# Qualitative and quantitative analysis of the CTX in relation to the period of intake of bisphosphonates: A systematic review

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**The aim of this systematic review was to determinate the true value of C-terminal cross-linking telopeptide test (CTX) in patient who takes Bisphosphonate. A comprehensive search of studies published up to March 2020 and listed in the PubMed/MEDLINE and Cochrane Library databases, was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search identified 99 publications; 6 studies were finally deemed eligible for inclusion according to the study criteria. These studies included a total 104 patients and was selected 101. The CTX value in the various study groups is less than 150 pg/ml. There is a difference between the age of the patient and the period of taking the drug. This systematic review indicates that the CTX test has diffent predictive value in determining the risk of osteonecrosis in patients taking bisphosphonate compared to previus standard.**

Osteonecrosis of the jaws is one of the most common complications in patients taking bisphosphonates, these drugs are taken to avoid metastasis or multiple myeloma. They are also taken in patients with osteoporosis (1-2). The use of bisphosphonates (BPs) as drugs for the treatment of bone pathologies originates from a discovery in the early 1960s which was due to Neuman and Fleisch (1961), who while studying the calcification mechanism induced by collagen, realized that organic fluids such as plasma or urine contained calcification inhibitors. Specifically, they showed how inorganic pyrophosphate, present in serum and urine, could prevent calcification by binding the forming hydroxyapatite crystals (3). The first descriptions of bisphosphonate-related osteonecrosis of the jaw (BRONJ) were reported in 2003 by Marx (4). A wide-range study on osteonecrosis indicates an incidence of BRONJ between 0 to 27.5%, relevant for individuals subjected to intravenous amino-bisphosphonates with an average incidence of 7% (5). The American Association of Oral and Maxillofacial Surgeons (AAOMS) define BRONJ as an exposed or probeable bone in the maxillofacial region without resolution for longer than 8 weeks in patients treated with an antiresorptive or an antiangiogenic agent who have not received radiation therapy to the jaws (6). Osteonecrosis of the jaw bones is a disabling necrotizing pathology with a progressive nature and with a low tendency to heal, which affects only the maxilla in 68% of cases, the jaw in 28% and both bones in 4% of cases. The mandible is more commonly affected than the maxilla (2:1 ratio), and 60% of cases are preceded by a dental surgical procedure (7).

A lot of types of bacteria (8) have been isolated, generally belonging to the resident flora of the oral cavity and germs commonly isolated in periodontal diseases and dental abscesses (9). Among these the most common one is Actinomyces. Spontaneous

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or provoked bleeding is possible. It has a tendency to extend to adjoining regions (10), such as (a) the skin (with secreting skin fistulas), (b) the mandibular canal, (c) the maxillary sinuses, (d) the pterygo-palatine fossa, (e) the oral floor and (f) the submandibular regions.

The selectivity for the jaw has been studied but we still do not have a specific cause but we have added many theories at this point still equally useful: (i) physiologically higher bone turnover of the jaws compared to the remaining skeleton (11) (ii) terminal vascularization of the jaw (12) (iii) presence of a thin mucoperiosteal coating to protect the underlying bone tissue, easily subject to traumatism (11) (iv) peculiar biofilm, microflora of the oral cavity (13) (v).

There is general consensus that dento-alveolar surgery and simple tooth extractions are the most significant risk factors associated with osteonecrosis in cancer patients taking anti-resorption drugs (14). Implant placement in cancer patients (15) is considered a potential trigger for osteonecrosis, although the true risk has not yet been assessed. Dental and periodontal infection significantly increases the risk of osteonecrosis in cancer patients undergoing anti-resorptive therapy.

Indeed, periodontal disease was diagnosed in 84% of cases (16) in a large sample of patients with osteonecrosis. However, periodontal disease is commonly observed in the general population aged> 40 years, which may represent a confounding factor in the epidemiological association assessment.

