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Bone Mineral Density and Lipid Metabolism After Alendronate and Strontium Ranelate Treatment

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BACKGROUND/AIMS
This study aimed to examine the alterations on metabolic changes in lipid levels and osteoporosis caused by alendronate (ALN) and strontium ranelate (SR) since shared biological linkages have great importance for new insights. Therefore, the treatments given for osteoporosis may also have a protective role against cardiovascular events.

MATERIAL and METHODS
In this retrospective study, 713 postmenopausal Turkish women were recruited. Biochemichal laboratory results and lipid parameters were recorded from the medical records of the patients. The lumbar spine (LI-L4), total femur (TF), and femoral neck (FN) were assessed for bone mineral density (BMD). Two hundred and sixty-three women were non-osteoporotic while 450 women were osteoporotic. Among the 450 osteoporotic women, 322 used ALN and 128 used SR. For each group, TF Dual energy X-ray absorptiometry (DEXA), FN DEXA and LI-L4 DEXA results and lipid changes were compared after 12-months treatment.

RESULTS
Patients who were given ALN showed significant improvement in the BMD measurement of LI-L4 and FN, but not in the results of TF DEXA. Significant changes similar to ALN were found in patients who were given SR. Patients using ALN had significantly higher levels of high-density lipoprotein (HDL). The SR group did not show marked lipid profile changes.

CONCLUSION
We demonstrated that osteoporosis in postmenopausal women may be related to atherosclerosis. ALN treatment has an enhancing effect on HDL levels; however, no effect was observed on serum lipid levels after SR treatment.

Keywords: Osteoporosis, lipid metabolism, alendronate, strontium ranelate

INTRODUCTION

Postmenopausal osteoporosis and atherosclerosis are two prominent conditions that are a major threat to women of increasing age. The postmenopausal decrease in estrogen levels causes a metabolic bone disorder referred to as osteoporosis (1). Due to the resulting lower bone mineral density (BMD) and microarchitectural worsening, the risks of fragility and fracture are higher (1, 2). Several studies have shown that patients with postmenopausal osteoporosis have a higher risk of developing cardiovascular diseases, and this is linked to the bone mass and lipid parameters (3-5). The inverse correlation between bone loss and cardiovascular events indicates that there is a parallel progression of common pathophysiological mechanisms of the two tissue damage processes. Cholesterol metabolism and lipid parameters are some of the risk factors considered in the progression of atherosclerosis and stimulation of osteoclastogenesis (6, 7). 3-hydroxy-3 methyl glutaryl coenzyme A (HMG-CoA) is responsible for the synthesis of mevalonate (MVA) through the enzyme HMG-CoA reductase. This metabolic pathway is an important route which plays a key role in different processes. MVA is further metabolized to farnesyl pyrophosphate, a precursor of cholesterol and sterols. These lipids are used in the modification of proteins that are involved in various aspects of cellular functions (8-10).

Various antiosteoporotic agents have been used to treat osteoporosis, including bisphosphonates (ex risedronate, ibandronate, zoledronate and alendronate (ALN)) strontium ranelate (SR), denosumab, raloxifene (selective estro-

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gen receptor modulator (SERM)), calcitonin and parathyroid hormone (4, 5).

Bisphosphonates are molecules that reduce the number and activity of osteoclasts resulting in a slowing down in bone metabolism and resorption (10, 11). ALN inhibits the enzyme farnesyl pyrophosphate synthase of the MVA pathway, thereby affecting the biosynthesis of sterol precursors, that are essential for prenylation of osteoclasts (11). Given that ALN influences the MVA pathway, it may play a role in the mechanism of lowering the circulatory lipid levels which may be protective against cardiovascular events.

