG	ΔHDL	ΔLDL	ΔCa	ΔALP
ΔBAP	-0.009^{NS}	0.008^{NS}	-0.250^{NS}	0.037^{NS}	-0.064^{NS}	0.157^{NS}
ΔNTx	0.160^{NS}	0.195^{NS}	-0.211^{NS}	0.131^{NS}	0.089^{NS}	0.257^{NS}

Values are correlation coefficients.
BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; Ca, calcium; ALP, alkaline phosphatase; BAP, bone-specific alkaline phosphatase; NTx, N-terminal telopeptide of type I collagen.
P-values for correlations of ΔBAP and ΔNTx with Δbiochemical parameters in patients with hypercholesterolemia: $^{NS}P>0.05$.

statins [5, 10]. Indeed, some clinical studies reported that statins increased bone formation markers [8]. However, most of them have shown that statins either did not alter [8–16], consistent with our finding, or decreased [7, 13, 15] bone formation markers. These discrepancies among previous clinical studies and ours might be explained partly by the statin used [3–5, 13, 20]. Stein *et al*. [13] actually described the difference between the effects of different statins on bone metabolism in humans, and some *in vitro* studies showed that beneficial effects on bone were found only in lipophilic statins such as atorvastatin, but not hydrophilic pravastatin [3, 4, 20]. We are aware of 5 clinical studies [8–11, 13] examining the effects of atorvastatin, which was used in our study, on bone metabolism. In agreement with our results, 4 of them [9–11, 13] found no significant changes of bone formation markers by atorvastatin. These results and ours do not support the hypothesis that clinical use of atorvastatin exerts anabolic effects on human bone metabolism.

On the other hand, the present study revealed that NTx significantly decreased after 3 months-treatment with atorvastatin, suggesting antiresorptive effects of atorvastatin. Moreover, this antiresorptive effect of atorvastatin was found to be all the more prominent in patients with higher NTx, suggesting beneficial effects of atorvastatin on bone health. Although this negative correlation between ΔNTx and NTx at baseline may indicate that atorvastatin could exert bone protective effects more in osteoporotic patients as in the case with bisphosphonates, the most powerful antiresorptive agent available, the mechanism of this correlation is unclear from our study. However, the fact that both bisphosphonates and statins exert their effects by inhibiting the same mevalonate pathway [6] supports our hypothesis. In addition, although some controversies exist, some clinical studies examining the effects of statins on bone metabolism have actually shown significant reduction in bone resorption markers [7, 9, 12, 16], consistent with our finding. A recently published study by Kuzuya *et al.* [9] showed that 1-year treatment

with atorvastatin did not alter BAP, but decreased urinary NTx in 16 elderly patients (3 men and 13 women) with hypercholesterolemia, very similar to our results. Moreover, an *in vitro* study has recently shown antiresorptive effects of statins as well as bone-formative effects [3]. More recently, Staal *et al.* [5] have shown that statins *in vitro* inhibit bone resorption but do not increase bone formation, consistent with our results. Based on all these observations above, it is likely that clinical use of atorvastatin may have beneficial effects on bone metabolism mostly by reducing bone resorption rather than by stimulating bone formation.

Although our study found potentially beneficial effects of atorvastatin on bone metabolism, whether statins can really increase bone mass to reduce the risk of fractures has not reached consensus yet [2]. Since it has been suggested that the bone turnover markers are good predictors for the subsequent change of BMD, and their improvement independently contributes to reduction of fracture risk [23], the significant improvement in bone turnover by atorvastatin in our study is expected not only to augment their bone mass but also to reduce the future risk of fractures. However, the magnitude of the antiresorptive effect of statins, as measured by changes of bone turnover markers in our study, seems to be far less pronounced than that of bisphosphonates [2, 24], probably due to their lower affinity to bone. Further studies are therefore needed to resolve whether this beneficial but relatively weak effect of atorvastatin on bone metabolism found in our study is of clinical relevance.

Since the present study has some limitations, our results should be interpreted cautiously. First, it did not include large numbers of patients. Second, we had no control subjects to compare and be more certain of the changes found in our study. Thus, the improvement of bone metabolism in our study may be explained partly by dietary and exercise advice given since the baseline. In addition, another possibilityis is that hypercholesterolemia itself might have been associated with higher bone turnover, and that reduced bone resorption found in our study might have only reflected the hypercholesterolemia improved by atorvastatin. Indeed, Koshiyama *et al*. [25] have recently reported the possibility that hypercholesterolemia may be the main cause of abnormal bone metabolism in type 2 diabetes mellitus [26]. However, ΔNTx did not correlate with ΔTC, ΔTG, ΔLDL or ΔHDL in our study. Third, whether our short-term results will similarly be found in a long-term study remains unclear. Lastly, our subjects were recruited from patients with hypercholesterolemia, but not those diagnosed as osteoporosis. As Rosenson *et al*. [15] stated in their report, the antiresorptive effect of atorvastatin found in our patients with hypercholesterolemia might be more pronounced in osteoporotic subjects, as in the case with bisphosphonates [27]. Some beneficial effects of atorvastatin on bone metabolism might have been partially obscured in the present study.

In summary, in a 3-month prospective study, we could not find that atorvastatin increased BAP in the patients with hypercholesterolemia, contrary to our expectations from previous *in vitro* studies in the literature. On the other hand, we found that atorvastatin significantly reduced NTx in these patients. These findings indicate that atorvastatin may exert beneficial effects on bone metabolism in patients with hypercholesterolemia mostly by reducing bone resorption rather than by stimulating bone formation. Further studies with more patients and longer duration are warranted to evaluate its effects, if any, on the prevention of osteoporosis and subsequent fractures.

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