The first clinical manifestations of osteonecrosis are characterized by unexposed alveolar bone necrosis which can mimic clinical and radiological manifestations (17) of periodontitis (tooth mobility, bone loss, loss of attachment and presence of pus), which can lead to incorrect diagnoses and overestimation of the association between osteonecrosis and periodontitis.

There are many factors influencing the onset of BRONJ: i) ADMINISTRATED DRUGS, in hematological and oncological patients, zoledronic acid appears to carry a statistically higher risk of ONJ than pamidronate. Insufficient data do not allow a definitive comparison with ibandronate (17-18) although it appears to be low risk, Clodronate is associated with a lower risk of ONJ than zoledronic acid ii) TYPE OF ADMINISTRATION (IV or OS): there is a higher risk with regard to intravenous intake especially of amino-bisphosphonates (14) this factor can be closely related to their prevalent use in patients with cancer, iii) DURATION OF INTRAVENOUS N-BP TREATMENT: on average, patients with ONJ were treated for longer periods than those without ONJ. The duration of intravenous treatment with N-BP is generally related to the total dose of drug administered. In a recent literature review, the mean / minimum time for the onset of ONJ was 1.8 years and 10 months (19) iv) COMBINED THERAPY WITH OTHER DRUGS: the combined use of the latest generation antiangiogenic agents and N-BP has recently been associated with an increased risk of developing ON (14). v) INDIVIDUAL GENETIC FACTORS: the largest study currently conducted (n = 94 ONJ cases) suggests that class II MHC polymorphisms is a genetic risk factor related to the development of ONJ (20) vi) BONE MINERALIZATION DISORDERS: a single study demonstrated the possible contributing effect of secondary hyperparathyroidism after administration of BP to the development of ONJ (21).Recently, a strong association between osteomalacia and ONJ was identified and the potential triggering effect of vitamin D deficiency on secondary hyperparathyroidism and bone mineralization defects has already been demonstrated in animal models and is currently being studied (22) Marx, in 2007, suggested the use of the "C-terminal cross-linking telopeptide" (CTX) as an indicator of BRONJ risk. The C-terminal telopeptide of collagen type 1 (CTx) is a marker of bone resorption. It is a peptide fragment that is formed starting from the C-terminal end of the proteins forming the bone matrix. Marx analyzes the CTX value of 30 patients with BRONJ. The authors reported that a value less than 100 pg / ml represented a high risk of BRONJ; from 100 to 150 pg / ml a moderate risk; higher than 150 pg / ml minimum or no risk. There are many studies that refute Marx's theory of CTX.

The aim of this prospective study was to determinate the efficacy of CTX test to prevent the development of BRONJ.

## MATERIALS AND METHODS

This systematic review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23]. The following inclusion criteria were applied:

a) randomized controlled trial or prospective study or retrospective study; b) performance of the CTX test for each patient include in the study; c) study with more than five patients; d) patients taking oral and/or intravenous bisphosphonates; e) study with number list of patients; f) that include the period of taking the drug; and g) that include the sex and the age of the patients.

The following exclusion criteria were applied: i) studies with patients who had received radiotherapy to the head and neck region; ii) single case reports; iii) no presence of age or sex; iv) study with CTX average; v) drug not specified; and vi) period of taking a drug not specified.

The PICOS Table I (patients, intervention, comparator, outcomes, study design) question recommended in the PRISMA statement was defined as follows: 1) population: patients taking bisphosphores; 2) intervention: assess the level of CTX based on the hiring period; 3) comparison: standar values of CTX; 4) outcome: analyze in relation to type of intake if the CTX is affected by the period of taking a drug; and 5) study design: randomized controlled trial or prospective study or retrospective study.

The author performed the selection of articles. Searches were performed in the PubMed/MEDLINE and Cochrane Library databases for articles published up to January 2020. The key words used in this study were: *"ctx & osteonecrosis"*. 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. The research strategy was according to PRISMA (Fig. 1.).