The divalent strontium salt of ranelic acid called SR, is a molecule which stimulates bone formation and at the same time, it suppresses bone absorption (12). Recently, SR has been widely used to increase BMD and improve postmenopausal osteoporosis. The danger of fracture is less with increased BMD (13). Although SR is used effectively, its processing mechanisms have not been fully understood (13, 14). In in vitro studies, SR has been shown to stimulate bone differentiation and mineralization by increasing critical osteoblast transcription factors and osteocalcin (14). Moreover, SR reduces the adipogenic potential of bone marrow stromal cells, and at the same time, increases the osteogenic potential (15). Peroxisome proliferator-activated receptor gamma (PPARG) is the key factor that controls adiposides and osteoblastogenesis. PPARG regulates fatty acid storage and stimulates lipid uptake (16, 17). Therefore, SR may act on PPARG, which will result in the stimulation of bone formation and lower the lipid levels in the bone marrow and in the circulation.

High levels of serum lipids are related to higher risk of cardiac events. In particular, reduced concentrations of high-density lipoprotein cholesterol (HDL) are linked to the increased hazard of cardiovascular diseases (18-20). It has been considered that BMD and HDL levels might be correlated (20, 21). In the literature, there are studies examining the correlation between serum lipids such as HDL, triglycerides (TG) and low density lipoproteins (LDL); however, the results were contradictory. Some studies showed a negative correlation, whereas some others found a positive correlation (22-24).

Main Points:

- In the present study, osteoporotic patients had higher levels of high-density lipoprotein (HDL) and lower triglyceride (TG) compared to healthy postmenopausal women. It was hypothesized that in cardiovascular diseases and osteoporosis, steroid metabolites could be a link between as a common cause of the association between lipid levels and bone mineral density (BMD).
- In our study, patients using alendronate (ALN) had significantly higher levels of HDL at the end of one-year treatment. The effect of ALN on increasing HDL can be explained by its effect on the mevalonate pathway; ALN inhibits the enzyme farnesyl pyrophosphate synthase.
- In postmenopausal women, low BMD and cardiovascular diseases are increased which results in elevated morbimortality. In our study, in accordance with the literature, we found a positive association between HDL and ALN.

This investigation study aimed to search for a change in total cholesterol (TC), LDL, HDL, and TG levels after ALN and SR treatment.

MATERIAL and METHODS

This retrospective study was conducted in the Department of Obstetrics and Gynecology of the Faculty of Medicine of Dokuz Eylul University, İzmir, Turkey. Dokuz Eylul University ethics committee provided ethical approval in 26.12.2013 and the ethics approval form number is 1274-GOA. All patients in the study provided signed approval consent. The study population included 2 186 postmenopausal women who consulted the menopause outpatient clinic between November 2012 and July 2015 for dual energy x-ray absorptiometry (DEXA) for BMD scanning. After being amenorrhic for one-year, the patients were determined as menopausal. In the analysis, patients who were in menopause and aged between 45 and 80 years were recruited. Exclusion criterias were as follows: disorders in bone metabolism which were diagnosed by radiography or blood chemistry evaluations; the presence of systemic diseases including cardiovascular diseases, diabetes, medications or illnesses effecting bone metabolism; patients who had been under hormone replacement therapy; those with drug or alcohol abuse; and a history of consumption of ≥ 2 cups of caffeinated coffee days per week. Four hundred and fifty Turkish postmenopausal women with osteoporosis were assessed in the final analysis (Figure 1).

Patient medical records were examined and blood test results were recorded for the evaluation of serum levels of LDL, TC, HDL, TG and calcium (Ca) levels. Commercially available assay kits (Abott) with an auto-analyzer (Aeroset, Abott) were used to check for the levels of TG, TC, HDL, and LDL. Auto-analyzer (Abbott Architect CI6000, IL, USA) kits were used to assess Ca levels.

