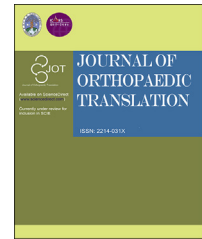




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REVIEW ARTICLE

Atypical femoral fractures and current management



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Summary With the rapid increase in patients receiving bisphosphonates (BPs) for treating osteoporosis, one of the clinical complications associated with its long-term use is atypical femoral fractures (AFFs). Although the absolute risk for AFFs is low and it was a consensus that AFFs were acceptable compared with the amount of osteoporotic fractures BPs have prevented, epidemiological studies have proved that BPs had a strong association with AFFs and possibly more people were going to suffer from this adverse effect with wide prescriptions of this drug. In addition, AFFs seemed to have impaired ability to heal. Thus, to understand the mechanism(s) behind AFFs is important and desirable for considering preventive measures. This article reviewed the clinical features of AFFs as well as potential underlying pathological characteristics, such as the decreased turnover rate caused by BPs that led to multiple-level alternations, e.g., changes not only at cellular and tissue levels, but also related to changes in bone micro- and macrostructure and organic/inorganic contents, leading to potentially compromised mechanical properties of cortical bone when exposed to prolonged BP therapy. Severely suppressed bone turnover may also be the underlying mechanism for impaired fracture healing in patients with AFFs. The rising concerns about the risk for AFFs in nonosteoporotic patients receiving high-dose BPs to treat cancers were also discussed. Detailed investigation will help develop potential targeted pharmacological treatments such as parathyroid hormone. In addition, potential innovative internal fixation implants were discussed with regard to dynamic and biological fixation for enhancing AFF repair.

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Introduction

We are stepping into a society with a significant ageing population, and it is known that one in six women will suffer from osteoporotic fracture at least once during their lifetime [1]. Bisphosphonates (BPs) have been developed and used as potent antiosteoporotic drugs for their bone-protective effect on primary osteoporosis (OP) in both female and male populations, and secondary OP such as glucocorticoid-induced OP. It has been proved that BP usage inhibits the bone remodelling process, elevates bone mineral density (BMD) and bone mechanical properties, and as a consequence, reduces the incidence of vertebral/nonvertebral fractures [2].

However, atypical femoral fracture (AFF), one of the potential complications of prolonged BP therapy for the treatment of OP, has raised reasonable concerns in recent years. Figure 1 shows the typical features of an AFF that developed in a 74-year-old female presenting to our department with low-energy subtrochanteric (ST) fracture of the right femur after 5 years of BP treatment. The evidence of the association between BP use and AFFs is strong, and the incidence of AFFs among patients taking BPs for over 10 years can be as high as 107.5/100,000 person-y [3]. In addition, it was estimated that in the USA, over 4 million women over 45 years of age were receiving BP treatment [4]. Thus, even though it still remains unknown if and how this long-regarded bone-protective agent causes another new-type fracture, the long-term effects of BPs on either the occurrence or the healing process as well as the treatment of AFFs should not be ignored.

In this review, we briefly summarize the epidemiological and pathological features of AFFs and the potential effects of BP usage on the development as well as the healing process of AFFs. The challenges and treatments of osteoporotic fractures, mechanism(s) on impaired healing, and proposed options or treatment protocols for achieving better healing or eventually healing enhancement will be discussed.

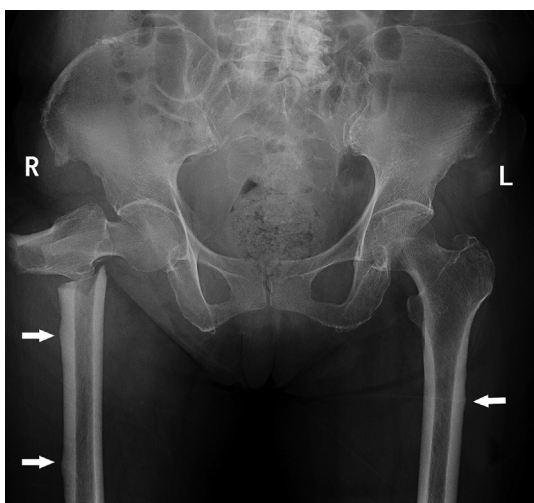


Figure 1 AFF radiograph of a 74-year-old female with a 5-year BP exposure history. Note the multiple involvement/local cortical thickness of the lateral side of the femurs indicated by white arrows. AFF = atypical femoral fracture; BP = bisphosphonate; L = left; R = right.

Definition of AFFs

In the first publication on AFF in 2005, Odvina et al [5] reported that nine patients receiving long-term alendronate therapy for 3–8 years developed spontaneous nonvertebral fractures later, with six patients having delayed fracture healing or nonunion. Transiliac bone biopsies from the most of the patients showed reduced or absent osteoblastic and osteoclastic activities with decreased or no tetracycline labelling, indicating inhibited bone remodelling either in cancellous or cortical bone. It was suggested that this phenomenon of severe suppression of bone turnover was caused by the long-term use of BPs, leading to increased susceptibility to as well as impaired healing of fractures. After this initial paper, many case reports on rising anxieties about the side effects of BPs on a special type of femoral fracture were published [6,7]. According to these clinical observations, BP-associated fractures shared similar and unique clinical and pathological features, including chronic pain, transverse fracture line, location in the femoral shaft (FS) or ST area, etc.

In 2009, the task force of the American Society for Bone and Mineral Research (ASBMR) reviewed published literatures about AFFs and developed their case definition [8]. In this report, an AFF was defined as a type of low-energy fracture located typically in the area of distal to the lesser trochanter to proximal to the supracondylar flare of the distal femoral metaphysis. Complete understanding of AFFs is challenging because of not only the low incidence of AFFs compared with other more common fracture types, but also the varying definitions of AFFs by different study groups. Thus, for the purpose of unifying the definition of AFFs, the task force of ASBMR suggested some major features that should all be present when making a diagnosis, and also minor features that were the factors found to be associated with AFFs but should not be necessarily included in the diagnostic criteria [8]. In 2014, an updated version of the case definition of AFFs provided a more precise definition that could better differentiate AFFs from regular ST/FS fractures [9]. In this new version, the localized periosteal reaction of the cortex was upgraded from the minor to major features considering the updated concept of an AFF as a kind of stress/insufficient fracture. Four out of five major features must be present in order to designate a fracture as an AFF, while in the old version all the major features were included.

Epidemiology of AFFs associated with BPs

Prior to the development of a stringent case definition of AFFs by ASBMR, potential AFFs were reported in the context of a more general concept, that is, ST/FS fracture, the incidence of which among women has been reported between 10 and 35 per 100,000 [9]. Since BPs were approved for the treatment of OP at that time, the incidence of femoral neck/intertrochanteric fractures, as typical osteoporotic fractures, has been reported to decrease given the preventive effect of BPs on bone, whereas the rate of ST/FS fractures remained stable [10] or increased [11]. As the case definition of ST/FS fractures was based on the International Classification of Diseases, Ninth Revision

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