

# Fibrin Rich in Leukocytes and Platelets (L-PRF) and Bisphosphonate-Induced Osteonecrosis: We Need to Advertise Now

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## ABSTRACT

The American Association of Oral and Maxillofacial Surgeons (AAOMS) reported in 2004 a new pathology that causes osteonecrosis in the Maxillomandibular complex. The condition was named Bisphosphonate-related osteonecrosis of the jaw (BRONJ), and later renamed by medication related to jaw osteonecrosis due to the appearance of severe alveolar bone loss in the Maxillomandibular complex resulting from the use of different drugs other than Bisphosphonates. Odontology, especially oral surgery, a field concerned with new biotechnologies, has been introducing innovations in tissue engineering. Oro-maxillofacial reconstruction is of great interest to current oral and maxillofacial surgeons, as part of the search for strategies in bioengineering and biomaterials, a major promoter of bio-dental research in our times. In order to verify the scientific evidences to analyse the effectiveness of leukocyte and platelet rich fibrin (L-PRF) on bone neoformation in Maxillomandibular complex's surgical procedures, a search for qualified articles was conducted in the Medline (PubMed), Embase and Cochrane Central Register of Controlled Trials databases. The works analysed were published from 2013 to 2018. This review concludes that the use of platelet rich fibrin (L-PRF) is significant in the complete healing of the lesion in short postoperative periods and in the resolution of the treatments, reducing the need for postoperative re-interventions, resulting in lower morbidity for the patients.

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## Introduction

Bisphosphonates are synthetic pharmacological substances that have high affinity for hydroxyapatite, analogous to pyrophosphates – a substance present in the bone matrix naturally – which act as anti-remodelling agents, used for treatments of metabolic bone diseases such as cancerous complications of bone metastases and in the prevention of osteoporosis<sup>1,2</sup>. They are medicament widely prescribed and widely used for the treatment of osteoporosis and other chronic bone diseases; these synthetic agents have great

affinity for calcium, acting on osteoclasts and osteoblasts, decreasing bone remodelling and inhibiting mediators of inflammation, decreasing bone turnover, altering the mechanism of bone tissue<sup>3,4</sup>.

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a complication caused by bisphosphonate therapy, which causes progressive bone destruction in the maxillofacial region<sup>5</sup>. The lesion is characterized by necrotic, avascular

bone in the maxillofacial area, exposed or not to the buccal environment and persists for more than eight weeks in patients who did not present oral cancer or history of previous radiation therapies in the craniofacial region<sup>6</sup>.

The first cases of BRONJ were described by Marx in 2003, detailing 36 cases of bone exposure in the oral cavity in patients undergoing intravenous use with bisphosphonates in cancer therapy<sup>7</sup>; whereas in 2004, Ruggiero observed 63 cases of Osteonecrosis in the oral cavity with a history of chronic therapy with bisphosphonates.<sup>8</sup> In 2006, several studies on BRONJ were reported<sup>9-11</sup>; since then several professionals identified and demonstrated how to manage the illness, based on their empirical experience and opinions<sup>12-14</sup>.

According to *American Association of Oral and Maxillofacial Surgeons, Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw*, patients must be diagnosed as suffering from BRONJ if all the following conditions are present: 1) current or previous treatment with bisphosphonates; 2) bone exposed in the maxillofacial region, persistent for more than 8 weeks; and 3) no history of radiation therapy for the jaw region. BRONJ may be asymptomatic or exhibit symptoms such as pain, oedema, dental loss and altered sensation (Figure 1)<sup>15,16</sup>.

Besides bisphosphonates, other medicaments have been associated with Osteonecrosis in the maxillofacial region, such as denosumab, bevacizumab, cabozantinib and sunitinib (AAOMS, 2004). As a result of that, the condition was then renamed Medication-related osteonecrosis of the jaw (MRONJ)<sup>15</sup>.

MRONJ, as a challenging complication related to the use of antiresorptive drugs, does not affect only the alveolar bone of the oral cavity, but also has presented oral mucosal loss in most patients with the disease, thus suggesting an adverse effect on the soft tissues of the oral cavity<sup>17</sup>.

