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Review article

Antiresorptive agent-related osteonecrosis of the jaw in osteoporosis patients from Asian countries

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ABSTRACT

Bisphosphonate (BP)-associated osteonecrosis of the jaw (ONJ) was first reported in oncology patients in 2003 and subsequently in osteoporosis patients in 2004. Since oral surgical procedures, such as tooth extraction, are also considered one of the major risk factors for ONJ, there is confusion among physicians, dentists, and patients – particularly osteoporosis patients currently taking BPs – regarding the safety of remaining on therapy surrounding these procedures. Many papers about BP-related ONJ (BRONJ) have been published to date. In addition to BRONJ, recent studies have reported an association between ONJ and the antiresorptive therapy denosumab (Dmab; a RANKL-inhibitor). BRONJ and Dmab-related ONJ are together referred to as antiresorptive agent-related ONJ (ARONJ). The pathogenesis of ARONJ still remains unknown. It is forecasted that there will be an increased incidence of patients with osteoporotic fractures and an increased number of prescriptions for antiresorptive agents in Asia in the future. However, prescriptions for antiresorptives for osteoporosis may be restricted in the Asian population as the occurrence of ARONJ may be higher as compared with those in other countries. In this review, we focused on the following topics as it pertains to the Asian osteoporotic population: the oral condition specific for osteoporosis patients; definition, staging, prevalence and incidence of ARONJ; imaging modalities for ARONJ; specific risk factors for ARONJ; prevention strategies for ARONJ, and; cooperation between physicians and dentists in the prevention of ARONJ. Ideally, the Asian Federation of Osteoporosis Societies would cooperate with one another and find more population-specific evidence for the prevention of ARONJ.

1. Introduction

Since Marx first described a new clinical entity, osteonecrosis of the jaw (ONJ), in oncology patients who had taken high dose intravenous (i.v.) bisphosphonates (BPs) in 2003 [1], a large number of investigators have reported BP-related ONJ (BRONJ) in both basic and clinical studies (randomized controlled trials, cohort studies, observational studies, case-controlled studies, case series, case reports) and numerous reviews, guidelines, consensus papers and position papers about its incidence and management have been authored. However, the precise pathogenesis of BRONJ remains unclear. BRONJ has also been reported in osteoporosis patients administered low-dose oral BPs [2], which caused confusion among physicians, dentists, and osteoporosis patients because there are many osteoporosis patients who have taken BPs worldwide but who have also had surgical dental procedures like tooth extraction which in itself is an important risk factor for BRONJ [3]. In addition to BPs, recent reports describe that another antiresorptive medication, denosumab (Dmab; a RANKL inhibitor), may also be associated with an increased incidence of ONJ [4]. ONJ associated with BPs or Dmab is termed antiresorptive agent-related ONJ (ARONJ).

Hip fracture rates are continuously rising in Asia, with the exception of Hong-Kong and Taiwan which possess fracture trends that more closely resemble those of western countries [5]. BPs are now the most frequently prescribed medication for preventing osteoporotic fractures. Although a Task Force of the American

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Society for Bone and Mineral Research (ASBMR) describes that the risk of BRONJ in Asia may be higher than that in other regions [6], access to BPs and Dmab should not be restricted for fear for very rare adverse events like ARONJ [7]. In Asia, accurate information regarding the risk of fracture if untreated versus the risk of ARONJ if treated should be shared among physicians, dentists, and patients.

In this review, the incidence and management of ARONJ in Asia is discussed in patients treated for osteoporosis with an antiresorptive medication (BP or Dmab). All studies considered for inclusion in this review were published in English with humans as study subjects.

2. Oral health specific to patients treated for osteoporosis in Asia

2.1. What kind of oral conditions do osteoporosis patients have?

Before discussing the pathogenesis of ARONJ in patients with osteoporosis, it is imperative to understand the important role basic oral health plays in the risk of ONJ independent of antiresorptive therapies. The risk of osteoporosis and oral infectious diseases, like marginal and periapical periodontal diseases, both increase with aging. However, since Daniell [8] first demonstrated the association between progression of osteoporosis and increased risk of edentulous jaws in postmenopausal women, numerous other investigators have also demonstrated the association between osteoporosis and loss of teeth and periodontal disease in the elderly.

