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The application of platelet rich fibrin in patients presenting with osteonecrosis of the jaw: A systematic literature review

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ABSTRACT

The aim of this systematic literature review was to summarise the available evidence regarding the administration of platelet rich fibrin (PRF) in patients diagnosed with osteonecrosis of the jaw (ONJ). A PRISMA-conform systematic literature review was conducted using a PICO-defined search strategy. MEDLINE was accessed and hits published before February 2020 were reviewed. All studies reporting on intraoperative administration of PRF into an osseous defect in patients presenting with ONJ were included. Eligibility of the studies was assessed by two independent reviewers according to prespecified criteria. Sixteen studies described the application of PRF for treatment of ONJ in 166 patients. Follow-up periods ranged from 30 to 1560 days. There was large heterogeneity regarding patient details and perioperative management. The only randomised controlled study (RCT) included suggested modest superiority in early recovery, infection rate and reported pain. No adverse events related to PRF were reported in any of the studies. The evidence regarding relative merits of PRF application versus standard of care in patients with ONJ is low. Current evidence is limited by small, non-consecutive patient samples and lack of a randomised control group. Because some observational reports and one RCT suggested improvements of early recovery, further studies are needed.

Introduction

Osteonecrosis of the Jaw (ONJ) has many known aetiologies. The most common associations are antiresorptive and antiangiogenic medication as well as high-dose radiotherapy [1]. Regaud [2], in 1922, was the first to describe the phenomenon of *osteoradionecrosis (ORN)*.

Approximately 80 years later, *Bisphosphonate-related Osteonecrosis of the Jaw (BRONJ)* was mentioned for the first time in a case report [3]. Observing and describing this new clinical picture, several medical associations published expert panel recommendations over the following years [4,5]. In 2014, as a growing number of osteonecrosis cases associated with other antiresorptive therapies (e.g. Denosumab) was observed, the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended the term *Medication-related Osteonecrosis of the jaw (MRONJ)* [6]. To date, numerous additional recommendations regarding the risk factors and treatment modalities of MRONJ have been published [7,8]. However, no specific treatment regimen has yet been defined as a standard of care.

In recent years, the role of platelet-rich fibrin (PRF) in the

Table 1
MeSH Terms and Key Words for literature search in MEDLINE.

	MeSH Terms	Key Words
Population	Bisphosphonate-Associated Osteonecrosis of the Jaw	osteonecrosis of the jaw, onj, medication related osteo- necrosis of the jaw, mronj, bisphosphonate related osteo-necrosis of the jaw, bronj, osteoradionecrosis, post-radiation osteonecrosis of the jaw, osteomyelitis, osteo-chemonecrosis, osteonecrosis of the mandib*, osteonecrosis of the maxilla, maxillary osteo-necrosis, mandibulary osteo-necrosis, jaw osteonecrosis
Intervention	Platelet-Rich Fibrin	platelet rich fibrin, platelet-rich fibrin, PRF, A-PRF*, I-PRF, L-PRF, P-PRF, sticky bone, fibrin rich plasma, fibrin-rich plasma

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Table 2
Detailed search string for MEDLINE.

((((Bisphosphonate-Associated Osteonecrosis of the Jaw[MeSH Terms]) OR ((osteonecrosis of the jaw[Title/Abstract] OR onj[Title/Abstract] OR medication related osteonecrosis of the jaw[Title/Abstract] OR mronj[Title/Abstract] OR bisphosphonate related osteonecrosis of the jaw[Title/Abstract] OR bronj[Title/Abstract] OR osteoradionecrosis[Title/Abstract] OR post-radiation osteonecrosis of the jaw[Title/Abstract] OR osteomyelitis[Title/Abstract] OR osteochemonecrosis [Title/Abstract] OR osteonecrosis of the mandib*[Title/Abstract] OR osteonecrosis of the maxilla[Title/Abstract] OR maxillary osteonecrosis[Title/Abstract] OR mandibulary osteonecrosis[Title/Abstract] OR jaw osteonecrosis[Title/Abstract]))))) AND ((Platelet-Rich Fibrin[MeSH Terms]) OR ((platelet rich fibrin[Title/Abstract] OR platelet-rich fibrin[Title/Abstract] OR PRF[Title/Abstract] OR A-PRF*[Title/Abstract] OR I-PRF[Title/Abstract] OR L-PRF[Title/Abstract] OR P-PRF[Title/Abstract] OR sticky bone[Title/Abstract] OR fibrin rich plasma[Title/Abstract] OR fibrin-rich plasma[Title/Abstract]))))

