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The effects of bisphosphonates on inflammatory markers and atherosclerosis

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ABSTRACT

Aims: Atherosclerosis and osteoporosis are prevalent conditions associated with significant morbidity and mortality worldwide. Evidence of literature suggests that bisphosphonates (BP) may play a role in inhibiting atherogenesis. The pathophysiological mechanisms underlying both atherosclerosis and osteoporosis share similarities, and numerous studies have shown an association between osteoporosis and cardiovascular events. This study aims to evaluate the effects of oral BP therapy on vascular inflammatory markers and carotid intima-media thickness (CIMT), a surrogate marker of atherosclerosis, in osteoporotic patients.

Methods: The study included 28 osteoporotic patients (study group) and 28 osteopenic patients (control group). BP therapy (alendronate 70 mg/week, risedronate 35 mg/week) was administered to the study group in a randomized controlled way. The patients of the both groups received daily supplements of calcium (1000 mg) and vitamin D (880 IU). Baseline and 12-month follow-up measurements included height, weight, body-mass index (BMI), high-sensitivity C-reactive protein (hs-CRP), homocysteine levels, CIMT, and bone mineral density (BMD).

Results: At the 12-month follow-up, hs-CRP levels decreased significantly in the study group, while they increased slightly in the control group (p=0.032). Similarly, homocysteine levels showed a significant reduction in the study group compared to the control group (p=0.002). No significant change in CIMT was observed between the two groups over the study period.

Conclusion: Our findings suggest that while oral BPs may influence certain vascular inflammatory markers, such as hs-CRP and homocysteine but they do not have a significant effect on CIMT. BPs may exert anti-atherosclerotic effects through the mevalonate pathway, but the results of this study warrant further investigation with larger sample sizes to confirm the broader implications of BPs in atherosclerosis management.

Keywords: Atherosclerosis, bisphosphonates, vascular inflammatory markers

INTRODUCTION

Osteoporosis is a metabolic bone disease that leads to an increased risk of fragility fractures by causing a reduction in bone mass and deterioration in bone microarchitecture. It is a significant cause of morbidity and mortality in the geriatric population, especially among postmenopausal women. Bisphosphonates (BP) are currently the mainstay antiresorptive agents used in the treatment of osteoporosis. Atherosclerosis is a progressive and widespread disease of the large and medium-sized arteries that primarily affects the intimal layer. Endothelial damage leading to endothelial dysfunction initiates a cascade of inflammatory and proliferative events, resulting in the development of atherosclerosis. Many studies have reported that high-sensitivity C-reactive protein (hs-CRP) and homocysteine may serve as markers of vascular inflammation and are associated with coronary events.[1] Carotid intima-media thickness (CIMT) measurement is a non-invasive method used to assess the effects of atherosclerotic risk factors, and serves as an independent predictor of generalized atherosclerosis, future cardiovascular events, and stroke risk.[2,3] Risk factors for atherosclerosis, such as age and homocysteine levels, are positively correlated with CIMT.[2-4] The mevalonate pathway is a metabolic route present in mammalian cells, responsible for the synthesis of essential lipid molecules, including cholesterol.[5] Nitrogen-containing BPs (N-BPs) inhibit certain enzymes in the mevalonate pathway, disrupt the functions of key regulatory proteins, affect cellular activities, and induce osteoclast apoptosis. Consequently, they prevent osteoporosis and reduce fracture risk. It has been suggested that BPs may exert favorable effects on atherosclerosis by suppressing cholesterol synthesis via the mevalonate pathway, and by modulating inflammatory markers, suggesting that BPs may also exert beneficial effects on atherosclerosis.[6] Based on these findings, the aim of our study was to determine the effects of

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orally administered N-BPs on atherosclerotic markers and to evaluate changes over the follow-up period.