DEXA was used to measure the BMD of femoral neck (FN), lumbar spine (LI-L4) and total femur (TF). A structured questionnaire was documented for patients to evaluate the risk for low BMD. The results of DEXA for each patient were accessed from the department of radiology and from the medical records of the patients. The definition of osteoporosis was a T score ≤ –2.5 in LI–L4, FN, and TF. The tool for the calculation for DEXA results was Lunar

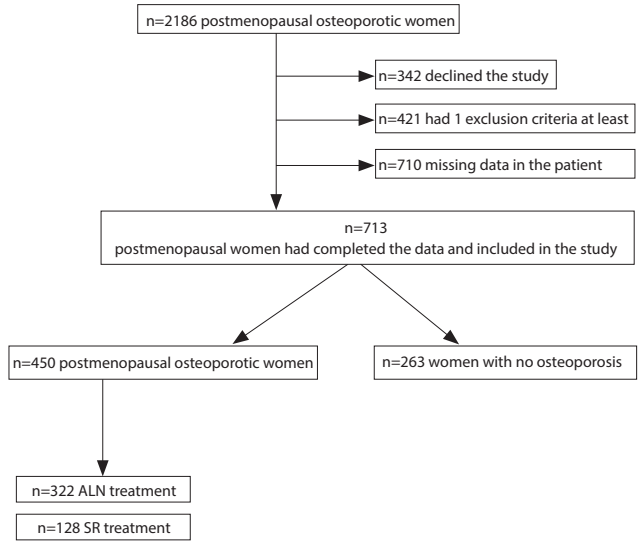

FIGURE 1. Flow chart of the study

TABLE I. Comparison of demographic characteristics and lipid parameters of osteoporotic and non-osteoporotic women

Descriptives	OP (n=450)	NOP (n=263)	*p
Age (years)	60.72±6.93	60.02±5.90	0.311
Gravida	3.70±2.10	3.59±2.08	0.562
Parity	2.32±1.34	2.22±1.30	0.064
TC (mg/dL)	212.75±38.16	216.55±37.22	0.615
TG (mg/dL)	121.90±56.54	123.29±45.89	0.004
HDL (mg/dL)	51.85±10.55	50.19±8.61	<0.001
LDL (mg/dL)	131.03±34.37	136.75±35.55	0.438
Ca (mg/dL)	9.45±0.61	9.12±0.58	0.141
BMI (kg/m^2)	26.97±3.65	26.95±3.69	0.458

Abbreviations: TC: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low Density lipoprotein, Ca: Calcium, BMI: Body mass index, OP: Osteoporotic women, NOP: Non-osteoporotic women
Independent t test is used
*p<0.05 is significant

TABLE 2. Comparison of demographic findings of osteoporotic women who were given alendronate and strontium ranelate

Descriptives	ALN (n=322)	STR (n=128)	P
Age	60.59±7.18	61.05±6.25	0.503
Duration of menopause	12.23±7.15	12.05±6.35	0.796
Menopausal age	48.24±3.68	48.91±3.03	0.050
BMI (kg/m^2)	27.07±3.69	26.70±3.56	0.324
Gravida	3.62±2.09	3.90±2.14	0.206
Parity	2.29±1.32	2.41±1.39	0.409
TC (mg/dL)	212.92±38.15	212.32±38.34	0.881
HDL (mg/dL)	51.37±10.09	52.37±10.26	0.726
LDL (mg/dL)	131.35±34.54	130.23±34.07	0.385
TG (mg/dL)	121.31±56.29	123.40±57.36	0.753
Calcium (mg/dL)	9.43±0.63	9.49±0.58	0.383
Lumbar I-Lumbar 4 DEXA	-2.82±0.54	-2.83±0.72	0.898
Total femur DEXA	-1.30±1.02	-1.26±1.02	0.670
Femur neck DEXA	-0.18±1.12	-0.15±1.23	0.823

Abbreviations: TC: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low Density lipoprotein, Ca: Calcium, BMI: Body mass index, DEXA: dual energy x-ray absorptiometry, ALN: Alendronic acid, SR: Strontium ranelate
Independent t test is used

DPX, GE Healthcare, USA; Software version:10.10.038. Calibration of the device was done daily. Patients in the osteoporosis group were further subdivided. Three hundred and twenty-two patients used ALN sodium and 128 patients used SR. For each group, after 12-months treatment, lipid parameters, serum Ca concentrations, and DEXA results were compared. The baseline characteristics of the groups are presented as the mean±standard deviation. A value of p<0.05 was considered as statistically significant.