MRONJ affects dramatically the patients' quality of life, thus justifying to actively seeking prevention in the risky cases<sup>18</sup>. Several clinical guidelines recommend discontinuation for a period of 3 months before being submitted to dental surgical procedures to patients who use these drugs as systemic therapy<sup>14</sup>. However, other guidelines do not concur that the interruption for a short period of time of antiresorptive medications should decrease the risk of Osteonecrosis in maxillofacial region<sup>19</sup>.

Factors associated with increased MRONJ risk are the following: (a) the potency of the drug used, (b) prolonged use of the drug, (c) advanced age and (d) history of inflammatory disease in the oral cavity<sup>14</sup>. Ruggiero suggests that patients who require antireabsorption therapy should undergo a thorough review with a specific health care provider to assess their oral health for dental extractions or other oral surgical procedures prior to initiating bisphosphonate or similar therapy<sup>14-16</sup>.

To date, there is still no standard protocol for MRONJ surgical treatment, which has been done empirically according to the clinical and radiographic evaluation of each professional<sup>20,21</sup>.

Conventional treatment is indicated for cases in the initial stages of the disease (Stage I). As for severe cases (Stage II,

III), surgery for resection of necrotic tissue and curettage is necessary. The AAOMS *classification of MRONJ*<sup>22,23</sup> is as follows: Stage 1- Exposed and necrotic bone or fistula, asymptomatic patient with or without infection; Stage II - Exposed and necrotic bone or fistulas associated with infection and pain, erythema in exposed bone region, with or without draining purulent secretion; Stage III - Exposed necrotic bone or fistula extending beyond the alveolar bone region and patient with pain, infection, and presence of one or more of the complications: pathological fracture, extra oral fistula, oro-antral or oro-nasal communication, osteolysis extending on the edge of the mandible or maxillary sinus (Figure 1).

Complementary treatments to surgery - such as laser therapy, Ozonotherapy, hyperbaric oxygen therapy and autologous platelet concentrates - have been used to improve the healing of bone and epithelial tissue, reducing lesion recurrence<sup>21-24</sup>.

In 1998 Marx reported for the first time in history the use of platelet rich plasma (PRP) to promote improvement in wound healing in the maxillofacial region<sup>25</sup>. Since then, several clinical reports have related the efficacy of the use of autologous platelet concentrates for the treatment and prevention of MRONJ<sup>26-28</sup>. Plasma platelet rich (PRP) showed promising results in the acceleration of soft tissue healing and bone regeneration in several studies in which the use of platelet concentrates has become popular<sup>29-31</sup>.

Faced with such evidence, Choukroun et al., developed the Fibrin Rich in Leukocytes and Platelets (L-PRF), the second generation of platelet immune concentrate, which represents a new biotechnology to stimulate bone regeneration and speed up the healing of soft tissues, because the PRF membrane forms a physical barrier against microorganisms, thus protecting the surgical wound from further contamination of the surgical site<sup>32,33</sup>.

Researchers use the term PRF, however L-PRF is more appropriate because it highlights the importance of leukocytes within the platelet concentrate<sup>34</sup>. Fibrin rich in leukocytes and platelets (L-PRF) is the most recently used method of blood concentrates. It allows a natural coagulation process without addition of chemical agents, unlike the process to obtain PRP<sup>35</sup>.

Furthermore, unlike PRP, L-PRF dissolves slowly after use, keeping it stable for a longer period of time, preserving the fibrin mesh, allowing longer cytokine life and a higher concentration of platelets, leukocytes, circulating stem cells incorporated within the physiological matrix of fibrin. Consequently, growth factors are allowed to be released more slowly at the surgical site, persisting for a longer time during wound cicatrization, from 7 to 28 days<sup>35,36</sup>.

L-PRF has been described as "*an immune and platelet concentrate in a single fibrin membrane, containing all constituents of the blood sample favourable for healing and immunity*"<sup>37</sup>.

The leukocytes present within L-PRF play a role as an anti-infective action, immunological regulation, ability to produce a great number of vascular endothelial growth factors (VEGF), which has caught the interest and curiosity of researchers<sup>38,39</sup>.

Taking into account the above considerations, it is important to further research whether L-PRF is effective in the treatment of MRONJ, stimulating the natural biological process of healing and tissue regeneration, compared to previous procedures related in the current literature. Consequently, the present article endeavours to review the relevant literature in order to evaluate the effect of L-PRF as a new biotechnology for the treatment of MRONJ.

