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Effects of intravenous zoledronate and ibandronate on carotid intima-media thickness, lipids and FGF-23 in postmenopausal osteoporotic women

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ABSTRACT

Objective: Osteoporosis and atherosclerosis are interconnected entities and share also some pathophysiological mechanisms. Moreover, recent literature data have supported the hypothesis that bisphosphonates (BPs) may have some antiatherogenic actions. This study aimed to evaluate the effects of one year with zoledronate or ibandronate given intravenously on lipid profile and on carotid artery intima-media thickness (CA-IMT).
Methods: Sixty postmenopausal osteoporotic women (mean age: 66.6 ± 7.8 years) were randomly assigned to 1-year treatment with zoledronate 5 mg i.v. annually or ibandronate 3 mg i.v. every 3 months. In all patients at baseline and after 12 months we measured CA-IMT, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), 25-hydroxyvitamin D (25OHD), bone alkaline phosphatase (B-ALP), type I collagen β carboxy telopeptide (βCTX), osteocalcin (OC), fibroblast growth factor 23 (FGF-23) and sclerostin.
Results: The osteoporotic women treated with zoledronate showed a greater reduction in CA-IMT than those treated with ibandronate. HDL-C and HDL-C/LDL-C ratio showed a significant ($p < 0.01$) increase in the 2 groups, whereas, LDL-C showed a reduction in the two groups which, however, reached statistical significance ($p < 0.05$) only in the zoledronate group. FGF-23 serum levels showed a similar and significant decrease in both the women treated with zoledronate and in those treated with ibandronate. At the end of the study period sclerostin serum levels showed a higher increase in the patients treated with zoledronate than in those treated with ibandronate.
Conclusion: In osteoporotic women both zoledronate and ibandronate given intravenously resulted in an increase in HDL-C/LDL-C ratio and a reduction of CA-IMT which was significant only for zoledronate. Further prospective studies are needed to clarify whether the change in FGF-23 and sclerostin levels is a marker or a potential mechanism of the action of BPs at a vascular level.

Introduction

Although osteoporosis and atherosclerosis are traditionally viewed as separate entities which increase in prevalence with aging, accumulating evidence indicates that they share not only common risk factors such as smoking, menopause and reduced physical activity, but also some pathophysiological mechanisms. An association between low bone mineral density (BMD) and increased mortality due to stroke and cardiovascular disease (CVD) was reported more than one decade ago [1,2]. More recently, Tanko et al. reported that postmenopausal women with osteoporosis have an increased risk of developing cardiovascular events, regardless of age and overall risk profile, and that the increased risk is proportional to the severity of osteoporosis [3]. Several additional studies have linked the progression of arterial calcification with concurrent bone loss and vertebral fractures, supporting a relationship between osteoporosis and CVD [4,5]. Other studies have reported that the intima-media thickness at the carotid artery (CA-IMT) was negatively correlated with bone mineral density in healthy individuals and in patients with osteoporosis [6,7]. Moreover, in literature there is growing evidence that calcification of atherosclerotic lesions is an active process which utilizes the same mechanisms as bone tissue. For this reason, we could consider a pharmaceutical agent as being able to treat osteoporosis and atherosclerosis at the same time. At present, among antiosteoporotic drugs only bisphosphonates (BPs) have been reported as having this potential [8].

BPs are potent antiresorptive agents, largely used for the treatment of osteoporosis, which causes osteoclast apoptosis mainly by the inhibition of farnesyl diphosphate synthase, a key enzyme of the mevalonate pathway [9]. Some studies have shown that BPs are deposited in the aortas of healthy and atherosclerotic rabbits and also in the internal mammary arteries of individuals receiving BPs [10]. Several animal studies have shown that BPs have a positive effect on atherosclerosis and that this effect appears to be due to a direct effect of BPs on the arterial wall [10,11], whereas Wu et al., in an in vitro study, have pointed out the direct effect of zoledronate by inhibiting vascular smooth

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muscle cell proliferation in atherosclerotic lesion [12]. Indeed, the way in which BPs influence the development of atherosclerosis has not yet been clarified. It is probable that the crucial point is represented by the fact that BPs interact with macrophages, inhibiting the ability of these cells to internalize atherogenic LDL and become foam cells [10].

It has been reported that etidronate decreases the intima-media thickness of the carotid artery in osteopenic type 2 diabetes mellitus patients [13]. In a previous study we demonstrated that intravenous pamidronate therapy in patients with Paget's disease produced a positive influence on lipid profile, with an increase in HDL-C/LDL-C ratio [14]. Recently, Celiloglu et al. reported that a 1-year period of alendronate treatment positively modified lipid profile and determined a significant reduction of intima-media thickness in postmenopausal osteoporotic women [15]. On the contrary, previous experience with alendronate has not shown any significant differences in the mean internal carotid artery measurements of women with postmenopausal osteoporosis during a 13-month period [16]. These controversial data may be explained by BP pharmacokinetics, BPs being poorly absorbed. Therefore, the effect of BPs on CA-IMT and lipid profile may be significantly different according to the administration route, with a possible more favorable effect on the extra-osseous targets for that given intravenously.