## RESULTS

The keyword research provides 80 results on PubMed / MEDLINE and 19 on The Cochrane Library, for a total of 99 articles. Of these 99 articles 8 was duplicates, so total selected articles were 91. Studies were selected for analysis based on their title and abstract, and in accordance with the inclusion

**Table I**. *PICOS=patients, intervention, comparator, outcomes, study design.*

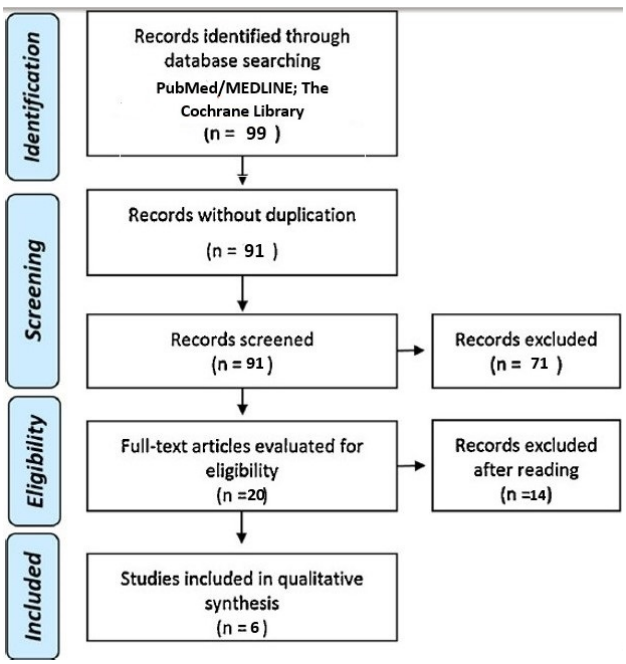


**Fig. 1.** *PRISMA flowchart.*

| | |
|---|---|
| **P** | PATIENTS TAKING BPs |
| **I** | Assess the level of CTX based on the hiring period |
| **C** | comparison with standard values (Marx RE 2007) |
| **O** | analyze the ctx value and the change in value |
| **S** | randomized controlled trial or prospective study or retrospective study |

and exclusion criteria. This process produced 20 studies for full text examination. Following the full-text review, 14 studies were excluded as they failed to meet the inclusion criteria. Thus, 6 studies were analyzed that form the basis of this review (Table II). From these 6 studies 104 patients were listed, of these 3 were excluded because the CTX value = 0 pg/ml or > 1000 pg/ml. The average CTX values was 126 pg / ml on the total of 101 patients, the average intake period is 50.3 months. The most common drug is ALENDRONATE taken by 88 patients, RISENDRONATE is taken by 8 patients, the intake of intravenous drugs is present in 7 patients, respectively 6 ZOLEDRONIC ACID and 1 PAMIDRONATE. The included studies run from 2007 to 2016, there are no recent studies that have included a list of patients with unique CTX values. 5 studies are prospective and only one is retrospective.

The author most involved in these studies is Yong-Dae Kwon, Director of Catholic Institute for Healthcare Management/Professor (2009, 2011 and 2016), the other studies are conducted by O'Connell conduced in Dublin at a University-based oral and maxillafacial surgery (24) in 2012, Kunchur professor of Plastic and Reconstructive Surgery in Australia, in 2009, Marx, Professor of Surgery and Chief in Miami, in 2007.

## DISCUSSION

There are many variables associated with CTX assessment, in the study of CTX and PIMP assessment (31) we know how the variables that influence blood sampling are many and although not having a lot of power alone in association they can modify the evaluation.