management of ONJ has been investigated. PRF was first described in 2000 by Choukroun et al. [9] as second-generation platelet concentrate, having two major advantages over traditionally prepared platelet-rich plasma (PRP). Firstly, its preparation is very quick, easy, and cheap, as only one single cycle of centrifugation is needed, and secondly, neither anticoagulant nor bovine thrombin is added for coagulation, which makes PRF a completely autologous product. The fibrin network within PRF confers upon it a strong, but flexible structure, progressively releasing high amounts of cytokines and growth factors over at least 7 days, which would appear to be responsible for the favourable healing properties attributed to PRF [10–12].

With further classification, PRF subtypes are specified by different capital letters: pure PRF (P-PRF), leukocyte-PRF (L-PRF), injectable PRF (I-PRF) and advanced PRF (A-PRF). L-PRF contains a significantly higher leukocyte concentration compared to P-PRF and releases growth factors and matrix proteins more slowly, albeit in a higher ratio than PRP [13]. Both L-PRF and P-PRF are applied as membranes or clots whereas I-PRF can be used in liquid or polymerized form [14]. Ghanaati et al. [15] have described a new protocol for the acquisition of A-PRF: more neutrophilic granulocytes can be obtained by decreasing the centrifugation speed (revolutions per minute) while increasing the centrifugation time compared to the standard procedure for P-PRF. In comparison to L-PRF, A-PRF seems to dissolve faster and release considerably fewer growth factors (TGFβ1, PDGF-AB, VEGF) [16]. Consequently, by following different centrifugation protocols, the final properties of the PRF-clot (dissolution, release of cells, growth factors and cytokines) can be modified [11,16].

Thus far, PRF has been widely used for prevention and therapy in different fields of oral and maxillofacial surgery such as sinus lifts, socket preservations and ridge augmentations, periodontology, and in MRONJ [17]. However, few systematic literature reviews regarding the application of autologous platelet concentrates in the prevention and therapy of ONJ have been conducted [17–21].

