Short communication

Effect of statins on bone turnover markers in postmenopausal women: a pilot study

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Introduction

Statins, which inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, are the first-choice drugs in the treatment of dyslipidemia. They are used both in primary and secondary prevention, including obligatory use after cardiovascular procedures. Dyslipidemia is the main modifiable risk factor for cardiovascular disease, which has been the leading cause of death in Poland for many years. In Poland, hypercholesterolemia affects as many as 70.3% of men and 64.3% of women over 20 years of age [1]. The prevalence of dyslipidemia and statin therapy seems to be particularly significant in the light of reports on the pleiotropic effect of statins, especially in the case of osteoporosis, which is a serious and growing public health problem significantly affecting the quality and length of life [2, 3].

Statins act in the same biochemical pathway as bisphosphonates, which are the first-line drugs for the treatment of osteoporosis by inhibiting bone resorption [2]. They probably also affect the activity of osteoclasts by increasing osteoprotegerin (OPG) expression [4]. Statins also stimulate mRNA expression for bone morphogenic protein 2 (BMP-2). This protein plays an essential role in the process of differentiation of the osteoblasts responsible for bone tissue synthesis [5].

Bone is a metabolically active tissue that undergoes continuous internal remodeling. We can assess the activity of these processes by measuring the concentration of bone turnover markers (BTMs) in the blood, which allow changes to be noted as soon as 1–3 months after a medical intervention. Current recommendations indicate the value of the C-terminal telopeptide of type I collagen (CTX-I) as a bone resorption marker and N-terminal propeptide of procollagen type I (P1NP) as a marker of bone formation for the assessment of fracture risk and monitoring therapy in clinical settings [6].

Our study hypothesized that, after introducing statin treatment, we would observe significant differences in BTMs, increases in osteogenesis markers, and a decrease in osteolysis markers.

If this hypothesis were confirmed, additional positive effects of dyslipidemia treatment could improve statin adherence in postmenopausal women, especially since it is lower among women than among men.

Aim

To the best of our knowledge, this is the first study to evaluate the effects of currently used high-potency statins (atorvastatin and rosuvastatin) on BTMs among postmenopausal women.

Material and methods

The pilot study included seventeen postmenopausal women under the age of 65 years (mean [SD] age, 59.2 [5.46] years), with newly diagnosed dyslipidemia requiring statin therapy. The exclusion criteria were 18 kg/m^2 > body mass index > 35 kg/m^2; chronic kidney disease (eGFR < 30 ml/min); decompensated endocrine diseases; diabetes; anorexia nervosa; absorption disorders; chronic obstructive pulmonary disease; asthma; level of aminotransferases three times higher than the normal upper limit; hematological diseases; rheumatoid arthritis; active neoplastic disease; smoking more than ten cigarettes a day; confirmed osteoporosis requiring pharmacological treatment; and chronic use of drugs such as systemic glucocorticosteroids, antiepileptic drugs, heparin, or oral anticoagulants.

The patients were randomly administered a statin. Eleven (65%) women received rosuvastatin and 6 (35%)

women were given atorvastatin. Statins were started at standard doses: 5–10 mg of rosuvastatin, 20 mg of atorvastatin (the patients were at low or moderate cardiovascular risk). Each patient underwent blood tests twice: before statin intake and after 6 months of treatment. Blood was collected by venipuncture to assess the concentrations of lipids (total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alkaline phosphatase (ALP), 25-hydroxyvitamin D (25(OH)D), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), calcium, inorganic phosphates. Blood was also collected and secured to assess the levels of BTMs: CTX-I, P1NP, and OPG.

Levels of CTX-I, P1NP, and OPG were quantified using commercially available enzyme-linked immunosorbent assay kits, following the manufacturer's instructions (for CTX-I, IDS, for P1NP, and OPG, Sunred Biological Technology). The remaining measurements were made by routinely used biochemical methods.

The Ethical Committee of Poznań University of Medical Sciences approved the study protocol (number 1292/18), and informed consent was obtained from all subjects.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 26 package. Descriptive statistics were calculated for all parameters. The normality of parameter distribution was checked using the Shapiro-Wilk test. The paired *t*-test was used for dependent samples. The level of significance was considered to be $\alpha = 0.05$. The effect size was measured using Cohen's *d* index, defined as the standardized difference between means (the difference between the means divided by the sample standard deviation).

Results

We investigated how the use of statins affected bone metabolism by assessing CIX-I, P1NP, and OPG. Table I presents tested biochemical parameters at baseline and after 6 months of statin treatment. It also shows the mean change from baseline to the sixth month of treatment.

The analysis showed no statistically significant differences between the levels of BTMs (whether for the bone formation markers P1NP and OPG, or for the bone resorption marker CTX-I) before and after statin implementation ($p > 0.05$ and > 0.1). The effect size was also small (Cohen's $d < 0.5$).

Discussion

Studies on the effect of statins on the risk of osteoporosis and bone tissue have been conducted for several years, but there are very few unambiguous results, and there are many controversial reports on the beneficial effect of statins on osteoporosis.

