Original article ■

Effects Of Simvastatin Therapy On Bone Mineral Density In Hypercholesterolemic Postmenopausal Woman

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SUMMARY

The aim of the study was to evaluate the effects of simvastatin therapy on bone mineral density in hypercholesterolemic postmenopausal women.

Fifty-three women, mean age $62{,}92 \pm 6{,}08$ years treated at the Institute for Treatment and Rehabilitation Niška Banja were included into this study. All patients were divided into two groups: I group - 32 women with total cholesterol level (Hol $\geq 7{,}8$ mmol/l) and II control group - 21 women with total cholesterol less than 7,8 mmol/l. Triglycerides (Tg), total cholesterol (Hol), HDL and LDL cholesterol (HDL-C and LDL-C) were determined. Bone mineral density (BMD) was determined on the lumbar spine (L_I-L_4), by "LUNAR DPX" densitometer. The results were expressed as absolute values (g/cm^2) and T score. All patients were treated with lifestyle and dietary modification, while patients in group I were treated with 20 mg of simvastat per day. Biochemical markers and bone mineral density were determined at the start and 12 months after.

Simvastatin therapy 20mg/day significantly reduced Hol (-12,68%; p<0,01) and LDL-C (-17,99%; p<0,005) levels after 12 months of follow-up. The concentration of TG and HDL-C showed insignificant changes. In II group, there were no significant changes in lipid parameters after 12 months of hypolipemic diet regimen. Increase in BMD +2,81%, (NS) was registered in I group, while decrease in BMD -3,45% (NS) was reported in II group. There was an inverse correlation between BMD changes and LDL-C (r=-0,08; p=0,686) in the patients on statin therapy compared to I group (r=0,166, p=0,626). Also, in the same group, an inverse correlation between BMD and Hol (r=-0,144; p=0,476) was reported, which was similar to I group (r=-0,125; p=0,715). These results did not reach statistical significance.

Conclusion: Simvastatin therapy showed a positive trend and increase in bone mineral densisty in hypercholesterolemic posmenopausal women after 12 months of follow-up, however, without statistically significant difference.

Key words: bone mineral density, statin therapy, postmenopausal women

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INTRODUCTION

Statins are hypolipemic drugs with blocking effects on 3-hidroxy 3-methil glutaril coenzyme A (HMG-CoA) reductase, the key enzyme in cholesterol synthesis. They have been used in the therapy of hypercholesterolemia as well as for primary and secondary coronary artery disease prevention, with proven efficacy throughout numerous studies (1).

Besides limiting effects on cholesterol synthesis and reduced mevalonate production, they exert some other (pleotropic) effects apart from their hypolipemic effects. This pleotropic effects are vasodilatation, antithrombotic, antioxidative, anti-inflammatory and antiproliferative effects (2). The effects of statins on bone mineral metabolism are of huge interest for post-menopausal women with increased risk for coronary artery disease development. This effect is mediated throughout several mechanisms: signaling proteins of osteoclastic activity reduction (3) and increased expression of morphogenetic bone protein 2 gene (4). These mechanisms could be the rationale for statins therapy in osteoporotic women. Some studies have shown decreased risk for bone fractures in hypercholesterolemic postmenopausal women on statin therapy (5-12). There are many questions related to the effects of statin therapy on bone mineral density. Some well-designed and large prospective studies are needed to provide answers on these questions.

AIMS

The aim of the study was to evaluate the effects of simvastatin therapy on bone mineral density in hypercholesterolemic postmenopausal women.

PATIENTS AND METHODOLOGY

Fifty-three women, mean age $62,92 \pm 6,08$ years treated at the Institute for Treatment and Rehabilitation "Niška Banja" in Niška Banja were included into this study. All the patients were hypercholesterolemic postmenopausal women. They were on cardiovascular rehabilitation program prior to study inclusion. The patients with secondary osteoporosis, endocrine or systemic diseases, steroid or hormonal substitution therapy, therapy with tiazides, biposhonates or statins were excluded from the study.

All patients were divided into two groups: group I - 32 women with total cholesterol level (Hol≥7,8 mmol/l) and II control group - 21 women with total cholesterol less than 7,8 mmol/l. All patients had diet with less than 30% of fats in total energy input, less than 7% of saturated fatty acids and less than 200mg/day of cholesterol. They also had therapy with 1200 mg/day of calcium and 400 IJ/day of vitamin D. Patients in group I were treated with 20 mg of simvastat per day.

The blood samples were taken in fasting state. Triglycerides (Tg), total cholesterol (Hol) and HDL cholesterol (HDL-C) were determined by Randox reagens with „Synchron CX5" analyser. LDL cholesterol (LDL-C) was determined by indirect Friedwald method. Bone mineral density (BMD) was determined on the lumbar spine (L_1-L_4), by "LUNAR DPX" densitometer. The results were expressed as absolute values (g/cm^2) and T score (SD deviation from young healthy population referent values). Biochemical markers and bone mineral density were determined at the start and 12 months after.

Statistical analysis was done by SPSS software, using average standard deviation, Student's t-test and Pearson's test for linear correlation.

