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Risk factors for development of atypical femoral fractures in patients on long-term oral bisphosphonate therapy

Paola Franceschetti [a], Marta Bondanelli [a], Gaetano Caruso [b], Maria Rosaria Ambrosio [a], Vincenzo Lorusso [b], Maria Chiara Zatelli [a], Leo Massari [b], Ettore C degli Uberti [a,*]

[a] Section of Endocrinology, Department of Medical Sciences, University of Ferrara, Via Savonarola 9, 44121 Ferrara, Italy
[b] Orthopaedic and Traumatology Department, Sant'Anna Hospital, University of Ferrara, Via Savonarola 9, 44121 Ferrara, Italy

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ABSTRACT

Bisphosphonates (BPs) are the first-line therapy for osteoporosis. In recent years, atypical femoral fractures (AFF) have been described in patients on BPs therapy. However, the relationship between BPs and AFF remains to be clarified. We evaluated clinical and hormonal characteristics of AFF patients, in order to determine AFF risk factors. We studied 11 females with AFF and 58 females with typical femoral fractures (TFF), admitted to our Department for surgical repair between January 2008 and December 2011. All AFF patients received BPs therapy for 6 to 13 yrs, whereas 36.2% ($p < 0.0001$) of TFF patients received BPs for shorter period (TFF, 6.1 ± 1.8 yr vs. AFF, 8.6 ± 1.9 yr, $p < 0.0001$). A higher prevalence of hypocalcemia was observed in AFF patients compared with TFF ($p < 0.02$), with significantly ($p < 0.05$) lower corrected calcium levels in AFF patients. By contrast a reduced prevalence of elevated PTH levels ($p < 0.05$) was found in AFF patients. No significant difference in prevalence of vitamin D defect was observed between the two groups. Younger age ($p < 0.004$), higher BMI (>30 kg/m^2, $p < 0.03$) and early menopausal age ($p < 0.05$) were observed in AFF patients. At time of fracture, prevalence of osteopenia/osteoporosis and levels of bone turnover markers were significantly ($p < 0.01$) lower in AFF compared with TFF patients. By multivariate analysis hypocalcemia, obesity, and younger age (<70 yr) were confirmed to be independent predictors of AFF; elevated PTH level was the predominant independent protective factor ($p < 0.004$). In conclusion, our data indicate that clinical characteristics and metabolic factors may favor the development of AFF in BP treated patients. We identified hypocalcemia due to latent hypoparathyroidism as primary risk factor for AFF; age, obesity, early menopause, and BMD may also influence the development of AFF. An adequate clinical and metabolic assessment is suggested to prevent the development of AFF in BP treated patients.

Introduction

In the last 15 yrs bisphosphonates (BPs) have became the first-line therapy for osteoporosis [1,2]. In post-menopausal osteoporosis, BPs reduce fracture incidence by 30–50% in patients at highest risk [3]. In recent years, atypical femoral fractures (AFF) have been described in patients on BPs, generating interest and anxiety as a possible clinical manifestation of a "frozen bone" due to bone turnover suppression and bone strength reduction [4]. These fractures have peculiar and striking clinical and radiological features. They occur in the subtrochanteric or diaphyseal region of the femur and are typically transverse or slightly oblique, characterized by radiological diffuse thickening of the femoral cortex and beaking at the lateral subtrochanteric region. Previous pain and lack of trauma prior to fracture are also reported.

Retrospective epidemiologic studies identified a possible relationship of AFF with oral BPs use, especially during long term therapy. Therefore, the American Society of Bone and Mineral Research (ASBMR), the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), and the International Osteoporosis Foundation (IOF) have published separate statements seeking to summarize the existing data in order to define AFF. These societies defined diagnostic major and minor criteria to identify AFF, however the risk factors for developing these fractures remain to be clarified [5–7]. In 2010, the Food and Drug Administration (FDA) noted that the available data have not shown a clear connection between BPs use and the risk of AFF calling for further studies on this issue.

