Review

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Regenerative Potential of Platelet—Rich Fibrin in Maxillary Sinus Floor Lift Techniques: A Systematic Review

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Background: Platelet-rich Fibrin (PRF) represents a type of autologous biomaterial investigated through the years by *in vitro* and *in vivo* studies to assess the real inductivity properties, presumed due to the growth factors presence. This systematic review aims to evaluate the efficacy of PRF in sinus lift procedures, compared and/or in addition to Deproteinized Bovine Bone Materials (DBBM) according to emerging scientific evidence.

Materials and Methods: Selected databases were PubMed, Scopus, and Cochrane Library. The search strategy included the following terms: "PRF", "platelet concentrate", "autologous platelet concentrate", "platelet-rich fibrin", "bone grafts" or "DBBM", "xenografts" or "Bio-Oss", "maxillary sinus lift", "maxillary sinus elevation", "maxillary sinus augmentation". Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used.

Results: Four studies were included in the systematic review, evaluating clinical, histological, histomorphometric, and radiological data. Three of four studies reported no statistically significant differences between the test and control groups. In one study, the presence of Leukocyte-Platelet Rich Fibrin (L-PRF) could allow earlier implant placement, achieving the same clinical, histological, histomorphometric, and radiological results of bone regeneration at an earlier time, compared to the DBBM used alone.

Conclusions: The regenerative potential of PRF associated with DBBM resulted in a valid alternative in the bone regeneration procedure to DBBM grafts. Further new studies are needed, with more rigid protocols, to investigate the potential of platelet concentrates in sinus lift techniques and to evaluate the real inductivity properties of DBBM.

Keywords: platelet-rich fibrin; bone grafts; Bio-Oss; maxillary sinus augmentation

Introduction

Maxillary sinus plays an important role in heating and humidifying the air [1,2] and the anatomical space where bone regeneration takes place after a sinus lift augmentation is different from other districts [3,4].

Derjac-Aramă *et al.* [5] demonstrated the intrinsic osteogenic potential of the Schneiderian membrane, due to the expression of several factors involved in cellular differentiation, of mesenchymal stem/stromal cells, expressed by the epithelium and vascular/perivascular layer.

The maxillary sinus and its floor are involved in different types of regenerative techniques to obtain a new volume of bone tissue in order to treat bone atrophies. There are two main approaches to obtain a maxillary sinus augmentation: The crestal approach and the lateral window approach [6–8]. The lateral window approach consists in obtaining an access window on the lateral wall of the maxillary sinus, then lifting the shneiderian membrane in order to increase the volume of the bone regeneration using bone grafts or autologous platelets concentrates.

Bone tissue and soft tissue healing is a biological process where several factors, such as immunity cells, growth factors, and proteins, are involved in repairing and eventually regenerating the damaged tissue [9]. Therefore, the wound healing process is composed of four macro-phases: Hemostasis, inflammation, proliferation, and maturation [9]. Numerous factors and a perfect activation time are involved in these phases to repair the damaged tissue. Autologous platelet concentrates (APCs), owning the necessary growth factors released by the platelets, activated by the centrifugations, could be a good solution to achieve good wound healing or tissue regeneration thanks to their properties [10]. APCs are autologous, easily obtained from the patient's blood, and contain most of the growth factors and cells involved in the natural tissue repair process.

Leukocyte-Platelet Rich Fibrin (L-PRF) is a solid autologous platelet concentrate representing the second gen-

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eration of platelet concentrates [11].

L-PRF is obtained through Choukroun's protocol that consists of two phases: (1) Collecting blood sample (venepuncture: From 10 to 100 cc of blood) and placing it in a 10 mL glass or glass-coated tube; (2) Centrifugation at 3000 rpm for 10 min [12].

After centrifugation, three layers can be distinguished in the tube: (1) Acellular plasma on the top; (2) Platelet-rich Fibrin (PRF) clot, in the middle; (3) Red corpuscles at the bottom [13].

Choukroun's protocol allows for obtaining a concentrate with a high percentage of growth factors such as Transforming Growth Factor-beta 1 (TGF-β1), Platelet-Derived Growth Factor (PDGF), Vascular Endothelial Growth Factor (VEGF), Insulin-like Growth Factor (IGF), Epidermal Growth Factor (EGF), [14] which have two important roles: Regulation of inflammation and wound healing.

