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Bone cross-sectional geometry is not associated with atypical femoral fractures in Asian female chronic bisphosphonate users

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ABSTRACT

Introduction: Atypical femoral fractures (AFF) tend to occur in Asian women with prolonged bisphosphonate exposure. Hip geometry is thought to contribute to the risk of AFF formation. We examined the hip structural geometry parameters in Asian female chronic bisphosphonate users who sustained an AFF and compared them to chronic bisphosphonate users who did not sustain any femoral fracture (NFF) and bisphosphonate-naïve patients who sustained an osteoporotic femoral fracture (OFF).

Materials & methods: Thirty-one patients with AFFs were gender and age-matched to 31 patients with NFFs and 49 patients with OFFs. The Hip Structural Analysis parameters analyzed were bone mineral density (BMD), cross-sectional area (CSA; a metric of resistance to axial compression), section modulus (SM; a metric of resistance to tensile loads), average cortical thickness (ACT; mean thickness of the femoral cortices), buckling ratio (BR; an index of likelihood of local buckling), and neck shaft angle (NSA; the angle between the neck and shaft axes). The regions analyzed were three cross-sections measured at the narrowest femoral neck diameter, the intertrochanteric area, and the proximal femoral shaft. One-way ANOVA with Bonferroni adjustment for multiple comparisons was used to compare parameters between the three patient groups, with statistical significance defined as $p < 0.05$.

Results: There were no statistical differences in parameters between patients with AFFs and patients with NFFs at all measured regions. Patients with AFFs and NFFs had statistically higher BMD, CSA, ACT, SM values and lower BR values at the NN and IT regions than patients with OFFs. Additionally, patients with NFFs had statistically higher SM values at the IT region than patients with OFFs, while patients with AFFs had statistically higher BMD, CSA, and ACT values at the FS region. All other measured parameters were not statistically different between the groups.

Conclusions: Chronic bisphosphonate users with and without AFFs had similar femoral structural geometries. Unlike in other populations, varus neck shaft angles were not found to be associated with AFFs in Asian female chronic bisphosphonate users. Thus, bone cross-sectional geometry is not likely to be associated with AFFs in Asian female chronic bisphosphonate users. Hip Structural Analysis does not show an increased predilection for tensile failure in AFFs.

1. Introduction

Within a decade, more than half of the United States population over the age of 50 will have osteoporosis [1]. Epidemiological studies further indicate approximately half of women and up to a quarter of men over the age of 50 will suffer an osteoporotic fracture in their lifetime, which account for 1.5 million fractures per year [2,3]. Alongside selective estrogen receptor modulators, recombinant parathyroid hormone, and strontium ranelate, bisphosphonates are commonly utilized for the prophylaxis of osteoporotic fractures and act by initiating osteoclast apoptosis, thereby decreasing bone resorption and increasing bone mineralization [4–6]. As they have been shown to reduce the incidence of hip fractures and improve bone mineral density, bisphosphonates remain the gold standard for the prevention of osteoporotic fractures

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and the reduction of bone loss in osteoporotic and postmenopausal patients [1,6–8].

Recent research has shown an association of prolonged bisphosphonate use with atypical femoral fractures (AFF), thought to be the result of over-suppression of bone turnover [1,5,6,9–11]. Given the prevalence of osteoporosis and the fact that bisphosphonates are ubiquitously prescribed, any osteoporotic patient with chronic bisphosphonate exposure is at risk of sustaining AFFs, which are associated with significant functional disability and slow recoveries [1,7,9–13]. Although newer evidence suggests that AFFs are a form of stress fracture, their exact pathophysiology and relationship to bisphosphonate use are not well understood [1,5,9,10,14]. As AFFs have been associated with monogenetic diseases such as hypophosphatasia, X-linked hypophosphatemia, and pycnodysostosis, genetic differences could be a factor predisposing to formation of AFFs [15,16]. Because the mechanical strength of bone is dependent on both bone quality and bone geometry, hip geometry is thought to contribute to the risk of sustaining an AFF [7,9,17–19]. Hip structural geometry in particular has been previously shown to predict for risk of fracture [20–22]. Previous studies have identified AFFs as occurring maximally in regions of high tensile stress in the femur, such as the proximal medial third of the lateral femoral cortex [12,14, 17]. Consequently, AFFs are hypothesized to initiate in regions of the femur that undergo high levels of tensile stress and individuals with geometries that exacerbate that stress may be at risk of developing AFFs [9,12]. Other studies have identified that patients with AFFs may possess femoral geometries, such as varus neck shaft angles or shorter limbs, which increase the mechanical load on the lateral femur and may play a role in AFF pathogenesis [7,18].