The aim of our study was to evaluate clinical and hormonal characteristics of patients admitted to our department for surgical repair of AFF, in order to determine the risk factors for these fractures.

* Corresponding author.: Fax: +39 0532 236514.
E-mail addresses: p.franceschetti@ospfe.it (P. Franceschetti), marta.bondanelli@unife.it (M. Bondanelli), gaetano.caruso@unife.it (G. Caruso), mariarosaria.ambrosio@unife.it (M.R. Ambrosio), vincenzo.lorusso@unife.it (V. Lorusso), maria.chiara.zatelli@unife.it (M.C. Zatelli), leo.massari@unife.it (L. Massari), ti8@unife.it (E.C. degli Uberti).

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Patients and methods

Study population and design

We performed an observational study of patients with AFF and a retrospective analysis of patients aged ≥50 yrs consecutively admitted to our Department for surgical repair of a new fracture of the femur over a 4-year period (January 2008–December 2011). Patients with periprosthetic or high energy fractures, old fractures, Paget's disease of bone, metastatic bone disease and/or metabolic bone disease other than osteoporosis were excluded. Eleven patients (all females) had AFF, and 64 (58 females and 6 males) had typical femoral fractures (TFF). We compared AFF (11 females, mean age: 75.5 ± 11.1 yrs, range 63–99 yrs) with 58 TFF females (mean age: 81.4 ± 8.2, range 56–99 yrs). TFF males were excluded from the study to obtain a gender-related control population. The study protocol has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and informed consent was obtained from all subjects or next of kin.

The following clinical data were collected for all patients: age, body max index (BMI), use of alcohol and cigarette smoking, co-morbidities (hypo–hyperthyroidism, diabetes mellitus, hypertension, chronic kidney disease, chronic obstructive pulmonary disease/asthma, depression), number of medications, history of osteoporosis and osteoporotic fractures, conditions or medications associated with risk of falls (osteoarthritis, rheumatologic conditions, dementia, and any dispensing of benzodiazepines or tertiary tricyclic antidepressants), and other medications of interest (oral glucocorticoid, proton pump inhibitors, levothyroxine) [8]. Type and duration of osteoporosis medications were obtained from hospital records and/or interview of the patients.

The following biochemical data were collected from clinical files: complete blood count, blood glucose, kidney function based on estimated Glomerular Filtration Rate (GFR) [GFR >90, normal kidney function (stage 1); GFR 60–89, mildly reduced kidney function (stage 2); GFR 30–59 moderately reduced kidney function (stage 3); GFR 15–29, severely reduced kidney function (stage 4); GFR <15 or on dialysis, very severe or endstage kidney failure (stage 5)], calcium corrected for albumin level [corrected calcium, mmol/l = total serum calcium, mol/l + 0.02 * (normal albumin, mg/dl–patient albumin, mg/dl)], phosphorous, magnesium, total alcaline phosphatase, osteocalcin, beta cross laps, 25-hydroxyvitamin D, parathyroid hormone (PTH), thyroid function, serum and protein electrophoresis. Biochemical determinations were performed by standard methods [9]. Normal range for PTH levels was 12–65 pg/ml. Vitamin D defect was defined by serum 25-hydroxyvitamin D levels <20 ng/ml. BMD measurements of femoral neck DXA (T-score and Z-score) were also collected. AFF patients were also observed at 6 months after the fracture event by clinical and hormonal evaluation (measurement of serum ACTH, cortisol, FT4, TSH, IGF-I, LH, FSH, PRL) [10].

Definition of atypical fractures

According to the ASBMR criteria, AFF was defined as a fracture located along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare, transverse or short oblique, associated with no trauma or minimal trauma, non-comminuted, complete extending through both cortices or incomplete involving only the lateral cortex. Additional minor features (generalized increase in cortical thickness, prodromal symptoms, bilateral fractures and symptoms, localized periosteal reaction of the lateral cortex, delayed fracture healing) were sometimes associated [5,11]. The characteristics of the AFF collected in this study also correspond to the new definition of the ASBMR Task Force 2013 [7].