First of all, it would be the case to standardize the time and the modalities of the blood sampling. Among the most important factors we certainly have

**Table II.** *List of studies analysed in this review.*

| AUTHOR | NUMBER PATIENS/ SEX (M/F) | AGE | TYPE OF DRUGS | INTAKE PERIOD | CTX VALUE |
|---|---|---|---|---|---|
| O'Connell et al[25] | 22/1 | 59 (± 9.68) | 19alendronate 2zoledronic acid IV 2risendronate | 30,39 (± 16.40) | 180(± 94.0) |
| Kwon et al[26] | 0/9 | 76,6 (± 9.36) | 6 alendronate 2risendronate 1 zoledronic acid IV | 38 (± 33) | 84 (± 36.7) |
| Kunchur et al[27] | 8/4 | 72,9 (± 10.20) | 6 alendronate 2risendronate 4 zoledronic acid IV | 51,25 (± 39.7) | 210(± 127) |
| Kwon et al[28] | 16/2 | 74,3 (± 6.8) | 17 alendronate 1 risendronate | 47.3 (± 25.2) | 111.7(± 74,2) |
| Marx et al[29] | 17/0 | 64.8 | 16 alendronate 1 risendronate | 79.1 (± 26.0) | 72.8(± 25.2) |
| Kwon et al[30] | 22/1 | 73,65(± 7.10) | 23 alendronate | 57.9(±31.3) | 93.1(± 49.4) |

the circadian rhythm, in fact we know that the CTX has high levels after midnight and low in the early afternoon (32), the power supply causes a decrease of about 20% of the circulating ctx, therefore it underestimates the value (33).

Age and sex are high impact variables, we know that ctx is high in childhood, decreased in early school age and then increased during puberty (34-35), the period in which it is lowest in men is in the fifth decade , fourth decade in women and then fluctuations in menopause (36), for men instead there is the possibility after 70 years of an increase in the value of CTX or at most of a constant trend (37).

The woman's state of menopause is also of great importance, in the post-menopausal phase the CTX increases (38). A study conducted in Spain (39) describe that CTX is closely related to hormones, in fact in this study conducted on women aged between 16 and 25, divided into two groups, one that does not take contraceptives oral and a group that takes it, it is clear that those who take the drug have a lower level of CTX.

Also, the Osteoporosis in correlated with hormones, it is estimated that osteoporosis affects around 5,000.000 people in Italy, 80% are postmenopausal women. (Italian ministry of Health). A study on 17251 patients conducted by the "International Osteoporosis Foundation and European Calcified Tissue Society Working Group" (40) found that after 3 months of taking bisphosphonates the CTX drops significantly, the alendronate on average causes a decrease in the CTX of 73%, l 'Ibadronato of 81% and Risedronate of 68%. Marx describes the variation of the ctx after a 6-month drug holiday, 17 patients are taken as the object of study, the average of their CTX is 71.2 pg / ml, after 6 months it is 231 pg / ml.

In this systematic review we try to indicate the parameters for standardize the CTX value. In a first investigation Table 4, the patients (84) were divided into groups by age and by the period of taking the drug, the age groups are ≤59 years, 60-69 years, 70-79 years and 80-89 years, the period of taking the drug is <36 months and ≥36 months. The investigation shows that only two groups have a CTX> 150 pg / ml and for both groups the common discriminant is an intake of less than 3 years. For the other groups the value is less than 150. Of these patients we do not know how many have osteonecrosis and how many, however the value of 150 pg / ml is not considered a correct parameter for this evaluation as a discriminant. The sample is small, but the data shown indicate that only two groups have value of CTX >150 pg/ml, so we could hardly ever perform low-risk surgery. In the first two groups (< 59 years, 60-69 years) that have a similar population, we see that subjects who have been taking the drug for less than 36 months have higher CTX values than those who have been taking the drug for more than 36 months.

A second investigation Table 5 (101 patients) instead related the period of taking the drug, regardless of the age of the subject or sex, the results are divided into <20 months, 20-39 months, 40-59 months, 60 -79 months, 80-99 months,> 100 months. Only the first group shows a ctx > 150 pg/ml, all the others have a lower value. The results obtained in this study show us that only one group has a CTX value with minimal risk, all the others are instead at medium risk; moreover, we are confirmed that at low risk there are those who have been taking the drug for relatively little time, of course the standard deviation has also been included because the values have a fair oscillation. The previously cited research showed that it was still only 3 months from the start of tak-