## Methods

A digital search was performed for relevant work in the Cochrane-Library (Cochrane), MEDLINE/Pub Med, Scopus and Embase databases, with no date or language limitation, articles dating from the year 2013 to September of 2018, related to the key words: "*leukocyte and platelet-rich fibrin, L-PRF, platelet-rich fibrin, bisphosphonate-associated osteonecrosis of the jaw, bisphosphonate-associated osteonecrosis, bisphosphonate related osteonecrosis of the jaw*".

Also, the search for new works was carried out in the references section of the selected articles (cross reference). The last article search was conducted in September 2018.

The search was limited to articles written in English. The studies that fulfilled the inclusion criteria were evaluated for the methodological quality with criterion methodology and the use of the JADAD scale due to the heterogeneity of the studies (Table 1). To be included, the studies had to report the results of surgical procedures performed in patients with MRONJ therapies, to whom L-PRF was the complementary therapy chosen for adjuvant use. Only studies that involved human patients were included in the review.

There were limitations regarding the size of the sample. The studies reported which anti-resorptive medications were used; stages of the disease and affected areas in the maxillofacial region. The resolution of the treatments had clear definitions to consider success of the procedure performed. Exclusion criteria were history of radiation therapy to the head and neck, oral cancer and treatments performed with other blood concentrates other than L-PRF or PRF.

The process of searching and sorting the articles was done by analysing the title and summary of each study. Those studies that did not meet the inclusion criteria of this review were excluded. The articles pertaining to the inclusion criteria were examined by two independent researchers, with a third party in case of disagreement regarding the inclusion of studies in the present review. Despite the inheritance found about the type of studies, those who addressed the topic directly and in a clear and concise manner were selected for the data analysis and included in the research.

The following data, when present, were extracted from the included studies: author / date, related disease, study follow-up period, number of patients treated, average age and gender, type of medication used, time of therapy, route of administration, type of surgical procedure performed, follow-up and resolution.

All patients in the articles studied were on therapy or would have been treated with antireabsorbable agents, had exposed bone in the maxillofacial region persistent for more

than 8 weeks and confirmed destruction of bone lesion radiographically or clinically, which required surgical intervention of accordance with AAOMS.

Stages of the lesion were verified according to the AAOMS clinical classification of MRONJ: Stage I: exposed and necrotic bone or fistula, asymptomatic patient with or without infection; Stage II: Necrotic and exposed bone or fistulas associated with infection and pain, erythema in exposed bone region, with or without draining purulent secretion; Stage III: Necrotic and exposed bone or fistula extending beyond the alveolar bone region and patient with pain, infection, and presence of one or more of the complications: pathological fracture, extra oral fistula, oro-antral or oronasal communication, osteolysis extending into the border of the mandible or maxillary sinus<sup>11</sup>.

## Results

Our literature review covered 14 studies in a total of 303 patients who had stage II or III of MRONJ – according to AAOMS classification – with necrotic bone exposure for more than 8 weeks and history of antireabsorption drug treatment, divided into maxilla and mandibles, women and men, average age of 60 years, who underwent bone necrotic tissue removal surgery, granulation tissue curettage, and L-PRF use as adjuvant to treatment.

The most commonly used drugs were Alendronate, Zoledronate, Bisphosphonates and Denosumab, with a treatment span of 2 to 10 years, and only two studies were of 6 to 8 months. Of the 14 studies, in the groups that used PRF or L-PRF in the treatment, 11 studies had a 100% total resolution index, 1 study had 93%, and 1 had a 77% brief total closure and 18% late closure, and 1 had 88% L-PRF and 96.7% with L-PRF + BPM2. In one of the studies, statistical analysis revealed  $p < 0.05$  in elimination of infection and rapid healing of the mucous membranes.

The publications related to the present literature review were published from 2013 to 2018, there was a predominance of studies in 2016 with six studies, 2013 with one study, 2014 with three studies, 2017 with two studies, and 2018 with 2 studies, in a total of 14 studies.

## Discussions

After careful consideration of the literature, it is observed that the risk of developing osteonecrosis of the mandible and its terrible consequences is still neglected by many physicians who use bisphosphonates to combat osteoporosis, as well as by dentists, who, for the most part, of the results of therapeutic failures when performing dental implants, especially in the elderly patient population<sup>8-10</sup>. Elderly patients and menopausal women who are more likely to have osteoporosis are not only affected by osteoporosis but also associated with the adverse effects of bisphosphonates, even in calcium replacement, demineralization<sup>17-9</sup>. In this group of patients, dental implant surgeries may not present the expected results, together with the risk of severe dental loss, implant losses, infections and other harmful consequences resulting from previously installed or ongoing mandibular necrosis<sup>21</sup>.

