EFFECT OF SIMVASTATIN TREATMENT ON BONE MINERAL DENSITY IN HYPERCHOLESTEROLEMIC POSTMENOPAUSAL WOMEN

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Statins are able to reduce cardiovascular morbidity and mortality mainly through their hypocholesterolemic effect. Beyond the inhibition of cholesterol synthesis, the identification of pleiotropic mechanisms has motivated many studies to evaluate the effects of statin use on bone mineral density (BMD) modification.

The aim of our study was to evaluate whether simvastatin treatment (20 mg/d) could modify BMD in hypercholesterolemic women (n=28) after one-year treatment as compared with a control group treated only with a diet (n=11). The exclusion criteria was current or previous therapy with statins, bisphosphonates and/or estrogens. The following parameters were determined at the beginning and after one year, and those are: total cholesterol, triglycerides, HDL-C and LDL-C (Friedewald equation). The BMD was measured at the lumbar spine by dual energy x-ray absorpiometry (DEXA).

In the simvastatin treated group, BMD showed an insignificant 2,812% increase after 12 months, respectively (0,965±0,111 v 0,992±0,110, P>0,05). The group treated only with hypolipidic diet demonstrated a 3,45% decrease in BMD (respectively, 1,042±0,181 v 1.006±0,182; P>0,05) after 12 months. Nevertheless, the comparison of average BMD changes between the two examined groups during one year showed a significant value diference (-0,027±0,037 v 0,036±0,036; P<0,0006).

As partly suggested by retrospective or observational data, this longitudinal study indicates that simvastatin treatment achieves a beneficial effect on BMD. *Acta Medica Medianae 2005;44(2): 61–65*.

Key words: *simvastatin, bone mineral density, hypercholesterolemia, postmenopausal women*

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Introduction

Statins, hypolipemic drugs, used worldwide to lower plasma concentrations of cholesterol-carrying lipoproteins, are able to reduce clinical events linked to atherosclerosis (1).

The key effect of statin therapy is the inhibition of hydroxymethyl glutaryl-coenzyme A reductase, the enzyme catalysing a rate-limiting step in hepatic cholesterol synthesis. Beyond this inhibition, statins also show pleiotropic effects, defined as all their vascular and nonvascular effects independent from the cholesterol reduction (2).

It has been hypothesized that one of the pleiotropic effects of statins could be the improvement of bone health due to the interference with bone metabolism through various mechanisms: the reduction of signal proteins regulating osteoclast activity (3) and the increased expression of bone morphogenetic protein-2 gene in the rat bone tissue (4). These mechanisms could represent the rationale for the use of statins in the treatment of osteoporosis, the most common disease of the bone characterized by an altered balance between bone formation and resorption. Some studies have found that the risk of fractures is markedly reduced in people using statins versus nonusers, (5-8) while other studies found no differences (9-11).

The aim of our study was to evaluate the modifications of bone mineraldensity (BMD) after 1 year of treatment with simvastatin in 28 hypercholesterolemic postmenopausal women compared with hypercholesterolemic women treated only with the diet.

Patients and methods

Twenty eight consecutive hypercholesterolemic women referred to theInstitute for Prevention, Treatment and Rehabilitation of Rheumatic and Cardiovascular Disease "Niška Banja", all in postmenopausal

age and with the presence of at least 2 major risk factors for atherosclerosis, were included in the study. All of them were affected by primary hypercholesterolemia diagnosed on the basis of anamnestic, clinical, and biochemical parameters and previously treated only with the diet. Eleven hypercholesterolemic women, with the presence of no more than two risk factors for atherosclerosis, were also included in the study. The two groups were matched for age, body mass index (BMI) and lipid parameters.

We excluded patients with secondary hyperlipemias, endocrinologic and/or systemic disease, and those previously treated with steroids, hormone replacement therapy, thiazides, bisphosphonates, calcium, vitamin D, and statins. Moreover, we also excluded all subjects affected by secondary osteoporosis.

All patients underwent clinical examination. Thereafter, blood was drawn in the morning after a 12-hour fast. The following parameters were determined: triglycerides (enzymatic colorimetric method), high-density lipoprotein-cholesterol (HDL-C) (enzymatic colorimetric method after precipitation with polyethilenglycole) and LDL-C (Friedewald equation). Hypercholesterolemic patients with two or more risk factors other than LDL-C (group 1) were treated with simvastatin 20 mg; the control group (group 2) was treated only with American Heart Association diet step II.