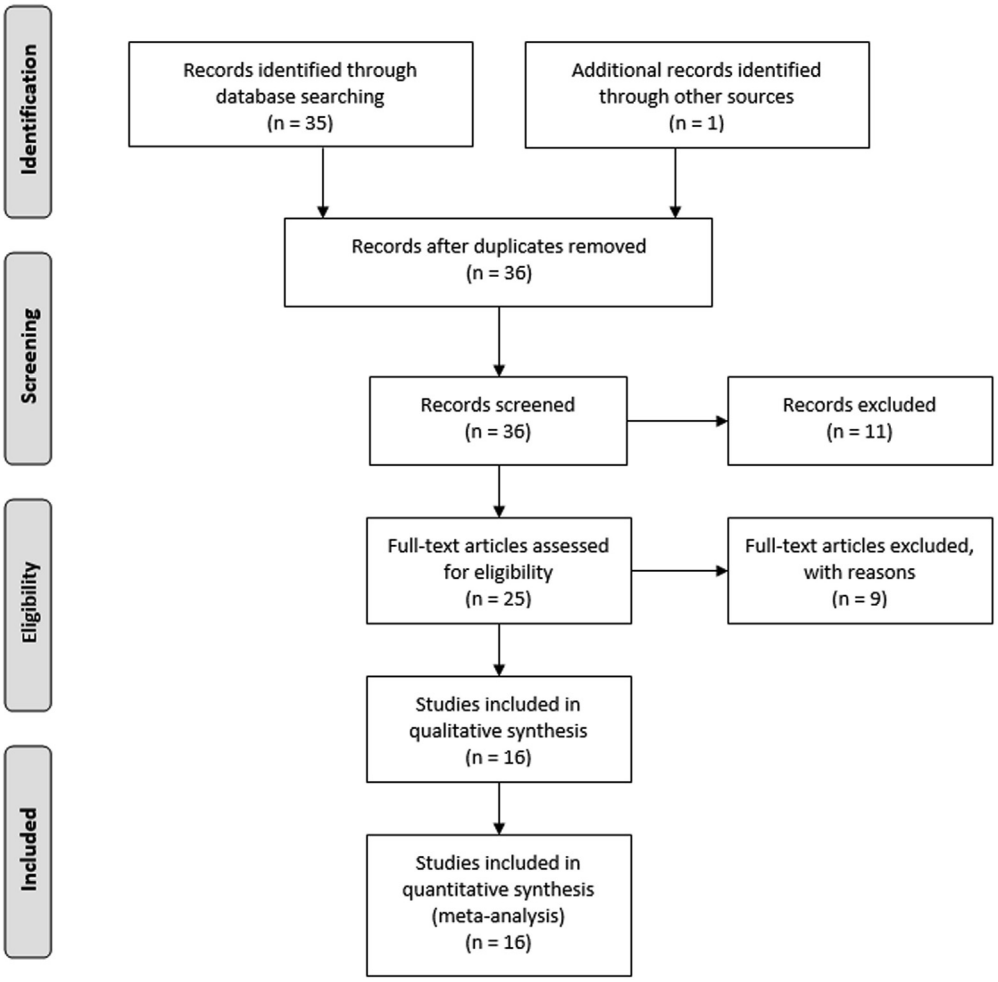

Fig. 1. Prisma flow diagram.

Table 3
Study design and population size according to the articles included in the systematic review.

Name	Authors	Study Design	Population Size
Ultrasonic Piezoelectric Bone Surgery Combined With Leukocyte and Platelet-Rich Fibrin and Pedicled Buccal Fat Pad Flap in Denosumab-Related Osteonecrosis of the Jaw	Şahin O, Odabaşi O, Ekmekcioğlu C	Case report	1
Medication-Related Osteonecrosis of the Jaw: The Use of Leukocyte-Platelet-Rich Fibrin as an Adjunct in the Treatment.	Valente NA, Chatelain S, Alfonsi F, Mortellaro C, Barone A	Retrospective study	14
The use of Platelet-rich Fibrin in the management of medication-related osteonecrosis of the jaw: A case series	Fernando de Almeida Barros Mourão C, Calasans-Maia MD, Del Fabbro M, Le Drapper Vieira F, Coutinho de Mello Machado R, Capella R, Miron RJ, Gomes Alves G	Case series	11
Platelet rich fibrin in the management of medication-related osteonecrosis of the jaw: a clinical and histopathological evaluation	Inchingolo F, Cantore S, Dipalma G, Georgako-poulos I, Almasri M, Gheno E, Motta A, Marrelli M, Farronato D, Ballini A, Marzullo A	Case series, letter to the editor	23
Use of Leukocyte- and Platelet-Rich Fibrin in the Treatment of Medication-Related Osteonecrosis of the Jaws	Maluf G, Caldas RJ, Silva Santos PS	2 Case reports	2
Does the Addition of Bone Morphogenetic Protein 2 to Platelet-Rich Fibrin Improve Healing After Treatment for Medication-Related Osteonecrosis of the Jaw?	Park JH, Kim JW, Kim SJ	Prospective study	25
Treatment of bisphosphonate-related osteonecrosis of the jaw using platelet-rich fibrin	Gönen ZB, Yılmaz Asan C	Case report	1
Surgery Combined with LPRF in Denosumab Osteonecrosis of the Jaw: Case Report	Maluf G, Pinho MC, Cunha SR, Santos PS, Fregnani ER	Case report	2
Surgical treatment of osteonecrosis of the jaw with the use of platelet-rich fibrin: a prospective study of 15 patients.	Nørholt SE, Hartlev J	Prospective study	15
Treatment of bisphosphonate-related osteonecrosis of the jaw with platelet-rich fibrin.	Tsai LL, Huang YF, Chang YC	Case report	1
Clinical and histopathological studies using fibrin-rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw	Dincă O, Zurac S, Stăniceanu F, Bucur MB, Bodnar DC, Vlădan C, Bucur A	Case series	10
Leukocyte-rich and platelet-rich fibrin for the treatment of bisphosphonate-related osteonecrosis of the jaw: a prospective feasibility study.	Kim JW, Kim SJ, Kim MR	Prospective feasibility study	34
Management of bisphosphonate-related osteonecrosis of the jaw with a platelet-rich fibrin membrane: technical report.	Soydan SS, Uckan S	Case report	1
Leukocyte-Rich and Platelet-Rich Fibrin (L-PRF) for the Treatment of Medication-Related Osteonecrosis of the Jaw (MRONJ) with Long Term Follow-up	Şahin O, Aliyev T, Tatar B	Case report	1
Use of platelet-rich fibrin and surgical approach for combined treatment of osteoradionecrosis: a case report	Chen YT, Chang YC	Case report	1
Can platelet-rich fibrin improve healing after surgical treatment of medication-related osteonecrosis of the jaw? A pilot study.	Giudice A, Barone S, Giudice C, Bennardo F, Fortunato L	Prospective, randomised, single-blind, monocentric clinical trial	24