METHODS

This study enrolled a total of 56 postmenopausal women aged 45–70 years who visited the Endocrinology and Metabolism and Internal Medicine outpatient clinics of Ankara University Faculty of Medicine between 2006 and 2009. The study protocol was approved by the Ethics Committee of Ankara University Faculty of Medicine (Date: 05.01.2009, Decision No: 144-4338), and the study was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants. Twenty-eight patients were included in the osteoporotic group, and 28 patients were assigned to the osteopenic (control) group. Participants had not used BPs within the past six months, were non-smokers or had quit smoking at least five years prior, and had no comorbidities that could lead to ischemic or atherosclerotic diseases (e.g., coronary heart disease, diabetes mellitus, chronic kidney failure, cirrhosis, familial hyperlipidemia syndromes, thyroid dysfunction). Bone mineral density (BMD) was measured at baseline and at the 12-month follow-up using dual-energy X-ray absorptiometry (DEXA) with a HOLOGIC Discovery A device. Based on the World Health Organization criteria, patients with a T-score between -1.0 and -2.4 SD were classified as osteopenic (control group), and those with a T-score of ≤-2.5 SD were classified as osteoporotic (study group).[7] Osteoporotic patients were randomized to receive weekly oral alendronate (70 mg/week) or risedronate (35 mg/week) therapy. All participants, regardless of group, were supplemented with oral calcium (1000 mg/day) and vitamin D (880 IU/day). Height and weight were recorded, and body-mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Biochemical analyses, including measurements of hs-CRP and homocysteine levels, were performed at the central laboratory of Ankara University Faculty of Medicine at baseline and at 12 months. Homocysteine was measured using the fluorescence polarization immunoassay method with the Abbott AXSYM System, and hs-CRP was assessed using the immunonephelometric method with the Dade Behring BN II device. CIMT measurements were conducted by a single endocrinologist using a General Electric® Logic 400 Doppler ultrasonography device with a 12 MHz probe. Measurements were taken from three different points (upper, middle, and lower) of both internal carotid arteries during systole, and the mean of the measurements was calculated. CIMT was reassessed at the 12-month follow-up. For statistical evaluation, the arithmetic mean of the right and left CIMT values was calculated for each follow-up [(right CIMT+left CIMT)/2 mm].

Statistical Analysis

Data analysis was performed using SPSS 15.0 software. Results were presented as mean±standard deviation and median (minimum–maximum). The normality of the data distribution was assessed. For normally distributed data, the Student's t-test was used to compare groups; for non-normally distributed data, the Mann–Whitney U test was applied. A p-value of <0.05 was considered statistically significant.

RESULTS

Fifty-six patients were included in the study between 2006 and 2009. The mean age was 59.1±6.3 years in the study group and 56.7±6.4 years in the control group. Mean height was 157.8±5.6 cm in the osteoporotic group and 158.3±3.6 cm in the control group. Mean weight was 70.1±13.6 kg and 70.7±10.2 kg; BMI was 28.0±4.7 kg/m^2 and 28.2±3.4 kg/m^2, respectively. There were no statistically significant differences between the groups regarding age, height, weight, or BMI. At baseline and 12 months, lumbar spine and femur T-scores were assessed. In the study group, lumbar spine T-scores improved from a median of -2.55 (-3.60 to -0.65) to -2.35 (-3.60 to -0.72) and femur T-scores improved from -2.52 (-3.39 to 0.40) to -1.40 (-3.54 to 0.90). Although the lumbar spine T-score improvement was not statistically significant (p=0.232), the improvement in femur T-score was statistically significant (p=0.002). In the control group, lumbar spine T-scores slightly decreased from -1.56 (-2.36 to 0.20) to -1.65 (-2.90 to 0.00), while femur T-scores increased from -1.62 (-2.39 to 0.66) to -1.10 (-2.23 to 0.50), and this increase in femur T-scores was statistically significant (p=0.003). High-sensitivity CRP (hs-CRP) and homocysteine levels were also evaluated at baseline and at 12 months. While hs-CRP levels increased in the control group, they decreased in the study group over the follow-up period. Changes in hs-CRP levels were significantly different between the groups (p=0.032). Homocysteine levels decreased in both groups during the follow-up period, and the difference in homocysteine reduction between groups was statistically significant (p=0.002). No significant changes in CIMT measurements were observed between groups over time. The patients' data are summarized in **Table**.

Table. Comparison of hs-CRP, homocysteine, and CIMT results between the groups at baseline and at the 12-month follow-up

	Study group (n=28)	Control group (n=28)	p
hs-CRP (baseline) (mg/L)	3.80±5.79*	3.07±2.05*	p>0.05
hs-CRP (12 month) (mg/L)	2.48±2.04*	4.21±3.35*	0.032
Homosistein (baseline) (mmol/L)	11.9 (6.4-25.7)	11.05 (6-17.6)	0.015
Homosistein (12 month) (mmol/L)	9.1 (5.2-14.7)	8.7 (5.3-21.1)	0.002
CIMT (baseline) (mm)	0.80 (0.28-1.06)	0.74 (0.51-1.08)	p>0.05
CIMT (12 month) (mm)	0.80 (0.50-1.03)	0.76 (0.56-1.05)	p>0.05

hs-CRP: High sensitive C-reactive protein, CIMT: Carotis intima-media thickness, *: Data are presented as mean±standard deviation. Other data are presented as median (minimum–maximum).

