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The effects of one-year simvastatin therapy on women's bone mineral density

Research Article

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Abstract: Only few studies have reported that bone fracture risk is decreased in hypercholesterolemic postmenopausal women treated with statin therapy. Because of a lack of longitudinal studies on the effect of statins on bones, the aim of our investigation was to estimate the simvastatin therapy effects on bone mineral density in hypercholesterolemic postmenopausal women. Our investigation was carried out on 53 postmenopausal women with hypercholesterolemia. The women included in the study were divided into two groups. Group 1 was comprised of women with two or more (n=32) atherosclerosis risk factors, whereas group 2 had women with less than two (n=21) of these risk factors. All the women included in the study were placed on a hypocholesterolemic diet and the women in group 1 were additionally treated with 20 mg of simvastatin daily. The parameters of lipid status, body mass index, and L2-L4 densitometry were determined at baseline and then after one year. The simvastatin-treated group showed significant improvement of lipid parameters and increased bone mineral density. Finally, changes in bone mineral density between the groups showed significant differences ($p<0.05$). Although our investigation was carried out on a small group, our results showed a positive effect of the simvastatin therapy on the bone mineral density of postmenopausal women.

Keywords: *Bone mineral density • Postmenopausal women • Hypercholesterolemia • Statins*

1. Introduction

Inhibitors of the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A reductase are drugs known as statins, which are used for the treatment of hypercholesterolemia and for primary and secondary prevention of coronary disease for over a decade. Their efficacy and safety are documented by numerous studies [1]. The key effect of statin treatment is the inhibition of the HMG-CoA reductase enzyme that catalyzes the rate-limiting step of cholesterol biosynthesis. Besides this inhibition, statins show other effects that cannot be attributed to a decrease in total cholesterol concentration. These pleiotropic effects include vasodillatatory, antithrombotic, antioxidative, anti-inflammatory and antiproliferative effects [2]. For postmenopausal women who are at a greater risk for the development of coronary disease and osteoporosis, however, an especially important effect is the mediation of statins on bone metabolism. This effect is possible through several mechanisms: by reducing signal proteins of osteoclast activity [3]; and by increasing gene expression of bone morphogenetic protein 2. These mechanisms can be a rational explanation for the reasonable use of statins for the treatment of osteoporosis. Until now, few studies have shown a decreased risk for bone fracture in postmenopausal women with hypercholesterolemia on statin therapy. Data about the statins' effect on bone mineral density are controversial and further extensive and well-designed prospective studies with a large number of patients are needed. Due to the lack of longitudinal studies on the effect of statins on bones, the aim of this current study was to estimate the

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effect of simvastatin therapy on bone mineral density in postmenopausal women with hypercholesterolemia.

2. Material and Methods

The study was carried out on 53 women with the mean age of 62.92±6.08 years, who were treated at the Institute for Prevention, Treatment and Rehabilitation of Cardiovascular Disease “Niska Banja” in Niska Banja. All patients were in their postmenopausal period, had clinical and biochemical parameters for hypercholesterolemia, and had been previously included in a non-pharmacological regimen. Patients were excluded from this study if they had secondary osteoporosis, or endocrine or systemic diseases, or if they had been previously treated with steroids, hormonal substitution therapy, thiasides, bisphosphonates or statins. The patients were divided into two groups. The first group (group 1) was comprised of 32 women with two or more risk factors for atherosclerosis and the second group (group 2) had 21 women with less than two risk factors for atherosclerosis. All patients were placed on the hypocholesterolemic step II diet, but patients in Group 1 were also treated with 20 mg of simvastatin daily.

Blood samples for the measurement of biochemical parameters were taken in the morning after a 12-hour fasting period. The Enzymatic Colorimetric Method was used for the measurement of triglycerides (TG), total cholesterol (TC), and cholesterol in high density lipoproteins (HDL-C). Cholesterol in low density lipoproteins (LDL-C) was determined by an indirect method with the Friedewald equation. Bone mineral density (BMD) was determined in lumbar vertebras (L_1-L_4) by DEXA densitometer LUNAR DPX, and the result was expressed as an absolute value (g/cm^3) and a T-score (SD of referent values for young and healthy populations) [4]. The clinical biochemical parameters and bone mineral density were determined at the beginning and after 12 months of research.

During this research no patient was excluded from the study, i.e. there were no clinical and hematological adverse side effects.