BMD was measured with dual energy x-ray absorpiometry (DEXA) on the lumbar spine (from the first to the fourth lumbar vertebra). According to the World Health Organization (WHO) classification,[12] diagnosis of osteopenia or osteoporosis was based on BMD expressed as T-score; a T-score represents a patient's bone density expressed as the number of standard deviations (SDs) above or below the mean BMD value for a normal young adult.

BMD, clinical and lipid parameters were initially determined and after 12 months.

Parameters are reported as mean and SD; 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 time and each control visit. Pearson's correlation coefficients tested the relationship between clinical and biochemical variables.

Results

Table 1 shows the baseline parameters. As requested by inclusion criteria, patients in the two groups were matched for age, BMI and BMD. The two groups were not matched for risk factors and lipid parameters.

Table 2 shows the percentages of normal, osteopenic, and osteoporotic patients in the two groups

Table 3 shows BMD and lipid parameters at baseline and after 12 months. As expected, the group treated with simvastatin showed a decrease of total cholesterol and LDL-C significantly higher than group 2. In group 1, BMD showed a nonsignificant increase after 12 months (P>0,05). In fact, there was an increase of 2,812%. Group 2, treated only with the hypolipidic diet, demonstrated a decrease in BMD after 12 months (-3,45%; P>0,05).

Table 1. Basal Characteristics of Simvastatin Group (group 1) and Controls (group 2)

	Simvastatin Group (n=28)	Controls (n=11)	P
Age	61,786±6,27	62,11±5,01	NS
Weight	66,5±6,497	66,25±6,13	NS
BMI	25,25±2,87	26,73±2,04	NS
BMD	0,965±0,111	1,042±0,181	NS
T CHOL	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

Table 2. T-Score in Study Population

WHO classification		Simvastatin Group	Controls
Normal	T-score >-1	2 (7,14%)	4 (36,36%)
Osteopenia	T-score from -1 to -2,5	18 (64,29%)	5 (45,46%)
Osteoporosis	T-score <-2,5	8 (28,57%)	2 (18,18%)

Comparison of average BMD changes betwen the two examined groups during one year (Table 4) showed significant diference (-0,027±0,037 v 0,036±0,036; P<0,0006). Moreover, we did not find any significant correlations between changes (the last determination minus the basal one) of BMD versus changes in LDL-C (respectively, r= -0.080; P= 0,686.; r= 0,166, P=0,626) and total cholesterol (respectively, r=-0.144; P=0,476; r=-0.125.; P=0,715) in group I. No patients were excluded during the follow up; we did not observe any clinical or hematochemical adverse effect of statins. During the 1-year follow-up, patients did not report any fractures.

aimed at examining the drug effect on mineral density. In fact, most of them examined the relationship existing between statin administration and the risk of fracture, with no univocal results (5-11). Nevertheless, another study had claimed that the lower incidence of fractures among statin users could be explained by the higher bone mass observed in subjects with higher LDL-C levels (13). However, our studied groups were both hypercholesterolemic with comparable baseline bone mineral densities, thus removing this confounder.

Other investigators, who specifically investigated whether statins can increase mineral density, have suggested that this class of drugs may exert this

Table 3. Bone Mineral Density and Lipid Profile During Study Follow up in Study Population

	Simvastatin Group (group 1)			Controls (group 2)		
	baseline	12 months	Percent of change (%)	baseline	12 months	Percent of change (%)
	Mean± Standard Deviation			Mean± Standard Deviation		
BMD	0,965±0,111	0,992±0,110	2,812	1,042±0,181	1,006±0,182	-3,45
T CHOL	8,083±1,740	7,058±1,139**	-12,681	6,598±1,084	6,639±0,612	0,62
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

*P <0,05 v basal value, **P <0,01 v basal value, †P <0,005 v basal value.

Table 4. Differences between average changes in bone mineral density during follow- up

	Simvastatin Group		Controls		P value
	Mean	SD	Mean	SD	
BMD	-0,027	0,037	0,036	0,036	0,0006*
T CHOL	1,025	1,273	-0,041	0,995	0,011*
TG	-0,111	0,833	-0,285	0,406	0,389
HDL-C	-0,026	0,311	0,080	0,277	0,313
LDL-C	1,101	1,271	0,090	0,843	0,004*

Discussion

The present study demonstrated an increase in BMD in postmenopausal hypercholesterolemic women treated with simvastatin compared with those treated only with the diet, who had a trend towards losing BMD. Our study is a longitudinal study specifically addressed to examining BMD in hypercholesterolemic women treated with simvastatin or diet for 1 year. Moreover, the two groups were also matched for risk factors, which can influence mineral density, such as smoking, BMI, and menopausal age.

