Int. J. Oral Maxillofac. Surg. 2017; 46: 151–156
http://dx.doi.org/10.1016/j.ijom.2016.10.009, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Systematic Review
Clinical Pathology

Efficacy of the C-terminal telopeptide test in predicting the development of bisphosphonate-related osteonecrosis of the jaw: a systematic review

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Abstract. This systematic review evaluated the efficacy of the morning fasting serum C-terminal telopeptide (CTX) test in predicting the development of bisphosphonate-related osteonecrosis of the jaw (BRONJ). A comprehensive search of studies published up to March 2016, and listed in the PubMed/MEDLINE, Web of Science, and Cochrane Library databases, was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This review has been registered in the PROSPERO international prospective register of systematic reviews (CRD42016036717). The search identified 542 publications; eight studies were finally deemed eligible for inclusion according to the study criteria. These studies included a total 1442 patients (mean age 66.7 years). The most prescribed drug was alendronate, with osteoporosis being the most frequent indication for the prescription of bisphosphonates. Tooth extraction was the most common trigger for BRONJ. Of all patients evaluated after bisphosphonate treatment, only 24 (1.7%) developed BRONJ. All eight of the selected studies found that CTX levels were not predictive of the development of BRONJ. In conclusion, this systematic review indicates that the CTX test has no predictive value in determining the risk of osteonecrosis in patients taking bisphosphonates.

Key words: bisphosphonates; osteonecrosis; C-terminal telopeptide; CTX; systematic review.

Accepted for publication 19 October 2016
Available online 19 November 2016

The first descriptions of bisphosphonate-related osteonecrosis of the jaw (BRONJ) were reported in 2003.[1,2] According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), BRONJ is defined as exposed or necrotic bone in the upper or lower jaw that has persisted for more than 8 weeks in a patient with a history of bisphosphonate use who has no history of radiotherapy in the head–neck region.[3]

The nature of BRONJ appears to be multifactorial. The current hypotheses include suppression of bone turnover, local infection involving bacterial growth or inflammation of the oral mucosa, and inhibition of angiogenesis.[4,5] However, the exact pathophysiology of the disease has yet to be determined and it is still unclear how to achieve a more accurate diagnosis and thus provide appropriate treatment.[4,6] Patients taking bisphosphonates have risk factors associated with dental surgery involving the jaws, including tooth extraction, dental implants, and other alveolar surgeries, all of which can initiate osteonecrosis.[7,8] Therefore, it is necessary to determine the risks and prognosis through examination, in patients who require dental surgery. The morning fasting serum C-terminal telopeptide (CTX) test is at present used widely for this purpose.[9,10]

CTX is a biological marker that can be used to measure bone resorption and remodelling. Type 1 collagen is the main constituent of the bone extracellular organic matrix, and on its degradation during bone resorption, CTX is released. Therefore, patients with suppressed bone resorption show decreased CTX levels.[11] However, there is no consensus in the literature on the use of CTX levels, with conflicting findings reported. Some have argued that measuring CTX levels is predictive of the risk of development of BRONJ,[9,12,13] and conversely, others have found that CTX levels cannot be used as a marker for the risk of BRONJ developing.[14–16] Therefore, agreement has yet to be reached regarding the utility of the CTX test to predict the development of BRONJ in patients treated with bisphosphonates who are to undergo oral surgery.

Materials and methods

Registry protocol

This systematic review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17] and was performed in accordance with models proposed in the literature.[18,19] Moreover, the methods used in this systematic review have been registered in the PROSPERO international prospective register of systematic reviews (CRD42016036717).

Inclusion and exclusion criteria

The following inclusion criteria were applied: randomized controlled trial or prospective study; performance of the CTX test before an oral surgical procedure; study with more than six patients; patients taking oral and/or intravenous bisphosphonates; articles published in the last 10 years; articles published in the English language.

The following exclusion criteria were applied: studies with patients who had received radiotherapy to the head and neck region; patients with previously diagnosed osteonecrosis; retrospective studies; case reports.

Thus, the PICO question recommended in the PRISMA statement was defined as follows: (1) population: patients receiving bisphosphonates and requiring dental surgery; (2) intervention: patients assessed with the CTX test before undergoing surgical procedures; (3) comparison: patients whose CTX levels were not assessed before undergoing surgical procedures; (4) outcome: analysis of the efficacy of CTX measurement as a predictive test for osteonecrosis in patients taking bisphosphonates.

Search strategy and information sources

Two of the authors (K.J.D.P and C.A.A.L.) performed the selection of articles independently. Searches were performed in the PubMed/MEDLINE, Web of Science, and Cochrane Library databases for articles published up to March 2016. The key words used in this study were: ''ctx osteonecrosis or ctx bisphosphonates''.

The studies were first classified according to the inclusion and exclusion criteria. After performing searches in the selected databases, a careful analysis was performed to identify any cases of disagreement between the authors. Studies were selected based on their titles and abstracts and assessed against the inclusion and exclusion criteria. After the first selection stage, the selected articles were analyzed based on their full content.

To complement this review, a search of the grey literature was performed. Furthermore, a manual search in the following specific journals was carried out: *Bone*, *International Journal of Oral and Maxillofacial Surgery*, *Journal of Bone and Mineral Research*, *Journal of Oral and Maxillofacial Surgery*, *Oral Oncology, Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics*, *Osteoporosis International*, *The Journal of Cranio-Maxillo-Facial Surgery*.

Risk of bias and additional analyses

The quality of the selected studies was determined according to their level of evidence, as proposed by the National Health and Medical Research Council of Australia.[20] The kappa (κ) test was used to verify the level of inter-examiner agreement for the process of inclusion of articles from the databases evaluated. Two researchers (K.J.D.P. and C.A.A.L.) performed the article selection process independently, and an inter-examiner agreement test was applied to assess the degree of agreement in each situation analyzed. Any disagreements were resolved by discussion and through consensus with all authors. The agreement for articles selected from the PubMed/MEDLINE databases was $\kappa = 0.88$, and for those from Web of Science and the Cochrane databases was $\kappa = 1.00$, indicating a high level of agreement between the reviewers.[21]

Results

General outcomes and details of the search strategy are illustrated in the flowchart shown in Fig. 1. The searches performed in the databases led to the retrieval of 542 articles in total: 270 from PubMed/MEDLINE, 216 from Web of Science, and 56 from the Cochrane Library. After the removal of 186 duplicate articles, 356 studies were selected for analysis based on their title and abstract, and in accordance with the inclusion and exclusion criteria. This process yielded 13 studies for full-text examination. Following the full-text review, five studies were excluded as they failed to meet the inclusion criteria.[12,13,22–24] Thus, eight studies were analyzed and form the basis of this review.[14–16,25–29]

All eight of the selected studies were prospective clinical trials. They included a total of 1442 patients with a mean age of 66.7 years. Females were more affected (78.3%) than males (21.7%). The number of patients developing BRONJ was reported in seven articles; only 24 (1.7%) of the 1392 patients evaluated after taking bisphosphonates developed BRONJ. The most prescribed drug was oral alendronate, whilst the most prevalent disease requiring the prescription of bisphosphonates was osteoporosis, corresponding to 95.7% of cases.