Bone 103 (2017) 64–69

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Fracture during oral bisphosphonate therapy is associated with deteriorated bone material strength index

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ARTICLE INFO

Article history:
Received 19 April 2017
Revised 18 June 2017
Accepted 22 June 2017
Available online 24 June 2017

Keywords:
Bisphosphonates
Fracture
BMSi
Microindentation
BMD

ABSTRACT

Background: Some patients experience fractures while receiving oral bisphosphonates (BPs) treatment. Clinical risk factors, advanced bone density loss, and microarchitecture deterioration have been associated with such fractures but bone tissue properties other than bone mineral density (BMD) have not been assessed.
Methods: In a cross-sectional study of postmenopausal women on bisphosphonates for at least 4 years with good adherence to treatment, 21 patients with incident fractures were compared with 18 treated patients without new fractures. Demographic and clinical variables, BMD, laboratory tests, and bone material strength index (BMSi) assessed by impact microindentation at the tibial diaphysis were recorded for all participants.
Results: Clinical and laboratory results did not differ between patients taking BPs with incident fractures and those without new fractures. However, BMSi was significantly lower (mean ± SD) in those who fractured (73.76 ± 6.49) than in no-fracture patients (81.64 ± 6.26; $p = 0.001$). Lumbar spine (LS) BMD was also lower in fractured patients ($p = 0.03$). Adjusted models including age, body mass index, years on BP treatment, and LS-BMD confirmed an increase in fracture risk per BMSi standard deviation decrease: adjusted OR 23.5 [95% CI 2.16 to 255.66], $p = 0.01$. ROC analyses showed an area under the curve of 0.82 (95% CI 0.68 to 0.95) for BMSi, higher than that for BMD at any location, which ranged from 0.64 (95% CI 0.47 to 0.82) for femoral neck (FN) BMD to 0.71 (95% CI 0.55 to 0.87) for LS-BMD.
Conclusions: Patients who fracture while receiving BPs treatment have worse BMSi scores than BP-treated patients without fractures. The potential for BMSi to provide an additional osteoporosis treatment target should be explored.

1. Introduction

Oral bisphosphonates (BPs), the cornerstone for osteoporosis treatment, substantially reduce fracture risk and are safe and generic, providing an excellent cost/benefit ratio [1,2]. This has made them the first-line osteoporosis therapy according to most clinical guidelines and public health agencies [3–5].

Despite these advantages and good adherence to therapy, some patients still experience fractures while receiving oral bisphosphonates. Treatment failure [6], a term that seems diametrically opposed to the concept of a treatment target [7], has been coined to define this situation. Several factors may contribute to the apparent lack of full efficacy, such as low levels of vitamin D, concomitant diseases, very low bone mineral density (BMD) and advanced deterioration of bone microarchitecture that induces a situation not fully compensated by the beneficial effects of the drugs [8,9]. Therefore, it would be interesting to explore whether bone characteristics at a tissue level can contribute to incident fractures in patients on active treatment. Several recent studies support the idea that bone material strength index (BMSi) measured by reference point microindentation reflects material properties at a tissue level and correlates with bone deterioration and fractures [10–12].

To elucidate the effects of long-term BPs exposure on microindentation properties and their potential role in explaining fractures while receiving oral BPs, we analysed a cohort of patients after long-term treatment, using the impact microindentation device to

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http://dx.doi.org/10.1016/j.bone.2017.06.018
8756-3282/

compare BMSi in individuals with incident fractures to those who do not fracture.

2. Subjects and methods

2.1. Population

Participants were recruited from a specialized osteoporosis clinic in a tertiary hospital. Consecutive unselected postmenopausal women with a diagnosis of osteoporosis were included if they had been receiving treatment with oral BPs for at least four years, had no previous fractures when BPs were started, and showed >80% adherence to therapy. Adherence was specifically assessed by a single investigator using a pre-specified questionnaire, and was recorded in the medical records. Patients were assigned to the fracture or no-fracture group, the former including women with an incident fracture that occurred at least one year after initiating BP treatment.

All measurements were performed within two weeks after the selection. The two BPs used were alendronate or risedronate and the same drug was used for the whole treatment period in all cases.

Patients were excluded if they had previously received other anti-osteoporosis treatments (except calcium and vitamin D supplementation), shown evidence of previous fragility fractures (osteoporotic fractures produced by low trauma in hip, wrist, arm, humerus and vertebra), had diabetes mellitus, chronic renal failure or any other endocrine or metabolic disease or treatment associated with secondary osteoporosis, or declined to participate. Details of the recruitment process are displayed in Fig. 1. The local Ethics Committee (Parc de Salut Mar) approved the study (2012/4652/I update 2016/6616/I) and written informed consent was obtained from all participants.