The aim of this systematic literature review was to summarise the available evidence regarding the administration of PRF in the treatment of patients diagnosed with ONJ.

Material and methods

A PRISMA-conform systematic literature review was conducted using a PICO-defined search strategy.

The formulation of the PICO question was as follows: In patients with osteonecrosis of the jaw, is PRF an effective therapy? The patient population was confined to patients presenting with any ONJ (aetiology was not further specified). PRF treatment was described as the intra-operative administration of PRF into an osseous defect. No comparison groups or specific outcomes were defined.

MEDLINE was accessed and hits published before February 23, 2020, were reviewed. MeSH terms and key words were chosen with respect to the different aetiologies of ONJ, as well as the different PRF subtypes (Table 1). The detailed search string for MEDLINE is presented in Table 2.

Inclusion criteria were formulated as follows: (1) any publication in English, (2) in vivo studies conducted in humans, (3) patients with the diagnosis of ONJ regardless its aetiology, and (4) use of PRF for therapy. In keeping with these, the following exclusion criteria were applied: (1) in vitro application of PRF, (2) animal studies, (3) application sites other than the maxilla or mandible, (4) preventive use of PRF, (5) simultaneous application of other agencies in addition to PRF (e.g. Bone Morphogenetic Protein-2, Simvastatin), (6) use of different autologous platelet concentrates (APCs) than PRF, and (7) literature reviews or no availability of full-text articles. Additionally, references from relevant articles were screened in the manner of a backward search.

Case reports, case series, retrospective as well as prospective feasibility studies were amongst the manuscripts included.

Two independent reviewers extracted the following data from the studies: study design, sample size, gender, age distribution, affected jaw, defect size and stage, reason for ONJ (radiotherapy vs. medication-related), type of antiresorptive therapy (e.g. monoclonal antibodies or bisphosphonates) and drug holiday after diagnosis of MRONJ, type and shape of the applied PRF (membrane vs. clot), use of antibiotics, outcome variables (including recovery, infection, relapse rate and no resolution) and follow-up duration. A control group was available in only one study. For this original contribution, data including gender, age distribution and affected jaw were extracted for both patient pools (intervention and control group) separately.

For data analysis of the studies included, the outcomes of ONJ treatment were allocated to “recovery” or “disturbance of wound healing/no resolution” in accordance to the authors’ descriptions. Relapse and infection were counted as disturbance of wound healing/no resolution.

Results

The results of the systematic literature search are displayed in the PRISMA flow diagram (Fig. 1).

The initial search strategy disclosed 35 results through MEDLINE. Through the backward search of the reference list of all relevant articles,

Table 4
General features and characteristics of studies without control group.