In the past years, retrospective studies have indicated a possible beneficial effect of statins on bone metabolism, but all these studies were not specifically

positive action; in a retrospective study the use of statins in diabetic patients reduces the bone loss in males (14); in a cohort study comparing BMD in statin users versus nonusers, a higher BMD has been observed among the first group (15); in a third study, the 1-year effect of fluvastatin and pravastatin on BMD was measured; fluvastatin therapy maintained BMD after 1 year (16). A recent longitudinal study of the one-year follow-up found a similar beneficial effect of simvastatin in a group of hypercholesterolemic postmenopausal women compared with a normolipemic group (17). Another recent cross-sectional study indicated that statins modulate bone cell function with an antiresorptive effect (18).

The link between statins and bone metabolism lies in several mechanisms. At first, the inhibition of mevalonate synthesis prevents the synthesis of isoprenoids, such as farnesylpyrophosphate and geranylgeranylpyrophosphate, which are used by osteoclasts to modify and activate intracellular proteins, such as glutamyl transpeptidases, as Ras and Rho; the inhibition of prenylation alters osteoclast activity (3,19). The second mechanism explains how statins have a biologic activity also on osteoblast activity: Mundy et al[4] demonstrated that statins increase gene expression of bone morphogenetic protein-2, a protein capable of increasing osteoblast maturation and bone formation. The anti-inflammatory effect of statins could be the third mechanism involved in protection from osteoporosis. In fact, inflammation, as evident in rheumatic disorders, is a main determinant of osteoporosis (20), and in the postmenopausal age there is an increase in inflammatory cytokines (21); statins may attenuate such influence by their the well-known anti-inflammatory effect (22).

In conclusion, this study, indicating a gain in BMD after 1-year simvastatin treatment, is consistent with previous observational and retrospective studies demonstrating a positive influence of statins on bone formation; these observations and results need to be supported by larger longitudinal studies specifically addressed to evaluate the possible role of statin treatment in osteoporosis.

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EFEKTI STATINSKE TERAPIJE NA KOŠTANU GUSTINU POSTMENOPAUZALNIH ŽENA SA HIPERHOLESTEROLEMIJOM

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Statini, uglavnom kroz svoj hipolipemijski efekat, redukuju kardiovaskularni morbiditet i mortalitet. Pored inhibicije sinteze holesterola, identifikacija pleotropnih mehanizama postakla je istraživanje efekata upotrebe statina na promenu koštane gustine (BMD).

Cilj našeg istraživanja bio je da proceni da li terapija simvastatinom (20 mg/dan) može da promeni BMD kod hiperholesterolemičnih žena (n=28) nakon jednogodišnje terapije, kao i kod kontrolne grupe tretirane samo dijetom (n=11). Aktuelna ili prethodna terapija statinima, bifosfonatima i/ili estrogenima bila je kriterijum za isključivanje iz studije. Ukupni holesterol, trigliceridi, HDL-C i LDL-C (po Fridewald-ovoj formuli) su određivani na početku i nakon godinu dana, a BMD je merena na lumbalnoj kičmi dvostruko energetskom Z-zračnom apsorpsciometriom (DEXA).

U grupi tretiranoj simvastatinom, BMD pokazuje nesignifikantno povećanje od 2,812% nakon 12 meseci (0,965±0,111 v 0,992±0,110, P>0,05). Grupa tretirana samo hipolipidemijskom dijetom pokazala je nakon 12 meseci smanjenje BMD od 3,45% (1,042±0,181 v 1,006±0,182; P>0,05). Pored toga, komparacija prosečne promene BMD između ispitivanih grupa u toku jedne godine pokazuje signifikantnu razliku.

Kao što i delom sugerišu retrospektivni i opservacioni podaci, ova longitudinalna studija pokazuje da terapija simvastatinom ima beneficijalne efekte na koštanu gustinu. *Acta Medica Medianae 2005;44(2): 61–65*.

Ključne reči: *simvastatin, koštana gustina, hiperholesterolemia, postmenopauzalne žene*