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LETTER TO THE EDITOR

"Fatigue" having a role in the pathogenesis of osteonecrosis of the jaws

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Sir,

In 2002, 9 months after zoledronic acid received Food and Drug Administration (FDA) approval for the prevention of cancer-related skeletal events, the FDA received clinicians' reports describing patients with cancer who had developed a severe and unusual complication, osteonecrosis of the jaw (ONJ), which was initially ascribed to being a later chemotherapy effect [1]. To date, there is still a lack of knowledge of pathogenesis, prevention and treatment regarding ONJ [2].

In 2008, another probable complication has been attributed to bisphosphonate use: Atypical fractures of the femoral diaphysis have been reported [3, 4] in patients with history of chronic alendronate use. Furthermore, bisphosphonate use has been associated with a unique X-ray pattern in sub-trochanteric/shaft fractures [5]. Based on this evidence, a recent review suggested that both ONJ and atypical fractures of the femoral diaphysis may be manifestations of "fatigue" in human bone. In material science, "fatigue" is the progressive and localised structural damage, which occurs when a material is subjected to cyclic loading and which is microscopically evident through the accumulation of microcracks in the material [6]. The bone is a living tissue, and bone cells fix microcracks that may happen during cyclic loading [7]. Consequently, in animal bones, "fatigue" does not occur because of the continuous bone remodelling, a process which is known to be impaired by bisphosphonates [7]. Hoefert et al. in an upcoming publication demonstrate the presence of microcracks in ONJ bone samples [2]. Importantly, the authors managed to quantify these microcracks and even compare their presence between various conditions with similar clinical presentation, namely osteoporosis, osteomyelitis and osteoradionecrosis. It appears that microcracks are prominent only in the jaws of patients who receive bisphosphonates, irrespectively of the clinical manifestation of ONJ [2]. The results reported by Hoefert et al. [2] are statistically significant, while the methodology applied warrantees reproducibility. The presented evidence supports the hypothesis that "fatigue" of the human bone may be a mechanism implicated in the pathogenesis of ONJ.

The authors discuss a potential linkage between the finding of microcrack accumulation and the local sensitivity to bacterial contamination in the jawbones of patients with ONJ. They also suggest that bisphosphonates may interact with the immune system and influence the circulating levels of local cytokines [2]. Of note, a large number of cell to cell endocrine and paracrine interactions have been reported to be impaired in patients receiving bisphosphonates [8]. An effort to attribute ONJ etiology to a single pathophysiological mechanism may be naive, while an effort to distinguish the most important pathophysiological mechanisms would be important to elucidate the complete aetiopathogenesis of the complication. In this regard the discussion by Hoefert et al. [2] is apposite. Furthermore, suggesting "fatigue" as a possible mechanism for ONJ development does not imply rejecting a number of evidence based hypotheses previously reported [8]. However, "fatigue" of the jawbone may be a key missing element, which could contribute to future research on the aetiopathogenesis of ONJ.

Based on their important findings, the authors propose that the state of accumulated microcracks without any clinical sign of ONJ could be named "non-symptomatic ONJ". A clinical obvious ONJ with fistulas, pain or

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exposed bone could be named as "symptomatic ONJ" [2]. This information may be accurate; however, it would necessitate a number of blind bone biopsies in every patient receiving bisphosphonates for a period of time, which also needs to be determined. What is more, the authors where not able to report an increased number of microcracks in 46% of the ONJ samples studied [2]; thus, should one decide to use the specific histology technique to classify "non-symptomatic ONJ", the sensitivity of the method would be limited. On the contrary, the specificity of the method could be acceptable since no cracks were identified in patients with osteomyelitis or previous irradiation but not in those with osteoporosis.

The essential information in the report by Hoefert et al. [2] concerns the presence of microcracks in the jawbones of patients receiving bisphosphonates. This information is of importance for clinicians and researchers not only of the maxillofacial region. Orthopaedic surgeons, oncologists and bone biologists need to be informed about the presence of microcracks in the jaws of patients receiving bisphosphonates. In patients receiving bisphosphonates, other sites of the human skeleton, namely the femoral diaphysis, need to be examined for the presence of microcracks. If "fatigue" can provide a novel rationale for the pathogenesis of ONJ and atypical fractures of the femoral diaphysis remains subject to future research.

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