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LETTER TO THE EDITOR

Response to "Fatigue having a role in pathogenesis of osteonecrosis of the jaws" and "BRONJ and the microdamage Letter to the Editor"

Sebastian Hoefert · Harald Eufinger

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Sir,

We are pleased by the response to our paper "Importance of microcracks in etiology of bisphosphonate-related osteonecrosis of the jaw: a possible pathogenetic model of symptomatic and non-symptomatic osteonecrosis of the jaw based on scanning electron microscopy findings" [1]. We read with great interest the letter by Kyrgidis and Vahtsevanos. Indeed, suppression of bone turnover seems to play a major role in the pathogenesis of bisphosphonate (BP)-related osteonecrosis of the jaw (ONJ). Furthermore, BPs may have toxic effects on the epithelium and may disrupt intraoral wound healing, which may lead to addition jaw bone exposure [2]. Animal experiments have demonstrated significantly reduced bone turnover and an increase in matrix necrosis after treatment with alendronate for 3 years. The highest effect was found at the alveolar crest [3], which is predominantly exposed to masticatory forces from the teeth. The accumulation of matrix necrosis may be the result of reduced bone turnover [2]. In addition, studies in beagle dogs with long-term application of risedronate and alendronate have demonstrated a suppression of trabecular bone turnover in the vertebrae and a significantly increased microdamage accumulation in all skeletal sites measured [4]. In earlier examinations of samples of 20 patients with BP-related ONJ, our own research group found a high number of microfractures containing bacteria and leukocytes [5]. The opportunity for oral microorganisms to deeply infiltrate jaw bone via these microfractures and the additional local immunosuppression in combination may be of pathogenetic importance. Furthermore, it was demonstrated that apoptosis of macrophages is induced by different BPs [6]. In clinical studies of large series of patients with ONJ, we showed a significant benefit for patients with a long term preoperative antibiotic regime compared to those with only short term preoperative treatments while keeping the surgical strategy and the postoperative medication identical for both groups (unpublished data). This observation gives a further indication in the importance of the infectious aspects of this disease.

Meanwhile, the American Association of Oral and Maxillofacial Surgeons introduced a stage 0 in a score of BP-related ONJ: This stage is described as "no clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms" [7]. This stage could be the clinical equivalent to our proposed "non-symptomatic ONJ" [1]. We agree with Kyrgidis and Vahtsevanos that this stage deserves further clinical investigation and that its existence may be confirmed by serial bone biopsies after different periods of BP treatment. However, such an investigation could hardly be performed prospectively in patients since it would stand in contrast to the demand of avoiding any surgical oral intervention.

In addition to the fractures of the femoral diaphysis mentioned by Kyrgidis and Vahtsevanos, nonspinal fractures occurring without adequate trauma during normal daily activities were observed in nine patients with long-term alendronate treatment [8], which may also support the "fatigue" hypothesis.

We are also grateful to Allen for his comments to our paper. Indeed, the en bloc staining with basic fuchsin can be regarded as the method of choice to demonstrate bone microdamage, but other methods like light microscopy, fluorochrome staining, laser scanning confocal microscopy,

S. Hoefert (✉) · H. Eufinger
Department of Oral and Maxillofacial Surgery–Regional Plastic Surgery, Knappschaftskrankenhaus, Klinikum Vest,
Academic Teaching Hospital of the Ruhr-Universität Bochum,
Dorstener Str. 151,
45657 Recklinghausen, Germany
e-mail: hoefert.sebastian@kk-recklinghausen.de

and microcomputerized tomography are mentioned by other authors [1]. The basic fuchsin technique is limited by its inability to stain all cracks and is not useful to study bone with highly variable densities within a single section because areas of low density can be overstained, areas of high density may be understained [9], and necrotic bone matrix is not stained [3]. Interestingly, one of Allen's coworkers verified and controlled the basic fuchsin technique by scanning electron microscopy, thereby indicating that the latter must be a method of major significance [10]. Basically every method has a risk of producing artificial damage during sample processing as mentioned by Lee et al. [11].

In fact the demonstration of cells or debris within the cracks has not been validated so far. Allen claims to exclude the possibility of this proof by the width of cracks, which he estimates to be 1–2 µm. This assumption stands in distinct contrast to the literature: Mohsin et al. described the microcracks in their three-dimensional analysis showing a length of 488±151 µm and a width of 88±21 µm [12]. O'Brien et al. suggested an elliptical shape of the microcracks and described a mean length of 404±145 µm and a mean width of 97±38 µm [13]. If microcracks showed elliptical shapes, openings of various widths can be expected at the surface of the bone samples. It is true that the surfaces of our samples could be resection margins. All samples in all patient groups were harvested by two surgeons using the same technique. Therefore, all samples should have been exposed to more or less the same mechanical stress, which begs the question: Why were there no cracks in the irradiation of the jaw or in the osteomyelitis groups? We regard the differences between the groups as very important in this respect, which was also pointed out by Kyrgidis and Vahtsevanos in their response to our paper. In contrast, the BP and the osteoporosis group showed no significant difference from the ONJ group. Because of these interesting findings, we still consider that microcracks might be a "first step" in ONJ etiology.

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