The present literature review aimed to catalogue evidence of the efficacy of PRF or L-PRF as adjuvant treatment for MRONJ. A universal protocol for MRONJ treatment is not yet

clearly defined, so there are several methods used, which makes it difficult to compare the studies proposed so far<sup>40-42</sup>.

The different types of treatments performed in studies reported in the literature to date for MRONJ treatment demonstrate a need for a standardized experimental design to better define the optimal treatment. The greatest concern regarding patients who may develop MRONJ is to maintain good oral hygiene, to perform dental treatments prior to the use of antireabsorbing drugs, to maintain the quality of life of the patient, to control pain and infection, and to prevent the appearance of new areas of necrosis<sup>6,20,39</sup>.

However, the use of L-PRF is a new, non-invasive and rapid alternative approach to managing bone exposure. L-PRF has been used as adjuvant therapy in the treatment of osteonecrosis which allows natural coagulation process<sup>43</sup>.

The results appear to be promising when compared to other techniques previously described as adjuvant to surgical therapy in stages II and III of the disease, since the surgical procedure can only compromise the outcome and do not present favourable conditions for the definitive end of therapy. L-PRF accelerates the healing of soft tissues, improving epithelial vascularisation and brief closure of the wound<sup>41,42</sup>.

According to the literature, MRONJ is associated with the inhibition of osteoclasts caused by the action of the antireabsorbing drug, presenting suppression of bone remodeling<sup>40,41</sup>, inhibition of angiogenesis<sup>42-45</sup> and direct toxicity in the buccal mucosa, being a hypothesis of pathophysiology of the disease<sup>45-48</sup>.

The present literature review had several limitations, especially a reduced number of randomized studies<sup>49-51</sup>. Amongst other limitations, 50% of the studies had small samples, consisting of one to two patients, two studies were comparative and two studies had a series of control patients<sup>52,53</sup>.

Because of the relatively recent pathology, when comparing bisphosphonates, calcium supply and replacement hormone therapy in the fight against osteoporosis and its comorbidities<sup>4-5</sup>. The present research presents some limitations on the quality of studies found and selected on the topic discussed, since most of them are non-randomized studies, with a reduced sample of patients, some of which are summarized only in case of reports, without peer selection or review, that is, with critical methodological biases<sup>43-47</sup>. However, the authors of this essay concluded that this type of discussion should be carried out to draw the attention of the scientific community to a severe health problem, still under diagnosed and therefore underreported<sup>21-23</sup>. Many professionals do not wish to publish their failures, and that in a very next, due to the aging of the world population can affect thousands of people who are included in the clinical characteristics addressed in this research. In addition to a social character, the other important objective of the present study was to alert multi-professional health teams to the rational use of these drugs, associated with active surveillance and, therefore, notification of this type of condition when it is digested<sup>35-37</sup>. Therefore, those other patients are not suffering or are surprised by therapeutic failures and severe health damages resulting from the consequent jaw necrosis<sup>1,2,49-51</sup>.

It has been observed that up to the present moment, there are not many studies in the relevant literature reporting the efficacy of PRF as a therapy for the treatment and prevention of MRONJ in patients taking osteoporosis medication, such as bisphosphonates and the likes<sup>18</sup>, most likely due to the fact that it is a recent illness and its proposed therapy is a rather new technology<sup>54,55</sup>.

### Conclusion

The use of L-PRF showed an expressive influence on the complete wound healing in short postoperative periods and in the resolution of treatments, drastically reducing the need for postoperative re-interventions, resulting in lower morbidity for patients. As they are presently commonly prescribed drugs, it is of great importance that the Dentist is aware when surgical interventions are necessary in patients who have or still use Bisphosphonates.

Based on the literature review and in the cases studied in the articles, it was concluded that L-PRF is considered a safe, fast and effective alternative method for the treatment of MRONJ. Further randomized and adequately planned controlled clinical trials with larger samples of the use of L-PRF in the treatment of MRONJ are necessary to confirm the effectiveness of the proposed treatment.