2.2. Measurements

Demographic characteristics and clinical history were recorded, with special focus on treatments received and adherence to BPs therapy. All patients had been diagnosed of osteoporosis in our Department and regularly attended annual follow-up visits. All new clinical fractures were recorded and spine X-ray was performed every two years or when the patient reported lumbar pain or >3 cm decrease in height. Vertebral fractures (VF) were diagnosed following the semiquantitative method published by Genant [13].

2.3. Vitamin D and biochemical markers

Competitive electrochemiluminescence protein binding assay intended for the quantitative determination of total 25-OH vitamin D (25-OHD) in human serum and plasma was used to measure vitamin D levels. The assay employs a vitamin D binding protein as capture protein, which binds to both 25-OHD-3 and 25-OHD-2 (Cobase602, Roche Diagnostics, Germany) with the following between-day precision: coefficient of variation (CV), 7.8% and 8.1% at mean concentrations of 15.7 and 26.2 ng/mL respectively, using quality control material provided by Roche® Diagnostics. Bone-specific Alkaline Phosphatase (bALP) was analysed with an electrochemiluminescence immunoassay from Beckman Coulter Access®; CV was <6%.

2.4. Bone mineral density

Bone mineral density (BMD) was measured at the lumbar spine (LS) (L1–L4), femoral neck (FN), and total hip (TH) at the time of microindentation, using a dual-energy X-ray (DXA) densitometer

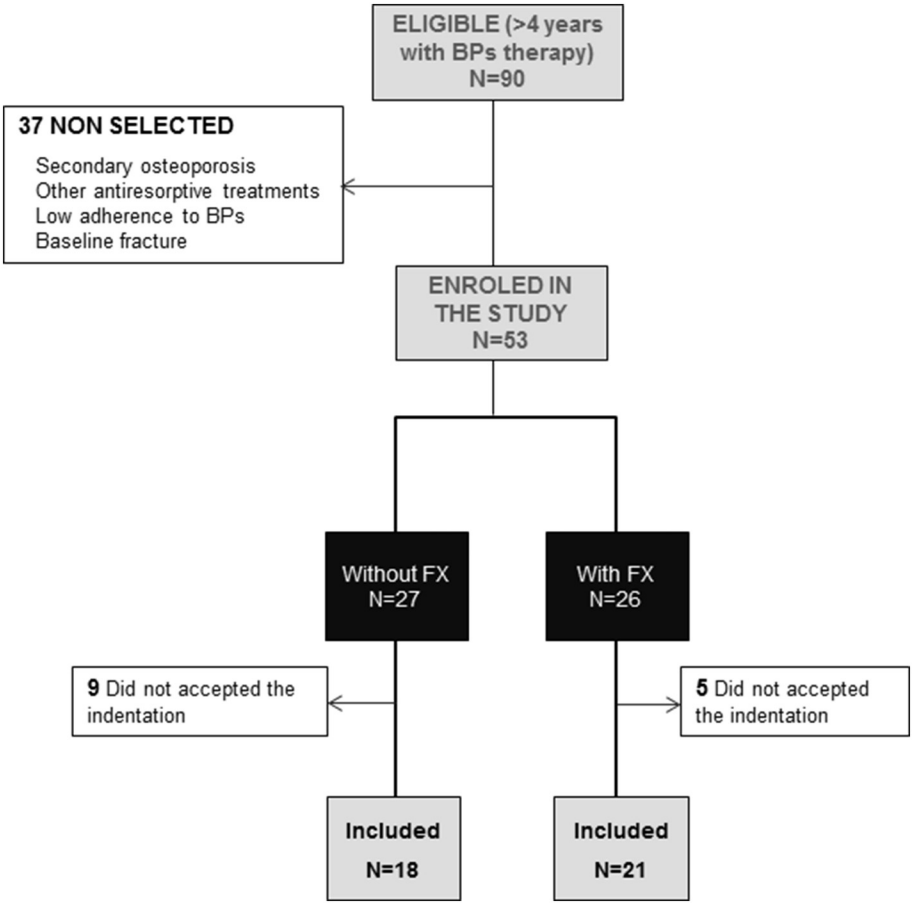

Fig. 1. Flow-chart showing the number of patients eligible and finally included in the study for microindentation. BPs: bisphosphonates; FX: fracture.