The SPSS package version 12.0 and Statcalc version 5 are used for statistical analysis. Parameters are reported as mean and standard deviation; statistical testing of differences in continuous variables between groups was made by the Student’s unpaired t test. An analysis of variance, for repeated measurements, was used to compare the variations from baseline. Pearson’s correlation coefficients tested the relationship between variables.

Table 1. T-score in patients with hypercholesterolemia according to WHO classification.

		Group 1		Group 2		Total	
		n	%	n	%	n	%
Normal value	T-score >-1	3	9.37	7	33.33	10	18.87
Osteopenia	T-score from -1 to -2.5	20	62.50	10	47.62	30	56.60
Osteoporosis	T-score <2.5	9	28.12	4	19.05	13	24.53

Bone mineral density (BMD) in patients with hypercholesterolemia, at study onset, was evaluated according to the T-score, as described in the Materials and Methods section. Abbreviations: n = number of patients in each group.

Table 2. Baseline values of measured parameters in study groups.

	Group 1 (n=32)	Group 2 (n=21)	P value
Age	63.11±6.27	62.78±5.01	NS
BMI	25.25±2.87	26.73±2.04	NS
BMD	0.965±0.111	1.042±0.181	NS
TC	8.083±1.740	6.598±1.084	<0.005
TG	1.751±0.656	1.723±0.584	NS
HDL-C	1.168±0.235	1.224±0.239	NS
LDL-C	6.119±1.736	4.591±0.992	<0.001

Parameter values at the beginning of the study were evaluated as described in the Materials and Methods section. All results were presented as mean±SD. Levels of TC, TG, HDL-C and LDL-C were given in mmol/l. Abbreviations: BMI = body mass index, BMD = bone mineral density, TC = total cholesterol, TG = total triglycerides, HDL-C = cholesterol in high density lipoproteins, LDL-C = cholesterol in low density lipoproteins, NS = no significant difference.

3. Results

By measuring the BMD, patients included in our study were divided into three different groups (normal BMD value, osteopenia, and osteoporosis) according to the T-score (Table 1). As shown in Table 1, 81.13% of women had decreased BMD at the beginning of the study; BMD was decreased in 90.62% of women in group 1 and in 66.67% of women in group 2.

In analyzing the basal values of measured parameters in the study groups, we found significant differences in total cholesterol (8.08±1.74 mmol/l in group 1 and 6.59±1.08 mmol/l in group 2; $p<0.05$) and LDL-C values (6.11±1.73 mmol/l in group 1 and 4.59±0.99 mmol/l in group 2; $p<0.001$) between the groups (Table 2). On the other hand, there was no significant difference in BMD and other lipid parameters at the onset of the investigation.

Results from repeated measurements of BMD and lipid parameters after a one-year treatment with simvastatin and hypocholesterolemic diet (group 1) or hypocholesterolemic diet only (group 2) are presented

Table 3. Changes in BMD values and lipid parameters in each study group, after one year treatment.

	Group 1, baseline	Group 1, after 1 year	Percentage Difference	Group 2, baseline	Group 2, after 1 year	Percentage Difference
BMD	0.965±0.111	0.992±0.110	2.812	1.042±0.181	1.006±0.182	-3.45
TC	8.083±1.740	7.058±1.139*	-12.681	6.598±1.084	6.439±0.612	-2.41
TG	1.751±0.656	1.863±0.906	6.362	1.723±0.584	2.008±0.607	16.54
HDL-C	1.168±0.235	1.194±0.273	2.222	1.224±0.239	1.145±0.261	-6.45
LDL-C	6.119±1.736	5.017±1.114**	-17.994	4.591±0.992	4.582±0.691	-0.19

*Parameters were measured (at study onset and one year afterwards) in study groups treated with either simvastatin and hypocholesterolemic diet (group 1) or hypocholesterolemic diet only (group 2). All results were presented as mean±SD. Levels of TC, TG, HDL-C and LDL-C were given in mmol/l. Abbreviations: BMD = bone mineral density, TC = total cholesterol, TG = total triglycerides, HDL-C = cholesterol in high density lipoproteins, LDL-C = cholesterol in low density lipoproteins, *P<0.01 vs. baseline value, **P<0.005 vs. baseline value.*

Table 4. Differences in BMD and lipid parameters between the groups, after the examination period.