	Population Size	F	M	Age range (years)	MRONJ (M)/ ORN (R)	UJ	LJ	UJ + LJ	Localisation unknown
Chen et al. [41] (2019)	1		1	53	R			1	
Şahin et al. [42] (2019)	1	1		63	M	1			
Valente et al. [27] (2019)	14	9	5	56–71	M	6	8		
Fernando de Almeida Barros Mourão et al. [22] (2019)	11	9	2	38–84	M	4	7		
Şahin et al. [43] (2018)	1		1	73	M		1		
Maluf et al. [40] (2018)	2	2		75–79	M	1	1		
Inchingolo et al. [23] (2017)	23	15	8	52–73	M				23
Park et al. [25] (2017)	25	22	3	59–97	M	10	15		
Gönen et al. [44] (2017)	1		1	77	M		1		
Maluf et al. [45] (2016)	2	1	1	44–69	M		2		
Nørholt et al. [46] (2016)	15	11	4	54–83	M	3	11	1	
Tsai et al. [39] (2016)	1	1		79	M		1		
Dincă et al. [28] (2014)	10	6	4	30–79	M	3	7		
Kim et al. [24] (2014)	34	34		71[a]	M	7	27		
Soydan et al. [26] (2014)	1		1	75	M	1			
Giudice et al. [29] (2018), PRF-population	24	10	14	63–83	M	2	18	4	
	166	**121 (72.9%)**	**45 (27.1%)**	**30–97**		**38 (22.9%)**	**99 (59.6%)**	**6 (3.6%)**	**23 (13.9%)**

F, female; *M*, male; *MRONJ*, Medication related Osteonecrosis of the Jaw; *ORN,* Osteoradionecrosis; *UJ*, Upper Jaw; *LJ*, Lower Jaw; *L-PRF*, Leukocyte-Platelet Rich Fibrin; *A-PRF*, Advanced-Platelet Rich Fibrin; a only average age available.

one additional manuscript was identified. No duplicates were included, resulting in 36 abstracts. Twenty-five articles qualified for full-text retrieval and analysis according to the stated inclusion/exclusion criteria. Nine articles were excluded (literature reviews, preventive application of PRF, combined treatment with Simvastatin or BMP-2, full-text article not available). The remaining 16 studies were included in the systematic review and are listed in Table 3, along with study design and population size.

In total, 11 case reports/series and 5 original contributions were reviewed (all data reported in Tables 4 and 5). In a prospective randomised cohort study, a comparison of PRF to a control-group, receiving minimal-invasive surgery only, was performed (Table 5). Application of PRF for treatment of ONJ was described for a total of 166 patients [121 women (72.9%), 45 men (27.1%), age range 30–97y]. In the control-group, 23 patients were included [14 women (60.9%), 9 men (39.1%), age range 58–85y]. Follow-up periods ranged from one month to just over 4 years. Medication was responsible for nearly all cases of ONJ except for one single case report of ORN.

There were many limitations with the dataset. For example, there was significant heterogeneity regarding both stage and localisation of ONJ, peri-operative management (e.g. administration of antibiotics), PRF subtype and mode of application, the reporting system of treatment outcome, as well as the documentation of these categories. Ninety-nine patients (59.6%) received treatment to the Lower Jaw (LJ), 38 patients (22.9%) to the Upper Jaw (UJ) and in 6 cases (3.6%) both jaws received PRF treatment. In one larger case series, the ONJ site was not further specified for 23 patients (13.9%). In six studies, including 38 patients (22.9% of all patients included in this literature review), the PRF subtype was not further specified. In 94 patients (56.6%), L-PRF was administered; in only 34 (20.5%) cases, A-PRF was implanted. The applied PRF shape was not recorded for 98 patients (59.1%). In 57 cases (34.3%), PRF was applied as membrane; in 11 patients (6.6%) the membrane was combined with a clot.

In the control group (total 23 patients), ONJ was reported in the LJ in 17 patients (73.9%). In 3 patients (13.1%), ONJ was recorded in the UJ or in both jaws, respectively.

