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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.

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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.

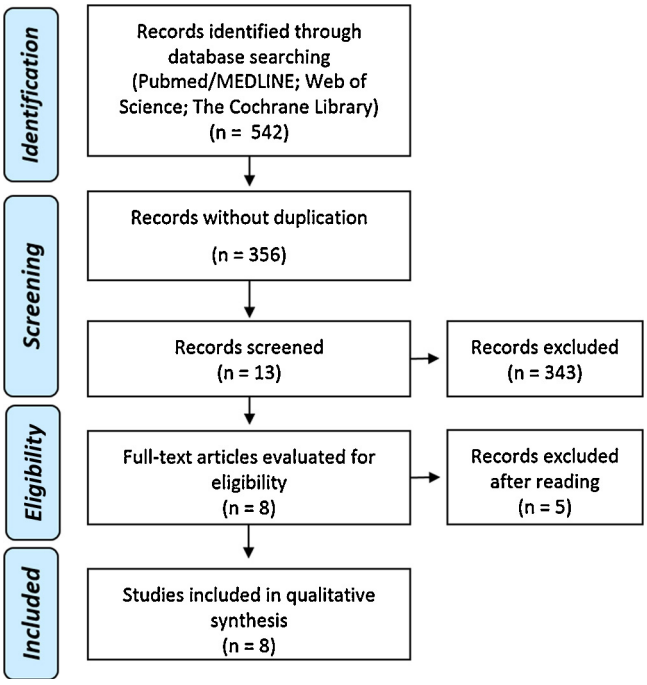

Fig. 1. Flow diagram of the literature search and results.

The most common surgical procedure associated with the triggering of BRONJ was tooth extraction, corresponding to 100% of cases (Table 1).

All eight selected studies (100%) found no direct correlation between CTX levels and the risk of developing BRONJ.[14–16,25–29] All studies had a level of evidence of III-2 (Table 2).

Discussion

The degradation of type I collagen by osteoclasts leads to the release of CTX, which can thus be used as a marker of bone turnover. Therefore, on suppression of bone turnover, CTX levels tend to decrease.[11] However, this systematic review showed that there is no evidence to support the examination of CTX levels as being effective in assessing the risk of development of BRONJ.

It has been proposed that measuring serum CTX levels represents a satisfactory assessment of the risk of oral BRONJ developing. Serum CTX levels of more than 150 pg/ml are associated with a low risk, levels of 100 to 150 pg/ml with a

Table 1. Characteristics of the studies included in the review.

Authors and year	Study design	Number of patients/ sex	Type of bisphosphonate	Mean duration of medication use	Bone disease	Route of administration	Surgical procedures
Hutcheson et al.[14] 2014	Prospective	F 727 M 223	Alendronate 560 Risedronate 373 Other combinations 17	NR	Osteoporosis 950	Oral 950	Extraction 2461
Migliorati et al.[15] 2013	Prospective	F 43 M 10	NR	60 months	Osteoporosis 40 Bone metastasis 13	Oral 32 IV 13	Extraction 53
O'Connell et al.[16] 2012	Prospective	F 22 M 1	Alendronate 19 Risedronate 2 Zoledronate 2	30 months	Osteoporosis 19 Osteopaenia 2 Multiple myeloma 1 Breast cancer 1	Oral 21 IV 2	Extraction 23
Flichy-Fernández et al.[25] 2012	Prospective	F 49 M 1	Alendronate 29 Risedronate 14 Ibandronate 3 Other combinations 4	42 months	NR	Oral 50	Dental implant 50
Carini et al.[26] 2012	Prospective	12	Alendronate 8 Risedronate 3 Ibandronate 1	NR	NR	Oral 12	Extraction 18 Dental cleaning 2
Lazarovici et al.[27] 2010	Prospective	F 63 M 15	Alendronate 44 Risedronate 3 Zoledronic 10 Pamidronate 10 Other combinations 11	40 months	Osteoporosis 51 Breast carcinoma 15 Multiple myeloma 10 Prostate carcinoma 1 Neurogenic carcinoma 1	Oral 51 IV 27	Extraction 74 Dental implant 1 Tooth apicectomy 1 Cyst enucleation 1 Closure of an oroantral fistula 1
Lee and Suzuki[28] 2010	Prospective	F 51 M 3	Alendronate 33 Risedronate 21	NR	Osteoporosis Osteopaenia	NR	Extraction 91 Implants 14 Sinus lift grafting 2 Bone grafts 4 Torus removal 3
Kunchur et al.[29] 2009	Prospective	F 165 M 57	Alendronate 139 Risedronate 76 Pamidronate 6 Zoledronate 1	38.7 months	Osteoporosis 209 Paget disease 5 Bone metastasis 3 Multiple myeloma 5	Oral 215 IV 7	Extraction 201 Other treatments 21

F, female; M, male; NR, not reported; IV, intravenous.

Table 2. Characteristics and values of the C-terminal telopeptide test in the studies included in the review.

