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Bone turnover markers and the factors associated with atypical femur fractures among Japanese patients

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ABSTRACT

Many previous reports have indicated that atypical femur fractures (AFFs) are associated with the administration of bisphosphonates (BPs). A number of risk factors and hypotheses regarding the pathogenesis of AFFs have been reported to date. The purpose of the present study was to identify the factors associated with AFFs in Japanese individuals and to elucidate the association between bone metabolism and AFFs by evaluating bone turnover markers (BTMs). We prospectively reviewed all patients with femur fractures and identified the patients with AFFs and typical femur fractures (TFFs). We collected the demographic and clinical data that were relevant to the present study, namely age, gender, affected side, affected site, concomitant medical history, and comorbid conditions, and measured the levels of BTMs within 24 h after trauma. Welch's test and Fisher's exact probability test were used for the statistical analyses. A total of 338 patients, including 10 patients with AFFs and 328 patients with TFFs, were analyzed under the inclusion criteria. The use of BPs ($p < 0.001$) and collagen disease and chronic granulomatous disease (CD/CGD) ($p = 0.025$) were more frequently observed in patients with AFFs than in patients with TFFs, while the levels of BTMs, including N-terminal propeptides of type 1 procollagen (P1NP), isoform 5b of tartrate-resistant acid phosphatase (TRACP-5b) and undercarboxylated osteocalcin (ucOC) were significantly lower in patients with AFFs than in patients with TFFs. Furthermore, the level of

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TRACP-5b was found to be significantly lower in patients with atypical subtrochanteric fractures than in atypical diaphyseal fractures (p = 0.025). Moreover, the levels of P1NP (p = 0.016) and TRACP-5b (p = 0.015) were found to be significantly lower in patients with AFFs than in patients with TFFs in a subgroup analysis of BPs users. The use of BPs was considered to be a factor associated with AFFs. Our comparison of the BTMs in patients with AFFs and TFFs indicated that the severe suppression of bone turnover was associated with the pathogenesis of AFFs. The extent of the influence of suppressed turnover on the pathogenesis of AFFs may differ depending on the fracture site.

Introduction

The prevention of fragility fractures, including hip fractures and vertebral fractures, has been recognized to be one of the most important challenges in many countries. Therefore, an appropriate treatment strategy for osteoporosis closely associated with such fragility fractures has also been discussed at length, and many agents for the management of osteoporosis have been developed in recent years. Of the available agents for osteoporosis, there is great evidence supporting the utility of bisphosphonates (BPs) in the prevention and treatment of osteoporosis and fragility fractures related to osteoporosis. Indeed, it has been reported that BPs, including alendronate and risedronate, prevent not only vertebral fractures but also non-vertebral fractures and hip fractures [1]. However, some BPs have been associated with adverse effects.

BP-related osteonecrosis of the jaw (BRONJ) was first reported by Marx et al. [2], and evidence regarding the epidemiology, pathogenesis and risk factors of BRONJ has been demonstrated [3]. Furthermore, Odvina et al. reported an unusual type of femur fracture after the administration of alendronate as a result of severely suppressed bone turnover associated with alendronate [4]. In addition, Lenart et al. reported "atypical" femur fractures (AFFs) occurring on the subtrochanteric or diaphyseal region in postmenopausal women following alendronate therapy [5]. Although many additional reports regarding AFFs have been published following the initial reports and the American Society for Bone and Mineral Research (ASBMR) task force reported that the available evidence suggested that AFF is a stress or insufficiency fracture, the pathogenesis and the factors associated with AFFs have not been well elucidated to date [6,7].

The purpose of this study was to identify the factors associated with AFFs in Japanese patients and to elucidate the association of bone metabolism with AFFs by evaluating bone turnover markers (BTMs).

Methods

Ethics statement

The protocol for this study was approved by the ethics committee of Gunma University. All of the included patients provided their written informed consent and approved of the sampling and measurement of the BTMs.

Study population

This study was conducted among 14 institutions as a prospective cross-sectional study to clarify the differences in the clinical data, including data reflecting bone metabolism, between patients with AFFs and "typical" femur fracture (TFFs), and to investigate the possible risk factors and pathogenesis of AFFs among Japanese subjects.

The coauthors, who are all practicing orthopedic surgeons, prospectively collected the cases of all patients with femur fractures that occurred between April 1, 2013, and March 31, 2015. Of those patients with femur fractures, we identified the patients with AFFs, which was diagnosed according to the definition of AFFs revised by the ASBMR task force (Table 1) [6]. We also identified patients with TFFs. Among patients with AFFs, patients with incomplete fractures were excluded due to the possible effect on BTMs, and patients in whom the measurement of the BTMs could not be performed within 24 h after trauma were also excluded. Among the patients with TFFs, those with high-energy, periprosthetic or pathologic fractures were excluded. We judged whether or not a fracture had been associated with high-energy trauma based on the patient's history. As with AFFs, we also excluded TFF patients in whom the measurement of the BTMs could not be performed within 24 h after trauma.

Table 1
ASBMR Task Force 2013 Revised Case Definition of AFFs [6].

To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.
In addition, at least four of five Major Features must be present. None of the Minor Features is required but have sometimes been associated with these fractures.
Major features[a]
The fracture is associated with minimal or no trauma, as in a fall from a standing height or less
The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
The fracture is noncomminuted or minimally comminuted
Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")
Minor features
Generalized increase in cortical thickness of the femoral diaphyses
Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh
Bilateral incomplete or complete femoral diaphysis fractures
Delayed fracture healing

ASBMR = American Society for Bone and Mineral Research; AFF = atypical femur fracture.

[a] Excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eq, Paget's disease, fibrous dysplasia).