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences software (SPSS v15, SPSS Inc.; Chicago, IL, USA). P-values less than 0.05 were regarded as statistically significant.

TABLE 3. Comparison of lipid profile, serum calcium levels and DEXA results of the patients who were given ALN or SR at the end of one-year treatment

		ALN	*p	STR	*p
TC (mg/dL)	Before	212.92±38.15	0.508	212.32±38.34	0.248
	After	214.18±38.71		208.72±32.61	
LDL (mg/dL)	Before	131.35±34.54	0.469	130.23±34.07	0.793
	After	132.60±33.12		129.46±27.52	
HDL (mg/dL)	Before	51.37±10.09	0.001	52.37±10.26	0.084
	After	53.32±10.66		51.17±9.91	
TG (mg/dL)	Before	121.31±56.29	0.311	123.40±57.36	0.271
	After	129.77±63.62		118.78±50.86	
Ca (mg/dL)	Before	9.43±0.62	0.001	9.49±0.58	0.001
	After	9.23±0.55		9.16±0.53	
Lumbar I-Lumbar 4	Before	-2.82±0.54	0.001	-2.83±0.72	0.001
	After	-2.47±0.88		-2.57±0.81	
Total femur	Before	-1.30±1.02	0.356	-1.26±1.02	0.298
	After	-1.37±0.84		-1.37±0.70	
Femur neck	Before	-0.56±1.06	0.001	-0.56±1.02	0.001
	After	-0.17±1.12		-0.15±1.05	

Abbreviations: TC: Total cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low Density lipoprotein, Ca: Calcium, DEXA: dual energy x-ray absorptiometry, ALN: alendronic acid, SR: Strontium ranelate
Paired samples are used
*p<0.05 is significant

RESULTS

The demographic characteristics and baseline findings of all 713 women are shown in Table I. Osteoporotic women were further subdivided and 322 were given ALN, and 128 were given SR. The initial characteristics of the osteoporotic women are compared in Table 2. In the intention-to-treat group, patients who were given ALN 70 mg/week showed significant improvement in BMD measurement of LI-L4 and the FN, but no change in TF DEXA results. In patients who were given SR 2 g/day, significant changes were found similar to those who received ALN after one-year follow-up (Table 3). Patients using ALN had significantly higher levels of HDL. There were no significant lipid parameter changes in the SR group. Serum Ca levels were significantly lower after one-year ALN and SR treatment (Table 3).

DISCUSSION

In clinical studies in the literature, SR and ALN have been shown to preserve bone loss and to decrease the risk of fracture. Several studies have shown that these drugs significantly improved bone mass and diminished the risk of fractures in the vertebra and hips (25-28). The current literature has shown that osteoporosis has a correlation with lipid metabolism and that ALN has effects on lipid parameters (21-24). In the current study, we examined the effects of ALN versus SR on BMD, lipid metabolism and serum Ca levels. Our results show that ALN and SR both increase the BMD of LI-L4 and the FN and reduce the risk of fracture. These results confirmed those of previous studies. Rizzoli et al. examined 88 osteoporotic postmenopausal women (26). For two years, the patients were randomized to ALN or SR treatment. Rizzoli et al found that an increase in cortical thickness and the cortical area were higher in the SR group compared to the ALN group (26). However, no dif-