Author	Mean value of CTX, pg/ml	Patients with CTX level <150 pg/ml	Patients developing BRONJ	Prediction of CTX	Level of evidence[a]	Follow-up
Hutcheson et al.[14]	NR	181	4	Negative	III-2	NR
Migliorati et al.[15]	202	NR	1	Negative	III-2	NR
O'Connell et al.[16]	180	11	0	Negative	III-2	3 to 11 months
Flichy-Fernández et al.[25]	NR	NR	NR	Negative	III-2	NR
Carini et al.[26]	286.9	NR	0	Negative	III-2	18 months
Lazarovici et al.[27]	282	15	18	Negative	III-2	2 months
Lee and Suzuki[28]	160.7	26	0	Negative	III-2	1 week to 2 months
Kunchur et al.[29]	283.5	82	1	Negative	III-2	NR

CTX, C-terminal telopeptide; BRONJ, bisphosphonate-related osteonecrosis of the jaw; NR, not reported.
[a] Levels of evidence were based on those of the National Health and Medical Research Council (NHMRC), Australia.

moderate risk, and levels of 100 pg/ml or less with a high risk of BRONJ developing after surgical procedures.[9,30] As regards CTX levels in control patients not treated with bisphosphonates, studies showed CTX levels above 150 pg/ml to be typical of healthy controls.[15,26]

Friedlander et al., in a systematic review, aimed to determine whether CTX levels of <150 pg/ml are associated with the development of post-extraction BRONJ in patients treated with oral bisphosphonates prior to undergoing oral surgery, and its association.[31] The authors selected only two studies and found that the CTX test featured both a high sensitivity and high specificity. They also highlighted the clinical importance of the test, as it allowed the identification of groups of patients at greatest risk of BRONJ, but not an absolute determination of the risk. However, the selected studies showed that patients with CTX levels below 150 pg/ml had normal healing after dentoalveolar surgery,[14,16,27–29] data that contradicted the authors conclusions.

It should be noted that the studies selected for the present review revealed a BRONJ prevalence of 1.7% in patients taking bisphosphonates. This value is similar to previously published data, showing a BRONJ occurrence rate varying between 0.8% and 12% in patients taking bisphosphonates intravenously and between 0.01% and 0.06% in patients taking them orally, with values increasing when patients undergo oral surgical procedures.[32]

The majority of the selected studies reported a small number of BRONJ cases. However, one study featured a higher number of patients who developed BRONJ.[27] This may be because that study included more patients with malignant disease who required increased intravenous administration of bisphosphonates. These data are consistent with the literature, which reports an increase in BRONJ risk in patients treated with intravenous bisphosphonates.[32,33] Furthermore, patients with bone metastases have an increased risk of developing BRONJ compared to those with osteoporosis, due to a higher inhibition of osteoclasts.[34] Moreover, as well as the prescription of bisphosphonates, comorbidities such as obesity,[3] diabetes, renal dialysis, anemia,[3,34] tobacco use,[34] and periodontal disease or periapical alterations[35] are associated with an increase in the risk of developing BRONJ.

Although all of the selected studies rejected the predictive efficacy of CTX, some reported that this examination is useful clinically and can be used to identify patients at increased risk of BRONJ,[14,16,26,27,29] allowing an appropriate treatment plan to be made,[26] and indicating those who may be candidates for a drug holiday before surgical procedures.[14,29] According to Marx et al., the rate of increase in CTX levels is 25.9 pg/ml per month following the cessation of bisphosphonates.[9] Thus, the drug should be discontinued until the CTX level exceeds a value of 150 pg/ml.

Another observation is that CTX levels do not correlate with the number and size of lesions in patients with already established BRONJ. Even in those patients with areas of osteonecrosis, CTX test values were found to be within the normal range.[22,36]

Alendronate was the most prescribed drug in the selected studies,[14,16,25–29] with the exception of one study that did not report the prescribed drugs.[15] Alendronate is a good choice for the treatment of osteoporosis.[37] Studies in the literature suggest that this drug is related to a potential risk of osteonecrosis.[1,3] In one study, CTX levels were lower in patients taking alendronate.[29] Hutcheson et al. reported that the patients who developed BRONJ had been taking alendronate orally.[14] However, in the other studies, even those patients taking alendronate did not develop BRONJ.[16,26,28]

The intravenous administration of bisphosphonates is associated with an increased risk of BRONJ.[27,32,33] However, one study observed that the mean CTX values did not differ significantly between the routes of drug administration (oral or intravenous).[29] Some studies have reported that longer durations of bisphosphonate treatment increase the risk of the appearance of BRONJ.[3,33] In contrast, Migliorati et al. reported that patients taking bisphosphonates for 60 months had a mean CTX value of 202 pg/ml,[15] whilst O'Connell et al. reported that patients treated with bisphosphonates for 30 months had a mean CTX value of 180 pg/ml,[16] very similar values despite the marked difference in drug exposure. Thus, the length of treatment does not appear to result in differences in CTX levels.

The prevalence of female patients and the high mean age may be related to postmenopausal hormonal changes, as the associated decline in oestrogen levels is a major cause of osteoporosis.[37,38]

Only prospective studies were considered in this systematic review; retrospective studies were excluded in order to reduce the level of bias. However, the results should be interpreted with caution because of the absence of randomized controlled trials. Thus, it is recommended that controlled and randomized clinical studies be carried out in order to reach a more definitive conclusion on the utility of the CTX test. In conclusion, this systematic review indicates that the CTX test has no predictive ability to detect the risk of osteonecrosis in patients taking bisphosphonates.

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Competing interests

The authors declare that there was no conflict of interest in the elaboration of this study.

Ethical approval

Not applicable.

Patient consent

Not applicable.

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