TFF were defined by low-trauma (fragility) fractures of proximal and distal femoral caused by a fall from standing height or less, without atypical radiographic features [12].

Radiographs of all patients were individually examined by two orthopedic experts and the fracture site was revised in double blind.

Cortical thickness (CT) was measured from radiographs of cases and controls both just distal to the site of fracture and 5 cm below the lesser trochanter by two orthopedic experts blinded to patients' characteristics. This method is commonly used to measure cortical thickness in cases of femoral fractures, including AFF [12–14]. X-rays were periodically performed after the fracture event in order to evaluate the resolution of fracture line and to determinate the bone healing.

Statistical analysis

Continuous data are expressed as mean ± standard deviation. Comparison between groups of continuous variables was performed by using paired or unpaired Student's *t* test. Categorical data are reported as numbers and percentages. Percentage comparison was made with Fisher's exact test. Mono- and multivariate logistic regression with 95% confidence interval (CI) was calculated for significant parameters at the Fisher's exact test. Values were considered statistically significant when p was <0.05. Analyses were performed by using InStat 3 (GraphPad Software, Inc., San Diego, CA) and SYSTAT software, version 5.0 (SYSTAT, Inc., Evanston, IL).

Results

Clinical and biochemical characteristics of patients

As shown in Table 1, AFF patients presented younger age ($p < 0.04$) and higher BMI ($p < 0.02$) at time of factures. Menopausal age was younger in AFF compared with TFF (46.6 ± 4.6 yr vs. 49.3 ± 5.5 yr, $p < 0.05$). None of the patients was treated with hormone replacement therapy. No significant differences were observed between the two groups concerning history of fractures, family history of osteoporosis, current smoking, alcohol use, comorbidities, and conditions associated with risk of falls. Only osteoarthritis had a higher prevalence in TFF patients ($p < 0.02$). One AFF patient had subclinical hyperthyroidism and autoimmune thyroiditis. Among TFF patients, one had hyperthyroidism treated with low dose metimazole, 7 had primary hypothyroidism (only two of them were taking L-thyroxine with inadequate replacement), and 3 had a low T3 syndrome. The mean number of medications dispensed at the time of fracture was significantly ($p < 0.0002$) lower in AFF patients compared with TFF, whereas no significant differences were observed on the type of medications including glucocorticoids, proton pump inhibitors, and levothyroxine. All patients were prescribed to take calcium and vitamin D, but none showed adequate supplementation.

History of osteoporosis and osteopenia, documented by femoral neck DXA, was present in 8/11 and 3/11 AFF patients, and in 43/58 and 9/58 TFF (ns), respectively. Moreover, T-score and Z-score at the beginning of BPs therapy did not significantly differ between the 2 groups (Table 2). All AFF patients (100%) received BPs therapy compared with 21/58 (36.2%) TFF ($p < 0.0001$). All AFF patients were treated with weekly oral alendronate for 6 to 13 yrs. One patient was also treated with strontium ranelate in the last 3 yrs and another one with oral ibandronate in the last 4 yrs. Nineteen TFF patients were treated with weekly oral alendronate for 1 to 11 yrs, and 2 with intramuscular clodronic acid; 1 TFF patient received only strontium ranelate therapy. Duration of alendronate therapy was significantly ($p < 0.002$) longer in AFF compared with TFF. At time of fracture, prevalence of osteopenia/osteoporosis was significantly ($p < 0.01$) lower in AFF patients compared with TFF. In particular, 3 AFF patients had normal femoral neck BMD, while 8 patients had T-scores < −2.5. All TFF patients showed osteoporosis (n 35) or osteopenia (n 8); BMD was not available in 15 TFF patients. Moreover, AFF patients had significantly higher BMD in terms of both T-score (AFF, −1.53 ± 0.80 vs TFF, −2.70 ± 0.60, $p < 0.001$) and Z score (AFF −0.45 ± 0.50, vs. TFF −0.85 ± 0.55, $p < 0.05$).