ferences were observed in trabecular thickness between SR and ALN groups (21). The mechanism of action of SR remains unclear. SR may enhance osteoblast differentiation, bone matrix mineralization, preosteoblast replication, and collagen type I synthesis by means of a Ca receptor and lower bone resorption (25). On the other hand, ALN has a high affinity to bone minerals and reduces the number and activity of osteoclasts which results in inhibition of bone resorption (27). In the study of Reginster et al., SR was compared with bisphosphonates (29). They found that for women older than 75 years and for women with higher risk of vertebral fractures aged 80 years, SR proved to be more efficient and not as expensive as bisphosphonates (29). Unlike Reginster et al, in our study, there was no statistically significant difference in the efficacy of SR and ALN.

Previous clinical data found that reduced bone mass was associated with elevated levels of cholesterol. A diet with excessive cholesterol increases the risk of low BMD, probably by inhibiting the differentiation and generation of osteoclasts (30). In the present study, osteoporotic patients had higher levels of HDL and lower TG compared to healthy postmenopausal women. In 2018, Yang et al. showed an inverse correlation between HDL and LDL with BMD (31). It was hypothesized that steroid metabolites could have a link between cardiovascular diseases and osteoporosis as a common cause of the relation between lipid levels and BMD. The pathophysiological link between lipid levels and BMD has not yet been fully understood. Genetic factors may also play a role in the shared mechanism. Dennison et al. established that there is a significant association between fasting TG concentrations and LI-L4 BMD (32). Equally, patients with increased risk of vertebral fractures had reduced concentrations of TG (32). TG can alter the protein matrix and bone mineral, leading to better bone quality. TG metabolism in bone tissue may be correlated with higher osteoblastogenesis and lower osteoclastogenesis.

In the present study, patients using ALN had significantly higher levels of HDL at the end of one-year treatment. The effect of ALN on increasing HDL can be explained by its effect on the MVA pathway; ALN inhibits the enzyme farnesyl pyrophosphate synthase. Adami et al. found that ALN treatment caused a significant decrease in LDL and Apo B levels and raised Apo A and HDL levels (33). In addition, Celiloglu et al. observed that the use of bisphosphonates decreases Apo B/Apo AI ratios significantly and this was cardioprotective (34). High cholesterol levels are correlated with increased risk of cardiac pathologies. In particular, reduced concentrations of HDL are associated with elevated risks of negative cardiovascular cases (18). There were no significant lipid parameter changes in the SR treatment group. In our hypothesis, we expected to find a significant change in lipid levels with SR usage; however, the study results did not show this effect. In general, ALN is more widely used compared to SR, and in our study, patients using SR were fewer. This may be the major limitation of our study. Another limitation to the study is that it is done retrospectively.

Serum Ca levels were significantly lower after one-year ALN and SR treatment. This may be due to the transport of serum Ca to the bones. In addition, the Ca levels were between normal ranges before and after treatment. Although the difference was statistically significant, this is not clinically important.

In conclusion, in postmenopausal women, low BMD and cardiovascular diseases are increased, leading to elevated morbimortality. We have shown that there may be a link between atherosclerosis and osteoporosis.

There are conflicting results in the literature on the association between atherogenic lipid profiles and BMD. In literature, it is shown that alendronate (ALN) increases high-density lipoprotein (HDL), and it has cardioprotective effects. In our study, in accordance with the literature, we found a positive association between HDL and ALN. There is no study that has examined the effects of SR on lipid profile, but our study supports the fact that SR has no significant effect on lipid parameters.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylul University Faculty of Medicine (26.12.2013/1274-GOA).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - B.A.; Design - Ö.E.Ö.; Supervision - B.A.; Resource - A.C.Ö.; Materials - Ö.E.Ö., A.C.Ö.; Data Collection and/or Processing - A.C.Ö., Ö.E.Ö.; Analysis and/or Interpretation - A.C.Ö.; Literature Search - B.A.; Writing - Ö.E.Ö.; Critical Reviews - A.C.Ö., B.A.

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