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Original Article

Atypical Femoral Fractures—Ongoing and History of Bone-Specific Therapy, Concomitant Diseases, Medications, and Survival

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Abstract

Although atypical femoral fractures (AFFs) are generally rare events; several studies have indicated a potential link between AFF and long-term bone-specific therapies (BSTs). The aim of this study was to analyze the frequency of AFF and potential associations with prior or ongoing BST. A total of 8851 Caucasian female and male patients with de novo hip fractures treated in the largest Austrian level 1 trauma center from 2000 to 2013 were selected. Of the total, 194 patients with a de novo low-traumatic subtrochanteric or shaft fractures were identified: 35 atypical and 159 typical fractures. Of these patients, concomitant diseases, medication, previous fractures, and survival data were retrieved and analyzed. Female patients in both groups were significantly older. The median survival was significantly shorter in patients with AFF (9 vs 18 months; $p < 0.0001$). Cardiovascular disease, sarcopenia, chronic kidney disease, type 2 diabetes, smoking (past or current history), and prevalent fragility fractures were more frequent in AFF patients, as well as the concomitant use of phenprocoumon, furosemide, and sulfonylurea. Although the number of patients with current BST was less in (14.5%) both groups, more patients in the AFF group were previously treated with BST (71% vs 49%; $p = 0.016$), and they received these therapies for a longer time period. A combination of severe comorbidities, long-term pharmaceutical therapies, and a history of previous or ongoing BST was associated with an increased individual risk for AFF.

Key Words: Antiresorptives; atypical femoral fractures; concomitant medications; osteoporosis; survival.

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A plenary oral presentation of this study was delivered at the Austrian National Osteoporosis Congress in St. Wolfgang on 9th May, 2014. A plenary poster was also presented at the American Society for Bone and Mineral Research 2014 meeting in Houston, TX, USA, on September 12, 2014.

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Introduction

Osteoporosis is strongly associated with low-trauma fractures, mortality, and economic consequences. Hip fractures typically occur in the femoral neck or intertrochanteric region but less frequently in the subtrochanteric or shaft region of the femur *(1,2)*. Atypical femoral fractures (AFFs) generally emerge after a minimal trauma with a characteristic radiographic pattern. AFFs may be stress or insufficiency fractures, potentially arising from increased tensile forces *(3–5)*. Case

reports and observational studies have raised concerns about a potential link between long-term bisphosphonate (BP) use, diverse medications, and AFF (6–9). A general warning for all BPs was pronounced by the Food and Drug Administration and the European Medicines Agency in 2010 and 2011 (10,11).

Although randomized trials have shown that treatment with BPs reduces the risk of osteoporotic fractures, long-term use may suppress bone remodeling sufficiently to negatively interfere with the process of microdamage repair in a subset of patients (6,12,13). Studies examining the potential association between AFF risk and long-term BP use are conflicting owing to the differences in size, design, outcome, and definition of AFF (2,14–16).

Concomitant diseases and long-term medications influence endocrinological pathways and bone metabolism and might increase the individual risk for an AFF. The main purpose of this study was to compare patients with AFF and typical fractures with regard to prior or ongoing bone-specific therapies (BSTs). Secondary objectives included the evaluation of potential associations with comorbidities, concomitant medications and laboratory values, and the survival in these 2 groups.

Methods

Data Source and Study Patients

This study was conducted at the Hospital of Meidling in Vienna, Austria. This hospital is the largest level 1 trauma center with >60,000 new ambulatory and inpatient patients per year (catchment area, 1.9 million people). Patients eligible for the present study were identified by International Classification of Disease 10 coding. All patients with de novo hip fractures treated between January 2000 and December 2013 with documented recent low-traumatic subtrochanteric or femoral shaft fractures and corresponding X-ray and complete medical data sets were selected.

Patient-related data were gathered at the time of the fracture in the hospital as well as by contacting the treating general practitioners to retrieve the respective duration of any medication or BST and further outcome after discharge from the trauma center. Demographic data (age, gender), data related to the incident, serum values, current medication, comorbidities, and the survival after fracture or the respective cause of death were collected. Areal bone mineral density (aBMD) measurements taken less than 1 year before the fracture were also evaluated. Sarcopenia was defined as muscle atrophy combined with progressive loss of muscle function and frailty and/or unintentional nonedematous weight loss of >5% over ≥6 months.

To select appropriate potential clinical risk factors for analysis, we screened the following different established research tools and risk calculators for osteoporosis and fracture risk before the initiation of the study: the FRAX calculator, the QFracture-2013 risk calculator, and the current osteoporosis guidelines of the Austrian-German-Swiss Osteology Association (DVO Osteologie).

Fracture Assessment

All subtrochanteric femoral fractures were independently and consecutively reanalyzed by 2 experienced blinded radiologists from 2 different centers. X-ray results of all de novo low-traumatic femoral subtrochanteric or femoral shaft fractures were categorized based on the latest major criteria defined by the American Society for Bone and Mineral Research (3).

The most frequent reason for classifying the fractures as "typical" was an extension of the fracture line into the region of the lesser trochanter. The second reason was the existence of multiple bone fragments or a more oblique configuration of the fracture line. Optional minor criteria were not available in all patients and are therefore not reported.

Ethical Aspects

This study was conducted in line with the Declaration of Helsinki and gained approval from the local ethics committee (AUVA-EC-number: 21/2011).

Statistical Analysis

Continuous variables are described by the median (interquartile range). Group comparisons of continuous variables were performed using the 2-sample t test. In case of non-normally distributed data, the nonparametric Wilcoxon rank sum test was used. Differences with respect to binary variables were tested using the chi-square test or, as appropriate, the Fisher exact test. A stepwise logistic regression analysis was applied to compare patients with AFF to patients with typical fractures in a multivariate, adjusted sense. Thereby, to reduce a possible overestimation of any effect, all concomitant diseases and medications were considered as variables in a forward selection approach to discriminate between these 2 patients groups, adjusted for age and gender. The Firth correction was used in logistic regression models for bias reduction of the estimates. The Kaplan-Meier method was applied to estimate the survival probabilities and the log-rank test was calculated to compare the survival curves. Univariate and multivariate Cox regression models were performed to evaluate the unadjusted and age- and sex-adjusted difference in mortality in AFF patients compared with patients with typical femoral fractures. Two-sided p values <0.05 were considered as indicating statistical significance. All our statistical calculations were based on patients, not on fractures. If a patient had an atypical and a typical fracture simultaneously, this patient was considered as an AFF patient. The SAS software (version 9.3; SAS Institute Inc., 2002-2010; Cary, NC) was used for data analyses.

Results

Between 2000 and 2013, a total of 8851 patients with de novo hip fractures were treated in the trauma center of Meidling, thereof 3337 (37.7%) with femoral neck fractures, 3233 (36.6%) with intertrochanteric fractures, and 1288 (14.5%) patients with subtrochanteric or femoral shaft fractures. The percentage of low-traumatic fractures was 73.2%