In particular, TGF-β1 is secreted by degranulated platelets during the early phase of injuries and induces the expression of extracellular matrix proteins; Besides, it influences the development of osteoblasts in its first step and simulates fibroblast in the production of collagen, resulting in promoting the regeneration of bone and cartilage [15]. PDGF, which was described by Ross in 1974, is produced by giant cells and promotes osteoblastic proliferation, angiogenesis, mesenchymal cell division, and cellular differentiation; PDGF particularly facilitates cell proliferation of fibroblast and its collagen synthesis [16]. These two factors described above have a critical role in improving tensile strength and callus formation so that they have a positive effect on soft and hard tissue healing [17,18].

IGF has an important role in promoting cellular differentiation and the process of osteogenesis. There are different types of IGF, such as IGF I and IGF II, that stimulate osteoblasts proliferation and type I collagen expression through a proper action of paracrine and autocrine regulators [19].

Finally, EGF is activated by different receptors of immune cells and cells involved in tissue repair processes, such as fibroblasts, endothelial cells, and keratinocytes [20].

Furthermore, the second component of PRF is represented by immunity cells as leukocytes, neutrophilic granulocytes, macrophages, and lymphocytes that regulate inflammation and wound healing and, at the same time, add to PRF antibacterial properties [21].

Finally, the third component of PRF is the three-dimensional fibrin matrix, which determines PRF's mechanical and technological characteristics, together with the activated platelets that release large amounts of cytokines. The polymerized fibrin matrix and platelets reinforce the matrix so that growth factors and leukocytes can be trapped in the fibrin network [22]. The result is a strong structure that stimulates a slow release of growth factors (the preexistent ones and the new ones produced by leukocytes) [20].

There are different categories of materials in dentistry that enhance the process of hard and soft tissue regeneration. The main histological difference between bone grafts and bone substitutes is tissue vitality [23]. In oral surgery, both categories of materials, bone grafts, and bone substitutes, are combined in order to reduce the limits of each one [1].

Thus a better result in human tissue healing is represented by the vitality of the newly formed tissue, which is the consequence of a higher level of integration of the graft as opposed to the residual graft material, leading to an effective bone regeneration which results in better predictability of implant osteointegration [1]. Regarding these indexes of tissue vitality, they were evaluated in the histomorphometric analysis of the biopsies taken in each study included in this systematic review [24–26].

Furthermore, the autologous platelet concentrates stand out for those clot with an important fibrin network formed during the different stages of centrifugation, which confers the conductive properties, and the growth factors released by the platelets [27]. Among autologous platelet concentrates, L-PRF represents the second generation of platelet concentrates [9], obtained through Choukroun's protocol [13,14], which allows for obtaining a concentrate, with a high percentage of growth factors, such as TGF-β1, PDGF, VEGF, IGF, EGF [15]. These growth factors are all essential in the regulation of inflammation and wound healing: Specifically, TGF-β1 induces the expression of extracellular matrix proteins, influencing the development of osteoblasts, fibroblasts collagen synthesis, and promoting the regeneration of bone and cartilage [16]. PDGF, produced by giant cells, promotes osteoblastic proliferation, angiogenesis, mesenchymal cell division, and cellular differentiation, also facilitating fibroblast proliferation and collagen synthesis [15–28]. IGF has an important role in promoting cellular differentiation and osteogenesis and its subtypes, IGF I and IGF II, stimulate osteoblasts proliferation and type I collagen expression, as paracrine and autocrine regulators [20]. Finally, EGF is activated by different receptors of immune cells and cells involved in tissue repair processes, such as fibroblasts, endothelial cells, and keratinocytes [21]. Third component of PRF is the three-dimensional fibrin matrix, which determines PRF's mechanical and technological characteristics, together with the activated platelets, with the aim to reinforce the matrix, so that growth factors and leukocytes can be trapped in the fibrin network [22], promoting a slow release of growth factors among the xenografts derived from animal sources, the most used is the Deproteinized Bovine Bone Material (DBBM), which owns a high conductivity property [29].