RESULTS

At the begining of the study, 81,13% od patients from both groups had decreased bone mineral density (90,62% patients in I group and 66,67% patients in II group). Average BMD was similar in both groups (Table 1).

Mean age and body mass index (BMI) of examined patients did not significantly differ between two groups (Table 1). Plasmatic level of total cholesterol in all patients was $7,66 \pm 1,71$ mmol/l at the begining of the study ($8,08 \pm 1,74$ mmol/l in patients from I group and $6,6 \pm 1,08$ mmol/l in patients from II group, p<0,005). Average LDL-C concentration was significantly higher in patients from I group compared to II group ($6,12 \pm 1,74$ mmol/l vs. $4,59 \pm 0,99$ mmol/l, p<0,001). Other examined lipid parameters did not show statistical difference between the groups (Table 1).

Simvastatin therapy 20 mg/day significantly reduced Hol levels (-12,68%; p<0,01) and LDL-C (-17,99%; p<0,005) after 12 months of follow-up. Concentration of TG and HDL-C showed insignificant changes of Tg (+6,36%) and HDL-C (+2,22%) compared to starting values. In II group we did not register significant changes in lipid parameters after 12 months of hypolipemic diet regimen. Increasing of BMD +2,81%, (NS) was registered in I group, while decreasing of BMD -3,45% (NS) was observed in II group (Table 2).

Comparison of BMD changes in groups I and II after 12 months of follow-up (Table 3) showed statistically significant difference (p<0,0006).

Patients on statin therapy had inverse correlation between BMD changes and LDL-C (r=-0,08; p=0,686) compared to I group (r=0,166, p=0,626). They also had inverse correlation between BMD and Hol (r=-0,144; p=0,476) similarly to I group (r=-0,125; p=0,715). These results did not reach statistical significance.

Table 1. *Investigated parameters at the begining of the study*

Investigated parameters	Group I (n=32)	Group II (n=21)	p
Age (years)	63,11+6,27	62,78+5,01	NS
BMI (kg/m^2)	25,25+2,87	26,73+2,04	NS
BMD (g/cm^2)	0,96+0,11	1,04+0,18	NS
Hol (mmol/l)	8,08+1,74	6,6+1,08	<0,005
TG (mmol/l)	1,75+0,66	1,72+0,58	NS
HDL-C (mmol/l)	1,17+0,24	1,22+0,24	NS
LDL-C (mmol/l)	6,12+1,74	4,59+0,99	<0,001

BMI-body mass index; BMD - bone mineral density; Hol - total cholesterol; Tg- triglicerides; HDL-C - HDL cholesterol; LDL-C - LDL cholesterol

Table 2. *Changing of BMD and lipid parameters during the study*

Parameters	Group I			Group II		
	beginning	after 12 months	Δ(%)	beginning	after 12 months	Δ(%)
	$\overline{X}$+SD			$\overline{X}$+SD		
BMD (g/cm^2)	0,96+0,11	0,99+0,11	2,81	1,04+0,18	1,01+0,18	-3,45
Hol (mmol/l)	8,08+1,74	7,06+1,14**	-12,68	6,6+1,08	6,44+0,61	-2,41
TG (mmol/l)	1,75+0,66	1,86+0,91	6,36	1,72+0,58	2,01+0,61	16,54
HDL-C (mmol/l)	1,17+0,24	1,19+0,27	2,22	1,22+0,24	1,14+0,26	-6,45
LDL-C (mmol/l)	6,12+1,74	5,02+1,11***	-17,99	4,59+0,99	4,58+0,69	-0,19

**p<0,01, ***p<0,005

Table 3. *Changes of BMD and lipid parameters' values after 12 months in the examined groups*

Parameters	Group I		Group II		p value
	$\overline{X}$	SD	$\overline{X}$	SD	
BMD (g/cm^2)	-0,03	0,04	0,04	0,04	0,0006
Hol (mmol/l)	1,02	1,27	-0,04	0,99	0,011
TG (mmol/l)	-0,11	0,83	-0,28	0,41	0,389
HDL-C (mmol/l)	-0,03	0,31	0,08	0,28	0,313
LDL-C (mmol/l)	1,1	1,27	0,09	0,84	0,004

DISCUSSION

In the past years, some prospective studies showed positive effects of statin therapy on bone mineral metabolism, but none of them aimed to investigate the effects of statins on BMD. Most of them have investigated the association between statin therapy and risk for bone fractures (5-12). Adami et al. (13) consider that lower incidence of bone fractures in patients on statin therapy could be explained by higher BMD observed in patients with higher LDL-C levels. In our study, all women were hypercholesterolemic, while those on statin therapy had higher average Hol and LDL-C levels compared to control group. BMD did not differ among the groups.

In a large retrospective study, Chung et al. demonstrated significant rise of BMD in men with diabetes mellitus type 2 on statin therapy (14). Edwards et al. (15) showed 10% increase of BMD in women on statin therapy compared to dietary regimen without statins. In this study, as well as in the study conducted by Chung et al, different statins were used without analysing particular statin effects on BMD. The effects of fluvastatin and pravastatin on BMD during one-year follow-up were analysed in the study conducted by Watanabe et al. (16). In this tudy, fluvastatin showed minimal effects on BMD compared to pravastatin which had no effects on BMD. This study showed different effects of statins on cholesterol reduction as well as BMD changes.