### Conflict of interest statement

Maria Faria, Eric Cabral, Wilkson Castro, Davidson Florentino, João Costa, Ricardo Pires, Fausto Guzen, Francisco Pinheiro, Amália Rêgo and Irami Filho declare that they have no conflict of interest.

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ITEMS	Asaka et al <sup>17</sup> 2016	Giudice et al <sup>22</sup> 2018	Soydan et al <sup>26</sup> 2013	Kim et al <sup>27</sup> 2014	Dinca et al <sup>46</sup> 2014	Gönen et al <sup>47</sup> 2017	Park et al <sup>48</sup> 2017
Was the study described as randomized?	No	Yes	No	No	No	No	No
Was the study described as double-blind?	No	No	No	No	No	No	No
Was there a description of withdrawals and dropouts?	Yes	Yes	No	Yes	Yes	No	Yes
Was the method for generating the randomization sequence described and appropriate?	No	Yes	No	No	No	No	No
Was the double-blind method described and appropriate?	No	No	No	No	No	No	No
<b>SCORE</b>	<b>1</b>	<b>3</b>	<b>0</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>1</b>
ITEMS	Norholt et al. <sup>49</sup> 2016	Maluf et al. <sup>50</sup> 2016	Inchingolo et al <sup>51</sup> 2017	Kim et al <sup>52</sup> 2016	Maluf et al <sup>53</sup> 2018	Tsai et al <sup>54</sup> 2016	Pelaz A et al <sup>55</sup> 2014
Was the study described as randomized?	No	No	No	No	No	No	No
Was the study described as double-blind?	No	No	No	No	No	No	No
Was there a description of withdrawals and dropouts?	Yes	No	Yes	No	No	No	Yes
Was the method for generating the randomization sequence described and appropriate?	No	No	No	No	No	No	No
Was the double-blind method described and appropriate?	No	No	No	No	No	No	No
<b>SCORE</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>

Table1. Assessing the Quality of Reports of Clinical Trials with Jadad scale45

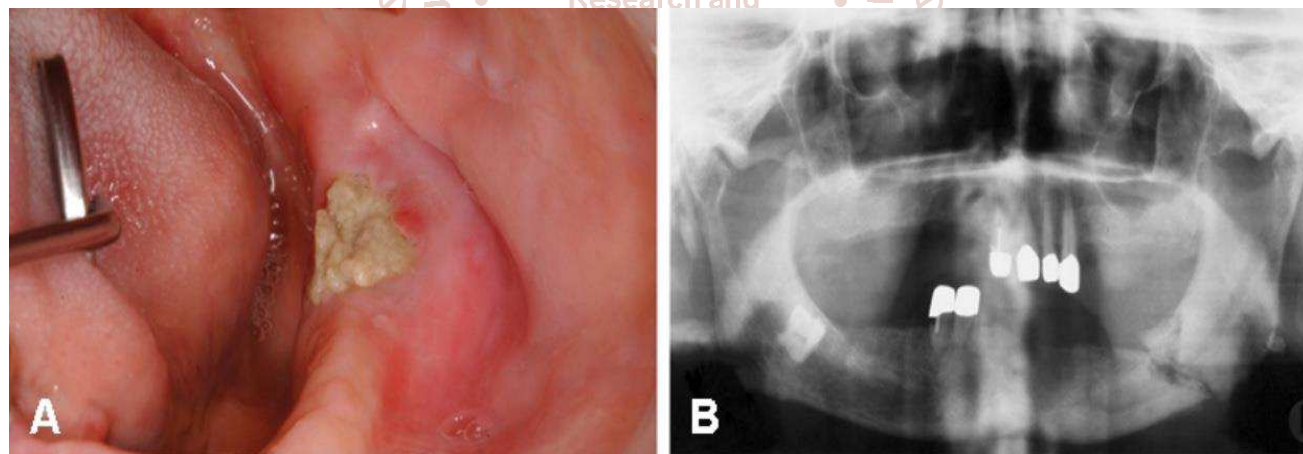


Figure1. (A) Intraoral view with exposure to the necrotic bone in the left jaw angle; (B) panoramic radiograph Preoperatively identifying the fractured mandible angle. MORRISON A. PathologyOutlines.com 2018 <http://pathologyoutlines.com/topic/mandiblemaxillaMRONJ.html>. Accessed September 4th, 2018