	Group 1	Group 2
BMD	-0.027±0.037*	0.036±0.036
TC	1.025±1.273*	-0.041±0.995
TG	-0.111±0.833	-0.285±0.406
HDL-C	-0.026±0.311	0.080±0.277
LDL-C	1.101±1.271*	0.090±0.843

*Values were presented as mean±SD after the examination period. Abbreviations: BMD = bone mineral density, TC = total cholesterol, TG = total triglycerides, HDL-C = cholesterol in high density lipoproteins, LDL-C = cholesterol in low density lipoproteins, *P<0.05 vs. the corresponding group.*

in Table 3. After the examination period, statistically significant decreases in TC ($p<0.01$) and LDL-C ($p<0.005$), compared to baseline measurements in the same group, were detected only in group 1. Even though during the examination period, the BMD values increased in group 1 and decreased in group 2, we found no significant differences in BMD changes in each group. There were no significant differences in measured parameters after the examination period in the group with hypocholesterolemic diet only (group 2).

However, by analyzing the parameters between different groups (Table 4) after the one-year follow-up, we found significant differences in BMD ($p<0.05$), TC ($p<0.05$) and LDL-C ($p<0.05$). On the other hand, we could not find any significant correlation in changes in BMD to LDL-C ($r = 0.080$; $P=0.686$; $r =0.166$; $P =0.626$) or to TC ($r =0.144$; $P=0.476$; $r =0.125$; $P=0.715$).

4. Discussion

Our research has shown an increase in bone mass in postmenopausal women with hypercholesterolemia treated with simvastatin, compared to women with therapeutically changed lifestyle, which instead showed a trend towards decreased BMD. This longitudinal study was specifically targeted at the investigation of BMD in women with hypercholesterolemia on simvastatin therapy and diet during the one-year follow-up, and the study groups were randomized according to the risk factors that affect bone mineral density (smoking, BMI, and age).

The retrospective studies in previous years showed a possibility of statins having a positive effect on bone metabolism, but none of these studies was specifically targeted to investigate the effect of this class of drugs on bone mineral density. The majority of studies investigated the connection between usage of simvastatin and fracture risk [6-12]. Adami et al. claimed that a decreased incidence of bone fractures in patients on statin therapy can be explained by higher bone mineral density in patients with higher levels of LDL-C [13]. In our study, both study groups had hypercholesterolemia and similar baseline values of bone mineral density and the results rejected this possible misunderstanding.

The other researchers, who investigated the capability of statins to increase bone mineral density, pointed out that this class of drugs could have a positive effect on bones. In a retrospective study on the use of statins by patients with diabetes, Chung and his colleagues confirmed decreased bone loss in men [14]. Another study compared the BMD of patients on statin therapy and those who were not, and found higher BMD in patients of the first group [15]. Later investigations compared the effects of fluvastatin and pravastatin on BMD after one year of therapy, and fluvastatin showed better effects [16]. Similar effects of simvastatin, after one year of research on a group of postmenopausal women with hypercholesterolemia compared to a normolipidemic group, were confirmed recently [17]. Rejinmark, in a cross-section study, pointed out that statins with their antiresorptive effect modulate the function of bone cells [18]. The key to the connection between statins and bone metabolism is in a few mechanisms. The first mechanism is the inhibition of mevalonate that stops the synthesis of isoprenoids (farnesyl-pyrophosphate and geranylgeranyl-pyrophosphate), which are used by the osteoclasts for modification and activation of intracellular proteins like glutamyl transpeptidase, Ras and Rho; the inhibition of prenylation changes osteoclast activity [3,19]. The other mechanism, which explains how statins can influence the biological activity of osteoblasts, was revealed by Mundy and his colleagues [5]. They showed that statins increase gene expression of morphogenetic protein 2, which is capable of accelerating the maturation of osteoblasts and bone formation. It is possible that the anti-inflammatory effect of statins is the third mechanism contributing to protection from osteoporosis, keeping in mind that inflammation is one of the essential determinants of ostheoporosis [20] and that inflammatory cytokines are increased in the postmenopausal period [21].

In summary, this study shows an improvement in bone mineral density after 12 months of treatment with simvastatin. These results need to be confirmed in large longitudinal randomized studies with the aim of assessing the possibility of statin therapy for osteoporosis. These studies should give answers to questions like how long statins should be used and who would have the greatest benefit from this therapy.

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