Due to the mentioned and investigated properties, through the years, several clinical studies and reviews attempted to compare the efficacy of these two types of grafts, also used in combination in Guided Bone Regeneration (GBR) and in maxillary sinus lift procedures for the sub-

sequent implants' placement, with contrasting results and claims [30–32].

This systematic review aims to evaluate the effectiveness of the PRF, combined with DBBM, in the regeneration procedure in maxillary sinus lift. This work focused on solely evaluating PRF and excluding other types of platelet concentrates, specifically Platelet-Rich Plasma (PRP) and Concentrated-Growth Factor (CGF). The first platelet concentrate now represents a technology superseded by the second generation of platelet concentrates, the PRF itself. CGF, despite having numerous features in common with the PRF [33], also shows differences in density of the fibrin network, which is higher than the PRF, and for young module, which is 0.35 Gpa in the PRF against 70 kpa in the CGF [34].

Several systematic reviews compare studies of different types of platelet concentrates, considering them overlapping, unlike this review which, however, was focused on the PRF, excluding other types of concentrates such as PRP and CGF. Besides, unlike the past reviews, in this systematic review, it was crucial to use a strict criteria of inclusion of only studies that have a comprehensive method of evaluating outcomes from 4 points of view, as clinical, radiological, histological and histomorphometric results, in order to understand beneficial effects of PRF, when combined with DBBM.

Materials and Methods

The current systematic review is registered on Open Science Framework database, with registration DOI: https://doi.org/10.17605/OSF.IO/PJTB9 accessed on 27 September 2022. The PICO method [35] was used to develop this systematic review, defining the following parameters:

- P: Population of patients who need to undergo unilateral or bilateral maxillary sinus lift operations.
- I: Use of PRF as a graft or membrane, combined with other bone grafts/non-use of PRF.
- C: Use of bone grafts only.
- O: Effectiveness of PRF in the regeneration process of soft and hard tissues, evaluating clinical, radiological, histological and histomorphometric results, and resonance frequencies analysis if required.

Search Strategy

This systematic review screened PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/search/form.uri?display=basic&zone=header&origin=searchbasic#basic), and Cochrane Library (https://www.cochranelibrary.com/) databases, to select clinical studies. We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [36,37].

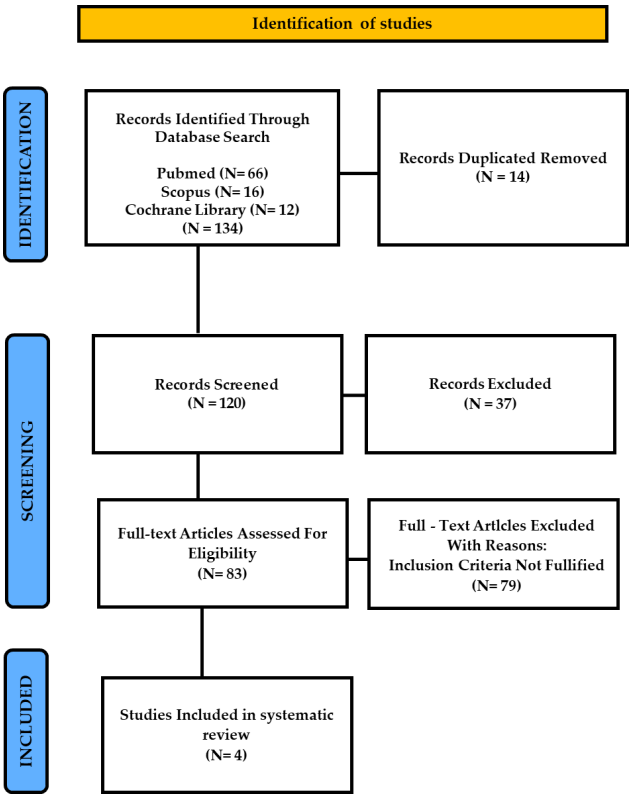

Fig. 1. PRISMA flowchart illustrating the experimental study search and selection process.