Although the 2013 American Society for Bone Mineral Research (ASBMR) Task Force on Atypical Femoral Fractures called for increased research identifying the femoral geometric factors predisposing patients to AFF development, there is a lack of scientific research on the femoral structural geometry potentially responsible for AFF formation [9]. While previous studies such as the Fosamax Actonel Comparison Trial [23] have analyzed and shown improvements in hip structural geometry parameters in bisphosphonate users, no such study has examined these parameters in patients with AFFs with chronic bisphosphonate exposure [24–27]. The purpose of this study was to characterize the hip structural geometry parameters of chronic bisphosphonate users who sustain AFFs and compare them with those of asymptomatic chronic bisphosphonate users and bisphosphonate-naïve osteoporotic fracture patients. We hypothesize that chronic bisphosphonate users who sustain AFFs have femoral structural geometries similar to those of asymptomatic chronic bisphosphonate users and different from those of bisphosphonate-naïve patients who sustain osteoporotic femoral fractures.

2. Materials and methods

2.1. Patients

All research protocols and procedures followed were approved by our institution's Institutional Review Board and performed in accordance to their ethical standards. Asian female patients treated at our institution from 2005 to 2013 for AFF were identified as meeting the ASBMR criteria for AFF and included for analysis. The inclusion criteria for this study were hip fracture meeting ASBMR criteria for AFF, female gender, history of prolonged bisphosphonate use (defined as at least 4 years of consecutive use), and femoral dual-energy x-ray absorptiometry (DXA) scan available at our institution. Exclusion criteria were pathological fractures, high energy or traumatic fractures, no BMD data available, prior hip implant, and trauma patients. Both subtrochanteric and diaphyseal AFFs were included for analysis.

In this study, the patients with AFFs were compared with a general population of patients with no bisphosphonate exposure who sustained osteoporotic femoral fractures (OFF), as well as a group of chronic bisphosphonate users who sustained no femoral fractures (NFF). The OFF group consisted of intertrochanteric and femoral neck fracture patients selected from all hip fractures patients treated at our institution between 2005 and 2013. Of these hip fracture patients, 26 intertrochanteric and 23 femoral neck fracture patients were matched in gender, age, and ethnicity to the AFF patient group. The NFF patients consisted of chronic bisphosphonate users with a history of at least four years of consecutive bisphosphonate use and no history of femoral fracture on follow-up at our institution. Of these chronic bisphosphonate users, 31 patients were matched in gender, age, and ethnicity to the AFF patient group. The same exclusion criteria applied to the AFF group were applied to the patients with OFFs and NFFs.

Information collected comprised of demographic data, date of operation, formal diagnosis, bisphosphonate exposure history, and all available DXA scans. Bisphosphonate history was determined by tracing all inpatient and outpatient prescriptions, as well as discharge summaries in Sunrise Clinical Manager (Version 5.5) and calculating total bisphosphonate exposure at the time the femoral BMD scan was taken.

2.2. Study design

All DXA scans were measured using Hologic QDR series machines from the Department of Nuclear Medicine at our institution. DXA image data was analyzed using the Hologic APEX QDR Workstation (Version 3.3.0.1) and the HSA program (Version 13.3.0.1) to generate hip structural geometry parameters. For patients with AFFs or OFFs, the femoral BMD scan analyzed was that of the contralateral uninjured hip at the time of fracture. For patients with NFFs, the femoral BMD scan analyzed was the latest femoral BMD scan available.

2.3. Hip Structural Analysis parameters

The Hip Structural Analysis (HSA) program utilizes data from DXA images of the proximal hip to generate morphological and biomechanical parameters from bone cross-sections corresponding to three thin regions of the proximal femur. The program operates on a principle first described by Martin and Burr that a line of pixels measured across the bone axis corresponds to a cross-section of the bone at that same location, from which morphologic and biomechanical properties can be calculated [28,29]. The regions of interest (ROI) analyzed include 1) narrow neck (NN), the distance across the narrowest diameter of the femoral neck, 2) intertrochanteric (IT), the distance along the bisector of the neck shaft angle, and 3) femoral shaft (FS), the distance 2 cm distal to the midpoint of the lesser trochanter, as illustrated in Supplemental Fig. 1 [30].

The HSA parameters measured at each ROI include bone mineral density (BMD), cross-sectional area (CSA; the total cross-sectional area of the bone subtracting away soft tissue, a metric of resistance to axial loads), average cortical thickness (ACT), section modulus (SM; a metric of bending resistance), buckling ratio (BR; a metric of local instability due to buckling), and neck shaft angle (NSA) [24–27,31]. In the NN and IT regions, where the bone cortices are particularly thin, mechanical failure is more commonly due to local buckling. As only one section of the bone is failing, the SM value tends to overestimate mechanical strength and the BR value becomes a better predictor for fracture [31, 32]. Due to the thickness of the FS cortices, buckling is unlikely to occur, thus BR value at the FS region is unlikely to be relevant [19]. The definition and relevance of each HSA parameter is described in Supplemental Table 1. The precision error or coefficient of variation (CV%) for HSA parameters derived from a precision analysis of Hologic QDR4500 machines is listed in Supplemental Table 2 [33].

2.4. Statistical analysis

Descriptive analysis was conducted to characterize the patient population. Sample means and standard deviations (SD) were reported