DISCUSSION

In the current literature several studies have suggested that BPs may play a role in inhibiting atherogenesis;[8-10] however, most of these studies were conducted in vitro or in animal models using doses much higher than those administered to humans. Some prospective studies in humans using guideline-recommended oral doses have demonstrated beneficial or neutral effects on atherosclerosis, but more research is needed. Thus, this study was designed to support and strengthen

existing evidence regarding the potential atheroprotective effects of BPs. The pathophysiological mechanisms underlying the development of atherosclerosis and osteoporosis or low BMD share similarities, and multiple studies have established that osteoporosis is associated with cardiovascular events and increased mortality.[11,12] Some studies have demonstrated that BPs not only prevent bone loss but also inhibit the progression of atherosclerosis.[13,14] Furthermore, epidemiological studies have indicated that decreased hip BMD is a marker of advanced atherosclerosis and vascular disease.[15,16] Therefore, BPs may potentially retard atherosclerotic changes through common pathways, including inhibition of the mevalonate pathway.[13] In our study, the study and control groups were similar in terms of age, height, weight, and BMI, with no statistically significant differences observed. None of the participants were current smokers, and those who had smoked had quit at least five years prior. We excluded patients with comorbidities that predispose to atherosclerosis, suggesting that the reliability of our results is high. BMD measurements showed significant improvement in femoral T-scores in both groups. The observed improvements indicate that both the study and control groups adhered to their prescribed therapies. As reported in the literature, hs-CRP and homocysteine levels are indicators of low-grade systemic and vascular inflammation.[1] In our study, at the 12-month follow-up, homocysteine and hs-CRP levels had decreased significantly in the BP-treated osteoporotic group compared to the control group. These findings align with previous studies suggesting that BPs may exert beneficial effects on atherosclerosis by modulating inflammatory markers.[6] Regarding CIMT measurements in our study, no significant changes were observed between the two groups over the study period. In a study conducted by Koshiyama et al.,[17] who investigated the effects of orally administered etidronate on CIMT in type 2 diabetics, a significant decrease in CIMT was observed in the etidronate group at the 12-month compared to the control group. Similarly, a study by Celiloğlu et al.[18] reported a significant reduction in CIMT in the alendronate group at the 12th month when compared to the control group. Some studies have demonstrated a positive effect of BP use on CIMT measurements, while other studies, including ours, have shown no significant impact on CIMT. Another study also demonstrated that alendronate had no therapeutic benefit on CIMT.[19]

In our study, the lack of a significant change in CIMT between the two groups at the 12th month can be explained by findings suggesting that when BPs are used at clinical oral doses, their absorption rates are very low (1%-10%), which results in insufficient systemic concentrations to exert a significant effect on tissues other than bone.[20,21] Indeed, oral BPs are rapidly absorbed by bone and remain in bone for prolonged periods.[22] To exert pleiotropic effects on other systems and tissues, these drugs must reach a certain tissue concentration, which is unlikely to occur with oral administration. In contrast, some studies investigating the effects of intravenous (IV) BPs at clinical doses have demonstrated significant pleiotropic effects. For example, Adami et al.[23] reported that neridronate, administered intravenously every two months for 12 months for osteoporosis treatment, had a marked effect on blood lipid parameters. However, it should be noted that the study mentioned above involved high-dose IV BP therapy. In our study, patients were treated with BPs at the recommended therapeutic doses, not supra-physiological doses, and oral administration was used.

A strength of our study is that the demographic characteristics of the patients in both groups were similar and homogeneous, and the rigid inclusion criteria allowed us to closely monitor these patients for one year.

The administration of identical doses and formulations of calcium and vitamin D to both groups, with the addition of BPs exclusively to the patient group, has eliminated potential concerns regarding the accuracy of treatment evaluation. The rationale for selecting osteopenic patients as the control group was to control for early bone metabolic changes while minimizing the confounding effects of underlying systemic diseases.

Limitations

Unfortunately, the limitation of our study is the relatively small sample size. Having 28 patients in each group may have limited the statistical power, particularly in detecting changes in slowly progressive parameters such as CIMT. To address this issue, a post-hoc power analysis was conducted based on a statistical power level of 60%. For the hs-CRP parameter, the observed effect size (Cohen's d=0.62) indicated that the current sample size was sufficient to detect moderate differences. In contrast, the statistical power was low for parameters with small effect sizes, such as homocysteine (Cohen's d=0.12) and CIMT (Cohen's d=0.31). Based on a 60% power level, the required number of patients per group was calculated to be 27 for hs-CRP, 103 for CIMT, and 682 for homocysteine. The limited sample size in our study has unfortunately reduced the overall statistical power.

CONCLUSION

As a result, our study suggests that oral BPs, when administered at physiologic doses recommended by clinical guidelines, lead to statistically significant differences in hs-CRP and homocysteine levels in the study group compared to the control group, but do not produce a significant effect on CIMT, although they may have an inhibitory effect on atherosclerosis. However, further studies with larger sample sizes would provide more definitive conclusions and allow for a more meaningful assessment of the effects of BPs on atherosclerosis markers, including CIMT.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was approved by the Ethics Committee of Ankara University Faculty of Medicine (Date: 05.01.2009, Decision No: 144-4338).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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