To the Editor:

The Journal has published the Canadian Consensus Practice Guidelines for Bisphosphonate Associated Osteonecrosis of the Jaw[1]. The report gives recommendations of a multidisciplinary group of experts, endorsed by the Canadian Association of Oral Maxillofacial Surgeons and other groups, regarding diagnosis, prevention and therapy of osteonecrosis of the jawbones (ONJ) associated with bisphosphonates. The authors claimed the report provides a "rational evidence-based approach to the diagnosis, prevention, and management of bisphosphonate-associated ONJ," and that their guidelines are based on the "best available published data and the opinion of national and international experts involved in the prevention and management of ONJ"[1].

We recognize the efforts of these authors in trying to clarify the controversial aspects of ONJ and provide clinical recommendations that could potentially reduce the risk of development of ONJ. However, we would highlight that some of the statements and recommendations presented are not based on best available evidence, the consequences upon clinical practice being potentially significant.

1. The authors state that "a link between ONJ and bisphosphonates has not yet been identified in the patient with osteoporosis in whom these agents are used in very low doses". This statement should be read with caution, as potency and bioavailability of bisphosphonates, further to overall dosage, is well known to determine the risk of ONJ[2]. Moreover, the authors seem not to consider the hundred cases of ONJ reported in patients with osteoporosis and diseases other than cancer treated with oral bisphosphonates — it already being admitted in 2006 by Merck[3] that the number of reported cases of ONJ associated with alendronate was approximately 170 as well as the increasing number of related litigations[4]. The latter can provide an indirect but more realistic estimate of the prevalence of ONJ associated with oral bisphosphonates as it also includes nonpublished cases (as of March 31, 2008, approximately 465 cases, which included approximately 940 plaintiff groups, had been filed and were pending against Merck in US federal or state court)[4]. Even though the overall prevalence of ONJ in this population is much lower than in cancer patients using intravenous bisphosphonates (< 0.1% vs 1%–12% at least)[5,6], an association between oral bisphosphonates (largely administered to patients with osteoporosis) and ONJ has been suggested by many authors and is largely accepted in the scientific community[6].

2. The authors' opinion and recommendations regarding the interruption of bisphosphonate therapy with the aim of reducing the risk of ONJ were controversial. They initially seemed concerned about the interruption of bisphosphonate therapy by "many patients due to limited and misleading public information regarding ONJ". They referred to an editorial by Khan[7] but did not provide any reliable figure regarding the characteristics of these patients (e.g., cancer vs osteoporosis) and how frequently this is happening. The authors, however, seemed to contradict their own initial statement as they recommended, in another paragraph, discontinuing intravenous or oral bisphosphonates for several months before oral surgical procedures if the medical condition permits and/or during the first weeks after dental surgery. We acknowledge that providing recommendations regarding the feasibility and effectiveness of bisphosphonate discontinuation is difficult as data are controversial. However, we believe that, until better evidence is available, clinicians should best focus on precautionary measures (i.e., careful dental examination and oral surgical procedures) prior to starting bisphosphonate therapy. This applies also to oral bisphosphonate, as middle-aged to older individuals are at increased risk of oral disease[8,9].

3. In the abstract the authors stated, "Osteoporosis patients receiving oral or intravenous bisphosphonates do not require a dental examination prior to initiating therapy in the presence of appropriate dental care and good oral hygiene." They basically recommended not performing any additional dental clinical/radiological examination in individuals affected by osteoporosis and scheduled for therapy with oral bisphosphonates, if regular preventive dental care has been practiced, and if no acute dental disease is reported. This is, however, very controversial as (i) chronic dental disease (e.g., chronic periodontal disease) and related surgical therapy has been reported to be associated with ONJ[10]; (ii) some chronic dental disease can be quiescent for months/years before causing acute dental infection; (iii) dental examination is a noninvasive, easy to perform 5-minute procedure that has the potential of identifying and removing easily the major triggers of ONJ (namely, dental infection and need of surgical procedures). This can lead clinicians to plan invasive procedures before the start of bisphosphonate therapy. Regular dental care does not necessarily address these issues.

4. The statement that "ONJ may occur spontaneously without exposure to bisphosphonates" is not supported by the indicated reference (Santini, *et al*[1]). Necrosis and infection of the jawbones is well known to occur also in relation to other therapeutic modalities (e.g., radiotherapy), medical disorders (e.g. sickle cell anemia, cemento-osseous dysplasia, osteopetrosis), and perhaps as a result of traumatic bone exposure in predisposed individuals (e.g., mucosal ulceration and bone sequestration along the surface of mandibular tori/exostoses). Nevertheless, this argument cannot be used to suggest, as the authors seemed to do, that cases of bisphosphonate related osteonecrosis are overreported and the likely result of a misdiagnosis. A single pathological process (bone necrosis) can in fact result from multiple and different pathogenetic factors, and it is currently suggested that bisphosphonate can represent one of the potential culprits of necrosis of the jawbones[11]. Moreover, the number of individuals affected by necrosis of the jawbones has significantly increased in the last few years and in association with the increased use of bisphosphonates, while previously only sporadic cases were reported.

5. The authors stated that the diagnosis of ONJ is mainly clinical and biopsy should be performed only when metastasis is suspected. However, there is growing evidence that imaging techniques can help in diagnosing ONJ, identifying areas of early involvement before occurrence of bone exposure, and evaluating the extension of the necrotic area and the presence of multifocal lesions[12,13]. Accordingly, radiologists are likely to play an important role in the evaluation and management of patients at risk of ONJ, and they should be actively involved in future research.

6. The authors did not mention risk-reduction strategies suggested by other authors[14-16]. Even though the evidence behind the majority of the previous recommendations is highly questionable, in some cases sensible nondetrimental practical advice for clinicians is provided[14,16]. As the paper by Khan, *et al* is reported to be based on a systematic review of the best available evidence, critical consideration of these reports would have been expected.

Clinical recommendations are important in medical practice, as they guide clinicians in taking evidence based decisions. When strong evidence is not available, expert opinions are considered an acceptable support for clinical advice, as long as they are based on comprehensive analysis of published data. The report from Khan, *et al* fails, in some parts, to satisfy this requirement.

There is clear evidence that the number of patients with bisphosphonate associated ONJ has been increasing worldwide, and these include individuals taking oral bisphosphonates for bone diseases other than cancer. A network of Italian centers of oncology, hematology, dentistry, and maxillofacial surgery has recently identified more than 1200 cases of bisphosphonate associated ONJ, with the percentage of individuals taking oral bisphosphonates varying between 5% and 30% where data were available (data not published)[17].

Further to expert opinion based recommendations, it is advisable for clinicians to take into consideration also the recommendations of national and international regulatory agencies. For example, the Italian Drug Regulatory Agency[18], the Australian Department of Health[19], the Medicines and Healthcare products Regulatory Agency in the UK[20], the European Medicines Agency[21], and the National Institutes of Health in the US[22] have recommended that a thorough dental examination should be considered before the start of oral and intravenous bisphosphonate therapy, suggesting that prevention is currently the most reliable tool to reduce the risk of ONJ.

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