Not all studies provided sufficient information about patient details, such as medical history and smoking habits, antibiotic regime, or the precise therapy outcome. Diabetes in medical history was recorded for patients in 7 articles [22–28]. Only 4 studies recorded whether patients included had to take corticosteroids [23–25,27]. Smoking habits were documented in only one single article [27]. Initially, in this literature review, 5 categories were built for the outcome assessment: infection, relapse rate, disturbance of wound healing/no resolution, stage-improvement and recovery. Due to the lack of information provided by the studies included, categories for the endpoint assessment had to be reduced to “recovery” (including cases with mucosal integrity and absence of infection) and “disturbance of wound healing/no resolution”. The latter section included all cases of infection and relapse rates as well as the complete absence of wound healing.

PRF-treatment yielded complete recovery in 154 cases (92.8%, including PRF-treated cases of the randomised cohort study by Giudice et al. [29]) and disturbance of wound healing/no resolution in 12 cases (7.2%). The follow-up period ranged from 30 to 1560 days.

Patients in the control group, having received a minimal-invasive surgical removal of the necrotic bone, showed complete recovery in 21 cases (91.3%) and disturbance of wound healing/no resolution in 2 cases (8.7%). The follow-up period was 365 days.

In the prospective randomised cohort study by Giudice et al. [29], the analysis of mucosal integrity, absence of infection, and pain assessment showed a significant difference in favour of the PRF group, being limited to short-term follow-up (T1 = 1 month). For the long-term follow-up periods (T2 = 6 months, T3 = 1 year) no differences were evaluated.

These findings were consistent with most of the other studies included: In general, less postoperative pain, less infection and higher short-term rates of complete recovery were reported for ONJ-patients treated with PRF. In all studies, no adverse events of PRF were reported.

Discussion

The aim of this systematic literature review was to summarise the available evidence regarding the administration of PRF in the treatment of patients diagnosed with ONJ. According to our analyse, this systematic literature review has the following findings: (1) overall, the evidence regarding the efficacy of PRF in the management of ONJ is low and limited to mostly observational data, (2) there exists large heterogeneity regarding the documentation of clinical and other relevant patient details (such as administration of antibiotics or smoking history), PRF subtype and mode of application, and with reporting treatment outcome, (3) the only randomised clinical trial by Giudice et al. [29] suggests a higher percentage rate of mucosal healing, as well as reduced postoperative pain and infections in patients treated with PRF compared to the control

L-PRF	A-PRF	PRF type unknown	Membrane	Membrane + Clot	PRF shape unknown	Recovery	Disturbance of wound healing/no resolution
		1	1			1	
1					1	1	
14					14	11	3
		11	11			11	
1					1	1	
2			2			2	
		23			23	23	
25					25	22	3
		1	1			1	
2			2				2
15			15			14	1
		1		1		1	
	10			10		10	
34					34	32	2
		1	1			1	
	24		24			23	1
94 (56.6%)	**34 (20.5%)**	**38 (22.9%)**	**57 (34.3%)**	**11 (6.6%)**	**98 (59.1%)**	**154 (92.8%)**	**12 (7.2%)**

Table 5
Summary of general features and characteristics according to the prospective randomised cohort study including a control group.

References	Giudice et al. [29] (2018)	
	Control Group	PRF-Population
Population Size	23	24
F	14 (60.9%)	10 (41.7%)
M	9 (39.1%)	14 (58.3%)
Age range (years)	58–85	63–83
MRONJ medication: Denosumab vs. Bisphosphonates	Various	
UJ	3 (13.05%)	2 (8.3%)
LJ	17 (73.9%)	18 (75%)
Both jaws	3 (13.05%)	4 (16.7%)
A-PRF	–	24 (100%)
Membrane	–	24 (100%)
Recovery	21 (91.3%)	23 (95.8%)
Disturbance of wound healing/no resolution	2 (8.7%)	1 (4.2%)

F, female; M, male; MRONJ, Medication related Osteonecrosis of the Jaw; UJ, Upper Jaw; LJ, Lower Jaw; A-PRF, Advanced-Platelet Rich Fibrin.

group, but in a small cohort and limited to short-term observation (1 month) only.