In animal experiments, the positive effect of statins on bone metabolism has been confirmed, including in trials with atorvastatin and rosuvastatin. An experimental study conducted in rats showed a significant decrease in the levels of bone remodeling biomarkers (such as alka-

Table I. Blood test results at baseline and after 6 months of statin treatment

Parameter	Baseline Mean (SD)	At 6 months Mean (SD)	Difference between mean values (6 months – baseline)	*P*-value	Cohen's *d*
P1NP [ng/ml] (*n* = 17)	63.05 (37.33)	59.6 (34.19)	−3.45	0.19	0.33
CTX-I [ng/ml] (*n* = 17)	0.25 (0.17)	0.26 (0.16)	0.01	0.71	0.09
OPG [ng/l] (*n* = 17)	98.01 (72.37)	86 (66.23)	−12.01	0.14	0.38
TC [mmol/l] (*n* = 17)	6.44 (1.09)	5.32 (1.27)	−1.12	0.003	0.83
LDL-C [mmol/l] (*n* = 17)	4.04 (0.91)	3.16 (1.17)	−0.88	0.019	0.63
HDL-C [mmol/l] (*n* = 17)	1.51 (0.47)	1.49 (0.47)	−0.02	0.88	0.04
TG [mmol/l] (*n* = 17)	2.04 (1.2)	1.76 (1.02)	−0.28	0.21	0.32
Calcium [mmol/l] (*n* = 17)	2.46 (0.21)	2.57 (0.12)	0.11	0.10	0.45
Alkaline phosphatase [U/l] (*n* = 17)	82.53 (20.5)	87.47 (23.85)	4.94	0.10	0.45
25(OH)D [ng/ml] (*n* = 17)	22.44 (10.64)	30.78 (14.09)	8.34	0.012	0.81
Inorganic phosphorus [mmol/l] (*n* = 17)	1.24 (0.19)	1.14 (0.17)	−0.1	0.044	0.59
Creatinine [µmol/l] (*n* = 17)	64.14 (7.06)	66.63 (7.11)	2.49	0.14	0.39
ALT [U/l] (*n* = 17)	40.00 (26.65)	31.63 (16.43)	−8.37	0.07	0.48
AST [U/l] (*n* = 17)	29.53 (16.15)	26.47 (8.85)	−3.06	0.24	0.32

ALT – alanine aminotransferase, AST – aspartate aminotransferase, CTX-I – C-terminal telopeptide of type I collagen, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, OPG – osteoprotegerin, P1NP – N-terminal propeptide of procollagen type I, TC – total cholesterol, SD – standard deviation, TG – triglycerides, 25(OH)D – 25-hydroxyvitamin D.

line phosphatase, osteocalcin, and inorganic phosphorus) in a group with orally administered atorvastatin, which was elevated in the control group of ovariectomized rats. Positive changes were also found in the histopathological examination of rat bones, where there were more numerous trabeculae, osteoblast cells, and blood vessels in the atorvastatin group [7]. Oral administration of rosuvastatin and atorvastatin for 3 weeks was also shown to significantly improve bone biochemical properties (ultimate tensile strength, elastic modulus, and yield force) in healthy rats, but did not affect bone mineral density [8].

Such reports suggested that commonly used statins could play a significant role in preventing osteoporosis. However, no such conclusive results have been obtained in clinical trials.

The effect of simvastatin on the bone turnover markers P1NP and CTX-I was assessed by Chuengsamarn *et al.* (2010), who compared the effects of statin and nonstatin lipid-lowering therapy on bone metabolism. The levels of P1NP were higher in the statin treatment group and were statistically highly significant. The levels of CTX-I were significantly lower with statin therapy. These changes were statistically significant, while no such statistically significant difference were seen in the nonstatin group [9]. Increases in P1NP have also been observed in women over 50 years of age taking 20 mg of pravastatin for 16 weeks [10].

In another study comparing the levels of bone turnover markers among statin users and statin nonusers, significantly lower P1NP and CTX-I levels were found in the statin group. There were no statistically significant differences between the groups receiving different doses and statins of different strengths. The duration of therapy also seemed to be significant: CTX-I values were lower after 3 years of using statins than in the group taking the statin for less than 3 years [11].

Studies have also been conducted on atorvastatin, but the results were inconclusive. In a double-blind, placebo-controlled, dose-ranging trial of postmenopausal women, 52 weeks of atorvastatin treatment showed no significant differences in the change in BTMs levels (serum type-I collagen crosslinked N-telopeptide (sNTX), CTX-I, osteocalcin, bALP, or P1NP, deoxypyridinoline) from baseline to week 52, between the atorvastatin and placebo groups [3]. A significant decrease in urinary CTX-I due to atorvastatin was found in the study of Jadhav and Jain [10]. Majima *et al.* also found a statistically significant decrease in sNTX after 3 months of using atorvastatin. This decline in bone resorption markers could indicate inhibition of bone resorption processes due to atorvastatin intake [12]. Clinical trials on rosuvastatin are still lacking.

Our study did not confirm the effects of the currently used high-potency statins on bone turnover markers after 6 months of treatment. However, this preliminary study has some limitations, including the small number of participants and the short duration of statin treatment.

Referring to the previously mentioned study conducted by Hernandez *et al.*, the results might differ with extended observation time. The study will be extended to assess bone mineral density assessment differences after 12 months of statin intake. We also plan to expand the study group. During the COVID-19 epidemic, we had difficulties establishing a sufficiently large study group, due to limitations in the functioning of the health service and the limited availability of external tests, such as densitometry.

Conclusions

To the best of our knowledge, this is the first study to evaluate the two most commonly used statins in terms of the recommended markers of bone turnover to assess bone metabolism. Our study did not confirm the effects of the currently used high-potency statins on bone turnover markers after 6 months of treatment. Our findings, however, require further research in a larger cohort of postmenopausal women.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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