Montagnani et al. (17) showed positive effects of simvastatin therapy 40 mg/day on BMD in postmenopausal hypercholesterolemic women compared to normolipidemic women in one-year follow-up study. In this study, the authors did not evaluate the association between lipid profile and BMD considering the results from Rejinmark et al. (18) who showed that statins therapy modulate bone cells function by antiresorbtive effects.

Our study indicates the increase in BMD in hypercholesterolemic postmenopausal women on statin therapy compared to women without statins. In our study, the increase in BMD in patients on statin therapy was smaller compared to the results from Montagnani et al (17). This was an expected result as we used simvastatin 20 mg/day. However, the intergroup analysis in our study showed statistically significant change of BMD compared to Montagnani et al[17]. BMD in hypercholesterolemic women from control group showed higher decrease compared to results from Montagnani et al. in normolipidemic women (17). This indirectly points to the importance of increased cholesterol level in BMD reduction.

The association between statins and bone metabolism could be explained by mevalonate synthesis inhibition. This inhibition stops the synthesis of intermediary lipid precursors which osteoclasts use for modification and activation of intracellular proteins (3,19). This mechanism connects the cholesterol level and BMD. In our study, a weak inverse conection between BMD change and cholesterol level as well as between BMD and LDL-C in patients on statin therapy after one year of follow- up was shown. The weak association between Hol and LDL-C with BMD indicates that statins have important spectrum of pleotropic effects on bone metabolism. Anti-inflamatory effects of statins could be one of the mechanisms involved in bone protection, having in mind the importance of inflammation in pathogenesis of osteoporosis (20). This is of special importance in postmenopausal period which is followed by increase in proinflammatory cytokines (21).

Having in mind the obtained study results, we can conclude that simvastatin therapy showed a positive trend and increase in bone mineral densisty in hypercholesterolemic posmenopausal women after twelve months of follow-up, however, without statistically significant difference.

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EFEKTI TERAPIJE SIMVASTATINOM NA MINERALNU GUSTINU KOSTI KOD ŽENA SA HIPERHOLESTEROLEMIJOM U POSTMENOPAUZALNOM PERIODU

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Sažetak

Cilj našeg ispitivanja bio je procena efekata terapije simvastatinom na mineralnu gustinu kosti kod žena u postmenopauzi sa hiperholesterolemijom.

U ispitivanje su uključene pedeset i tri žene sa hiperholesterolemijom u postmenopauzalnom periodu, prosečne starosti 62,92+6,08 godina, koje su lečene u Institutu za lečenje i rehabilitaciju reuma-tičnih i kardiovaskularnih bolesti Niška Banja. Ispitanice su podeljene u dve grupe: sa vrednostima ukup-nog holesterola (Hol≥7,8 mmol/l) sačinjavale su grupu I (n=32), a ispitanice sa vrednostima ukupnog holesterola manjim od 7,8 mmol/l (n=21) sačinjavale su kontrolnu grupu II. Ispitanice grupe I lečene su, pored higijensko dijetetskog režima, sa 20 mg simvastatina dnevno. Određivani su trigliceridi (Tg), ukupni holesterol (Hol), LDL holesterol (LDL-C) i holesterol u lipoproteinu velike gustine (HDL-C). Mineralna gustina kosti određivana je na lumbalnoj kičmi (LI-L4), pomoću denzitometra marke "LUNAR DPX", a rezultat je izražavan kao apsolutna vrednost (g/cm^2) i T skor. Biohemijski parametri i mineralna gustina kosti (MGK) određivani su na početku i nakon 12 meseci ispitivanja.

Nakon 12 meseci primene simvastatina u dozi od 20mg/dan u grupi I došlo je do značajnog smanjenja nivoa Hol (-12,68%; p<0,01) i LDL-C (-17,99%; p<0,005) i do neznačajnih promena nivoa Tg (6,36%) i HDL-C (2,22%). U grupi II je nakon 12 meseci primene hipolipemijske dijete došlo do nesignifikantnih promena lipidnih parametara. U grupi I, MGK pokazuje porast od 2,81% (NS), dok u grupi II dolazi do njenog smanjenja za -3,45% (NS). Kod ispitanica koje su bile na statinskoj terapiji utvrđena je negativna korelacija između promena MGK i LDL-C (r=-0,08; p=0,686; r=0,166, p=0,626), kao i između promena MGK i Hol (r=-0,144; p=0,476; r=-0,125; p=0,715) tokom godinu dana ispitivanja. Ovi rezultati ne pokazuju statistički značaj i nisu prikazani grafički.

Terapija simvastatinom dovodi do trenda porasta mineralne gustine kostiju kod žena sa hiperholesterolemijom u postmenopauznom periodu života nakon 12 meseci terapije, ali bez statistički značajnog porasta.

Ključne reči: mineralna gustina kostiju, statinska terapija, žene u postmenopauzi