**Table III.** *CTX value in relation to age and intake period.*

| **AGE(years)** | **<59 ( 13F/ 1M)** | | **60-69 (20F/ 6M)** | | **70-79 (22F/ 6M)** | | **80-89 (13F/ 6M)** | |
|---|---|---|---|---|---|---|---|---|
| **INTAKE PERIOD (years)** | <3 anni (8) | >3 anni (6) | <3 (14) | >3 (12) | <3 (4) | >3 (24) | <3 (4) | >3 (15) |
| **CTX (pg/ml)** | 176 | 131 | 137 | 122 | 97 | 120 | 203 | 138 |

ing the drug to have a high decrease in the CTX value. However, it can be noted that the decrease is not constant but settles in all the other groups, remaining in the range of 101 pg / ml to 134 pg / ml with an average of 114 pg / ml.

The last study table 6 have a low-quality relevance, that because we have a small sample size, we also assessed how the parameter is influenced by the type of drug. The drugs as mentioned are ALENDRONATE (88 patients), RISENDRONATE (7), ZOLEDRONIC ACID (6).

It's difficult to critically analyze these data, the samples are very disproportionate to each other, not only as regards the number of subjects but also as regards the intake period. In the case of zoledronic acid the intake period is 27 months on average, for alendronate 53 and Risedronate 37, they are also different drugs that have different power of action and mode of intake (41). Despite this we see that by setting an ideal parameter of CTX before administration of the drug, common to all subjects and related to the period of intake and the potency of the drug, the data obtained are the expected ones, as zoledronic acid is the more powerful but it is taken for less time, compared to Risedronate which has an average power between the three drugs taken into consideration but taken for longer and alendronate which is the least powerful, 10 times less than Risedronate and 100 times less than zoledronic acid (42-43).

CTX is one of the few parameters that has not been absolutely excluded to assess the risk of osteonecrosis associated with bisphosphonate drugs, in the evolution of the studies certain bone markers have been introduced and subsequently eliminated.

In the literature, however, there are no articles confirming the usefulness of CTX, in the systematic review of Del Prà made in 2017 it is stated that CTX does not have a predictive value, the review is based on a total of 1447 patients and after the evaluation of the CTX, which considered the parameters imposed by Marx as reference parameters, saw the development of the pathology of osteonecrosis in only 24 patients, corresponding to 1.7%.

Another systematic review conducted by Awad in 2019, gives us an idea about the test itself stating that the sensitivity of the CTX test, considering a value greater than 150 pg/ml as a positive value, is 34.26%, while the sensitivity of the test is 77.08%. At the conclusion of this study it is therefore stated that the use of CTX before dental procedures is unjustified and that the value greater than 150 pg / ml is not predictive for determining the development

**Table IV.** *CTX value in relation to intake period.*

| INTAKE PERIOD in months (patients number) | CTX | STD DEV |
|---|---|---|
| **<20 (15)** | 177 | 132,7064 |
| **20-39 (34)** | 119 | 99,99702 |
| **40-59 (15)** | 103 | 133,0314 |
| **60-79 (16)** | 134 | 123,019 |
| **80-99 (9)** | 101 | 149,3557 |
| **>100 (12)** | 116 | 134,9194 |

**Table V.** *CTX value in relation to type of drug.*

| DRUG | CTX (pg/dl) | DEV STD |
|---|---|---|
| **ZOLEDRONIC ACID** | 145 | 114,5059 |
| **ALENDRONATE** | 124 | 84,11 |
| **RISENDRONATE** | 89 | 87,77813 |

of osteonecrosis. The study says that you must start looking for new markers.

The results obtained show us that the value of 150 pg / ml is in fact disproportionate, since it is difficult to find patients with higher values and above all it is impossible to think that for lower values, we would always encounter osteonecrosis (43-51).

The study carried out must necessarily be in-depth and must necessarily concern a larger sample but invites to formulate values in relation to more stringent parameters, considering not only the drug but also the age of the subject and the period of intake in the first place.

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