Moreover, recent literature data support the hypothesis that in the pathogenesis and evolution of atherosclerosis, also "nonclassic" factors connected to the calcium/phosphate homeostasis, such as parathyroid hormone, osteocalcin, vitamin D metabolites and circulating products of bone metabolism, could also be involved [8]. Among the latter there has recently been a growing interest in fibroblast growth factor 23 (FGF-23), a bone derived hormone which has the property of controlling the tubular reabsorption of phosphate and mineralization [17] and also in sclerostin, the SOST gene product, which is expressed almost exclusively in the osteocytes and is an inhibitor of the canonical Wnt/β-catenin signaling pathway [18]. However, at present the role of FGF-23 and sclerostin in the atherosclerotic process remains controversial [19–21].

The aim of the present study was twofold: firstly, to assess as to whether one-year treatment with zoledronate or ibandronate given intravenously may have different effects on carotid artery IMT; and secondly, to investigate the effect of these two BPs on the lipid profile and on serum levels of either bone turnover markers or FGF-23 and sclerostin.

Subjects and methods

Population

A cohort of consecutive postmenopausal osteoporotic women (age range: 55–80 years) who applied to the Metabolic Bone Diseases Outpatients Clinic of the Department of Internal Medicine at the University of Siena (Italy) between March, 2011 and February, 2012 and for whom a treatment with intravenous bisphosphonates was indicated, were considered for enrolment in this study. The choice of treatment with intravenous bisphosphonates was made independently of the study by doctors not directly involved. The patients previously treated with antiosteoporosis drugs, except calcium/vitamin D supplements, and those who were suffering illness (hyperparathyroidism, multiple myeloma, cancer etc.) or were receiving therapies able to influence bone metabolism were excluded. Also, the women with serum levels of 25-hydroxivitamin D less than 30 ng/mL or glomerular filtration rate less than 60 mL/min were excluded.

The patients with a history of ischemic heart disease or cardiovascular diseases or those who were receiving therapies (steroids, levothyroxine, estrogens, statins, etc.) or showed diseases (such as diabetes, hypo or hyperthyroidism, chronic renal failure) able to influence lipid metabolism and atherosclerosis were also excluded from the study.

Sixty patients (mean age: 66.6 ± 7.8 years) met the eligibility criteria and were randomly assigned to 1 year treatment with zoledronate 5 mg i.v. annually (n = 30) or ibandronate 3 mg i.v. every 3 months (n = 30). Moreover, participants were supplemented with 600 mg of calcium and 400 IU of vitamin D daily. Since this was a pilot study, the number of sixty patients appears to be adequate.

Written consent was obtained from all participants, and the study was approved by the Institutional Review Board of Siena University Hospital. For all subjects, a detailed medical history was obtained. Twenty subjects presented a history of fragility fractures (vertebral fractures in 19 and ankle fractures in 2). The daily dietary calcium intake was assessed by a validated Food-Frequency Questionnaire including foods that account for the majority of calcium in the Italian diet [22]. Moreover, all patients were instructed to maintain their usual diet during the whole study period. In addition, height and weight were measured in a standardized fashion. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

IMT and DXA measurements

In all patients CA-IMT was measured in the supine position by high-resolution ultrasonography (MyLab™60, Esaote, Italy) with a linear probe of 7.5 MHz, both before the first infusion of BP and after 12 months. The images of the right and the left carotid arteries of each participant at the common carotid artery (1 cm proximal to the dilatation of carotid bulb), at carotid bulb and at internal carotid artery (1 cm distal to the tip of flow divider) were obtained digitally and were then archived. IMT values were analyzed by a computer software program. IMT is the distance between the lumen–intima interface and the media–adventitia interface. A statistical evaluation was performed on the calculated average of the left and right carotid artery IMT measurements. The inter-observer and intra-observer coefficients of variation were 2.7% and 2.1%, respectively. To avoid inter-observer variability all measurements were performed by one examiner (T.L.) who was blind of the treatment of the patients.

In all subjects we also measured BMD at the lumbar spine [LS-BMD], at femoral subregions (femoral neck [FN-BMD] and total hip [TH-BMD]) and at the total body [WB-BMD] using a dual-energy X-ray absorptiometry device (Lunar Prodigy; GE Healthcare, Waukesha, WI). Osteoporosis and osteopenia were diagnosed according to the World Health Organization (WHO) definition: a T value lower than −2.5 was diagnosed as osteoporosis and a T value lesser than −1.0 but higher than −2.5 was diagnosed as osteopenia. Sex-matched Italian reference data were used for the calculation of T-score.

Laboratory evaluation

In all subjects, fasting venous blood samples were drawn at baseline and after 12 months in order to assess serum levels of total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), 25-hydroxyvitamin D (25OHD), intact parathyroid hormone (PTH), serum calcium and phosphate, bone alkaline phosphatase (B-ALP), type I collagen β carboxy telopeptide (βCTX), osteocalcin (OC), fibroblast growth factor 23 (FGF-23) and sclerostin. All samples were stored at −80 °C while awaiting analysis, and then they were batched and measured in one assay. All lipid parameters (TC, TG, HDL-C and LDL-C) were measured using a colorimetric method (Autoanalyzer Menarini, Florence, Italy). In our institution the intra- and inter-assay coefficients of variation were, respectively, 1.8 and 3.8% for TC, 2.0 and 3.0% for HDL-C, 1.7 and 2.9% for TG, and 1.5% and 2.3% for LDL-C assessment. The serum B-ALP was measured by a chemiluminescent immunoassay method (Beckman Coulter, Fullerton, CA). In our institution the intra- and inter-assay coefficients of variation for B-ALP were 4.2% and 7.9%, respectively. Serum PTH was assessed by an immunoradiometric assay (DiaSorin, Saluggia, Italy) and the intra- and inter-assay coefficients of variation were 3.6%