2.2. Association between osteoporosis, loss of teeth and periodontal disease

In a cross-sectional study of 1914 Japanese subjects aged 48–95 years recruited from the Adult Health Study, the self-reported number of teeth present was significantly associated with a greater femoral neck bone mineral density (BMD) in both men and women [9]. In the Korean National Health and Nutrition Examination Survey (KNHANES) 2008–2010 (3364 men over 50 years of age and 3951 postmenopausal women), Jang et al. [10] observed a significant association in postmenopausal women between the number of remaining teeth and presence of osteoporosis, most strongly when diagnosed at the femoral neck site. In a longitudinal study, Iwasaki et al. [11] observed a significant relationship between a change in BMD of the lumbar spine and femoral neck and number of lost teeth during a five-year study period in 404 Japanese community-dwelling postmenopausal women. Although there is little data describing the association between BMD and the loss of teeth in Asia (except Japan and Korea), it is likely that Asian osteoporosis patients have a higher probability of having tooth extraction in comparison to individuals without osteoporosis.

In a cross-sectional study of 9977 participants aged $\geq$40 years from KNHANES, Kim et al. [12] reported a significant association between increased risk of periodontal disease and BMD of the lumbar spine, total hip, and femoral neck. Iwasaki et al. [13] demonstrated that a low BMD, measured at lumbar spine and proximal femur, was associated with severity of periodontal disease in 397 Japanese community-dwelling postmenopausal females. Similar findings have been observed in Hong Kong, Taiwan, India and Jordan [14–17]. In a longitudinal study of a Taiwanese population-based database including data from 2527 patients with osteoporosis and 7575 matched non-osteoporosis individuals, Chang et al. [15] reported that the adjusted hazard ratio for periodontitis in patients with osteoporosis compared with individuals without osteoporosis during the 5-year follow-up was 1.14 (95% CI = 1.05 to 1.24, P < 0.01). These findings suggest that an Asian elderly population with osteoporosis may have an increased risk of periodontal disease, a major infectious disease of the oral cavity.

It has been previously shown that in 253 postmenopausal women with self-reported periodontal symptoms included gingival swelling, gingival bleeding, purulent discharge and tooth mobility that the odds of having low spine BMD was 2.01 (95% confidence interval [CI] = 1.15 to 3.50) [18]. In 5127 osteoporosis patients and 50,498 non-osteoporotic controls from the Longitudinal Health Insurance Database of Taiwan, Huang et al. [19] found that in those participants with good oral hygiene maintenance, patients with periodontitis had 1.29-fold risk of osteoporosis as compared with those without periodontitis (95% CI = 1.12–1.49). On the other hand, in those with poor oral hygiene maintenance those patients with periodontitis had a 6.02-fold increased risk of osteoporosis as compared to those without periodontitis (95% CI = 4.65–7.81). This suggests that oral hygiene maintenance may also complicate the understanding of ONJ as it also appears to have an influence on the association between osteoporosis and periodontal disease.

2.3. Osteoporosis and delayed wound healing after tooth extraction

If osteoporosis patients have an increased risk of having periodontal disease and loss of teeth, then they may also have a greater chance of suffering from delayed wound healing after tooth extraction because it is likely that the infection due to severe periodontal disease may contribute to inhibiting the promotion of wound healing. Huang et al. [20] compared 19,399 osteoporosis patients who received dental extractions between 2000 and 2010 (osteoporosis cohort) with 38,669 age- and gender-matched controls selected from dental extraction patients without osteoporosis or osteonecrosis history (comparison cohort). They finally concluded that osteoporosis itself played a very important role for the development of ONJ in that those individuals with osteoporosis had prolonged wound healing after tooth extraction, while BPs had a synergistic effect. In a recent study designed to elucidate the association between osteoporosis and delayed wound healing after tooth extraction, self-reported kyphosis was used as a surrogate marker for spine fractures, owing to its significant association with spine fractures [21]. In this study, which included 518 subjects (134 men and 384 women) aged 55–97 years, those who self-reported mild-moderate kyphosis were significantly more likely to have delayed wound healing after tooth extraction as compared with those who reported no kyphosis (odds ratio [OR] 4.98; 95% CI, 1.86–13.38) [22].

The process of fracture healing by intra-membranous ossification and/or endochondral ossification involves many well-orchestrated events including the signaling, recruitment and differentiation of mesenchymal stem cells during the early phase; formation of a hard callus and extracellular matrix, angiogenesis and revascularization during the mid-phase; and callus remodeling at the late phase of fracture healing. Cheung et al. [23] described that through clinical and animal research, many of these factors are shown to be impaired in osteoporotic bone. Impairment of the bone healing system also may contribute to prolonged wound healing after tooth extraction in patients with osteoporosis.

2.4. BPs and periodontal disease

If osteoporosis or low BMD is associated with an increased risk of periodontal disease and subsequent tooth loss, osteoporosis medications like BPs may then reduce the risk of periodontal disease. In fact, investigators in some countries have observed a protective effect of BPs against the progression of periodontal disease in randomized controlled trials [24–26] and in a clinical trial [27]. In the USA, Lane et al. [25] found that BP therapy group (n = 43)

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