The results and limitations of the present work are consistent with previous systematic literature reviews about the application of PRF in ONJ [18,20,21,30,31]. Though all are based on the rather low-evidence level studies, a trend for a beneficial effect of PRF in the treatment of MRONJ is suggested. However, the comparison with earlier literature reviews is limited, as some of them do not investigate the application of PRF specifically, but of APCs in general [20,21,30], or discuss various dental and maxillofacial application fields of PRF [31]. None of the literature reviews found included the application of PRF in ORN.

Several major limitations were observed for this literature review. First, no more than one control group study could be included. In addition to this prospective, randomised clinical trial by Giudice et al. [29] a retrospective examination by Szentpeteri et al. [32], including an intervention-group of 28 patients and a control-group of 73 patients, was found when MEDLINE was screened. Due to discrepant data presented, the article had to be excluded [33,34]. In addition, only three prospective studies and one retrospective study could be included. Among the remaining articles, there were case reports and case series. Therefore, the results of this review need to be put into perspective, taking into consideration the known risk of bias linked to such study designs.

The sample populations of the studies included was highly heterogenous, both clinical and methodological. This was particularly noticeable regarding clinical patient history, such as type of prior medication (bisphosphonates vs. denosumab), administration routes, follow-up duration, administration of antibiotics and smoking history. Considering high-risk factors for ONJ, as defined by well-respected ONJ position papers [7,35,36], it seems surprising how few studies collected patient data about smoking history, diabetes, glucocorticoid exposure, immunodeficiency and prior periodontal disease. Furthermore, heterogeneity of data pertained to the PRF therapy itself (such as the subtype and application form of PRF) and, importantly, to the assessment of outcome. As previously described, the final properties of the PRF-clot or -membrane, its rate of dissolution and the release of growth factors and cytokines is largely affected by the centrifugation protocol. Standardised documentation of this protocol and the resulting PRF subtype would therefore be desirable.

Only one study that discussed the application of PRF in ORN was found. A possible explanation for the limited data of PRF therapy in ORN management could lie in the latest pathophysiological understanding of ORN as a radiation-induced fibro-atrophic process, leading to potential treatment with an oral antioxidant regimen [37,38]. However, the limited data available does not allow any conclusions to be drawn about the effectiveness of PRF in the therapy of ORN.

Most of the studies included in this review showed a trend towards encouraging wound healing properties attributed to PRF, especially concerning improved mucosal healing [22,26,29,39], decreased infections [29,39,40] and reduced postoperative pain [22,29]. Giudice et al. [29] were the only research association to relativize the effect of PRF: the intervention group showed a higher quality of life (due to reduced postoperative pain) and reduced re-intervention rate, but limited to a short-term observational interval window only. In the long-term evaluation, no statistical differences between the PRF and control group concerning mucosal healing and the absence of infection were observed. The limitations of this study consist mostly in the small study sample, the monocentric design and the heterogenous drug administrations [29]. All remaining authors concluded that PRF led to favourable clinical improvements, but the limitations of the corresponding studies reviewed did not allow for conclusive recommendations regarding the application of PRF in ONJ.

PRF is a cheap, safe, autologous, and easy to prepare treatment option for ONJ. The present literature review was confronted with many limitations: only one randomised trial could be included and most of the other studies consisted of case reports or case series. Furthermore, the studies investigated lacked a systematic assessment and approach regarding comorbidities, PRF administration protocol and definition of the clinical endpoint, making a standard investigation protocol desirable.

Therefore, the results of this literature review are not sufficient to prove any beneficial effect of PRF in the treatment of ONJ. Well-designed, randomised controlled studies are needed to assess the therapeutic potential of PRF in this field.

Conclusions

The evidence supporting the relative merits of PRF application in patients presenting with ONJ is low. This seems particularly limited by heterogenous treatment definitions and mode of administration, small and often inconsecutive patient samples and the lack of randomised control groups. Although the use of PRF in ONJ appears to be safe, only weak indications for a possible benefit in its use are described in the patient cohorts reviewed. Some observational reports and one RCT suggested improvements of early recovery. Therefore, further studies are needed before any recommendation as to the role of PRF in the management of ONJ can be made.

Ethics statement/confirmation of patient permission

No Ethics Approval was necessary for the literature review. No Patient permission/consent was necessary for the literature review.

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Declaration of competing interest

None.

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