***CORR* Insights®: Are Race and Sex Assessment Associated With the Occurrence of Atypical Femoral Fractures?**

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Where Are We Now?

The introduction of bisphosphonates to osteoporosis treatment is associated with a decrease in vertebral fractures by 70%, hip fractures by 40% to 50%, and peripheral fractures by 20% [2]. However, bisphosphonates are also associated with atypical femoral fractures, which can cause substantial morbidity; they present with minimal trauma in the subtrochanteric and femoral shaft, and they have a specific radiologic appearance. These fractures often are associated with prolonged (exceeding 5 years) bisphosphonate treatment. To address this problem, the Association for Bone and Mineral Research established a task force and released

two reports [4, 5] that created criteria for atypical femoral fractures, while also addressing the risk and pathophysiology of these injuries.

The task force noted that several groups found associations between atypical femoral fractures and bisphosphonates [4, 5]. The relative risk of prolonged bisphosphonate use is high for these fractures, and increases with duration. The absolute atypical femoral fracture risk is low, ranging from 3.2 to 50 cases per 100,000 person years. However, the rate increases to 100 to 200 cases per 100,000 person years for individuals whose treatment reaches 8 years. While the association has been established, causality has not been proven by the Bradford-Hill criteria [3]. A temporal relationship exists between bisphosphonate and atypical femoral fractures. The cessation of bisphosphonate treatment lowers the risk of atypical femoral fractures. However, the task force recognized that causality remains unresolved, and additional antiresorptive agents may have the same association. The exact etiology of the atypical femoral fractures has not been determined, and at-risk patients have yet to be identified.

This CORR Insights® is a commentary on the article “Are Race and Sex Assessment Associated With the Occurrence of Atypical Femoral Fractures?” by Marciano and colleagues available at:

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Where Do We Need To Go?

Currently, issues of causality, etiology, and risk remain unsettled for atypical femoral fractures. The contribution of bisphosphonates and other anticatabolic agents to the generation of atypical femoral fractures requires a thorough understanding of the pathophysiology. Bisphosphonate primarily decreases bone resorption and secondarily bone formation. Several theories suggest an atypical femoral fracture's pathogenesis starts with low bone turnover and would include microdamage accumulation, reduced bone matrix heterogeneity, accumulation of advanced glycation

end-products that alter collagen strength, crack propagation, loss of bone toughness, and unique bone geometry [4, 5].

Risk issues are more fully developed. Although an association with bisphosphonates and its duration has been established, most individuals utilizing long-term bisphosphonates do not experience atypical femoral fractures. It is worth noting that these drugs have markedly lowered the risk of osteoporotic fractures. Several registries [1, 4, 5] have reported that Asians may have an increased risk. Marcano and colleagues strongly support this view, and also call attention to Hispanics, who be at higher risk as well. None of the investigators have information on drug compliance, confounding diseases, or bone geometry to explain this added risk. There is a pressing need to establish clear criteria for the patient that requires treatment, the choice of treatment and duration, and identification of those individuals at risk for adverse events, including atypical femoral fractures.

How Do We Get There?

There are several avenues that may help us better understand atypical femoral fractures. Prospective hip and femoral fracture registries must be established, and should be coupled with osteoporosis registries to identify the potential risk and etiologic factors. No institution has a sufficient amount of atypical femoral fracture cases to resolve these issues. Therefore, large multiinstitutional cooperative efforts are required, similar to The Kaiser Permanente and Ontario cooperative efforts. The critical clinical, laboratory, radiologic, and historical data points need to be universally established for these investigations. As novel agents are introduced, how do they relate to atypical fractures? Are there drugs that actually rescue the low turnover bone? What drugs are preferred in the setting of the atypical femoral fractures? Clinical trials addressing these questions are required.

There is a need for detailed structural analysis of individuals on long-term bisphosphonate therapy with and without atypical femoral fractures. Additionally, bone biopsies of the involved femurs would be helpful,

particularly from the site of the fractures. There are several laboratories that have the special techniques required, including Fourier transform infrared imaging, microindentation, glycation product determination, and bone histomorphometry. Collaborative programs are needed to match the biopsy with these special laboratories. Detailed standardized data sets on the patients should accompany the investigations.

Major clinical groups overseeing osteoporosis should provide some guidelines on how clinicians approach a potential drug holiday. Osteoporotic drug use has steadily declined during the last 5 years despite the unequivocal evidence for their efficacy in preventing fractures. Clear recommendations regarding treatment are needed for the clinicians by the bone biology community.

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