Search Terms

Electronic search was conducted, using the following search terms: "PRF", "platelet concentrate", "autologous platelet concentrate", "platelet-rich fibrin", "bone grafts" or "DBBM", "xenografts" or "Bio-Oss", "maxillary sinus lift", "maxillary sinus elevation", "maxillary sinus augmentation".

Inclusion Criteria

Articles were included if they met the following inclusion criteria: Randomized controlled trials (RCT), controlled clinical trials (CCT), retrospective and prospective, with comparison test and control groups; Publications of the last 10 years; *In vivo* human studies; PRF used as grafting material or membrane; Surgical treatment of sinus floor elevation using crestal approach or lateral window technique; Coexistence of post-treatment clinical and radiographic, histological and histomorphometric results, and studies in English.

Exclusion Criteria

Articles were excluded if they met the following exclusion criteria: *In vivo* and *in vitro* animal studies; Use of other specific concentrates as PRP, Mineralized Plasmatic Matrix (MPM), CGF or PDGF other than PRF results of poor quality; Studies involving patients with systemic contraindications or acute maxillary sinusitis, or suffering from

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Table 1. Assessment of methodological quality.

Criteria	Yes	No	Others (CD; NA; NR)*
(1) Is the review based on a specific question that is adequately formulated and described?	×		
(2) Have the eligibility criteria been defined and specified a priori in order to identify the included and excluded studies?	×		
(3) Does the literature search strategy use a comprehensive and systematic approach?	×		
(4) Have the titles, abstracts and full text of articles been dual and independently reviewed to minimize bias?	×		
(5) Was the quality of each included study independently assessed by two or more reviewers, using a standard method to assess the internal validity of the individual studies?	×		
(6) Have the included studies been listed, along with the important characteristics and findings of each study?	×		
(7) Have the BIAS been evaluated?	×		

*CD, cannot determine; NA, not applicable; NR, not reported.

periodontal disease; Case report, case series studies, pilot studies and systematic reviews.

Study Selection

Two independent authors (Davide Gerardi and Nicolò Santostasi) dealt with the primary literature research. The same researchers conducted a second re-evaluation of the selected titles, in which the studies that were not adapting to the established eligibility and inclusion criteria were deleted. Therefore, the remaining reports were intensely screened, considering the full-text articles for compatibility (Fig. 1). In case of disagreements between the authors after independent evaluation, a consensus was reached by re-evaluation and discussion. In the event of discrepancies in the data, reference paper authors were contacted by email for further explanation when possible. The remaining studies were finally reviewed for qualitative synthesis.

Data Collection

Data were extracted, including the year of publication, type of study, duration of follow-up, number of patients, number of sinuses, type of intervention, comparison groups, post-healing, radiological, clinical, histological, and histomorphometric results. These data were subsequently grouped in a summary Table. The considered outcomes were:

- Percentage data of success.
- Histomorphometric analyzes.
- Clinical data.
- Percentages of residual bone.
- Residual bone substitutes.
- Newly formed bone.
- Soft tissue.
- Radiographic data.
- Resonance frequency analysis.

Quality Assessment of Systematic Reviews and Risk of Bias

The critical evaluation system of systematic reviews, provided by the "U.S. Department of Health & Human Services" [38] which expects to meet a series of criteria in order to assess the quality of the systematic review, as well as the risks of bias, was used in this systematic review (Table 1).

Results

PRISMA diagram schematically shows the selection process (Fig. 1). Through digital research, carried out on three different databases (PubMed, Scopus, and Cochrane Library), 134 studies were identified: Among these, 66 studies were selected by the scientific research platform "Pubmed", 16 studies come from the same research carried out on "Scopus" digital database and, finally, 12 studies were selected from the "Cochrane Library" platform. Before this screening, 14 duplicated studies were excluded; The remaining 120 studies were subjected to a preliminary analysis. The title and the abstract were evaluated to identify any further studies to be excluded. From this first screening survey, a further 37 studies were excluded, reducing the total of studies subjected to final screening to 83. Inclusion and exclusion criteria were applied, with the exclusion of 79 studies. Finally, 4 studies were selected and considered eligible (Table 2, Ref. [24–27]), as they met the selection criteria.

The four included studies evaluated a population of 60 patients in total, whose clinical picture was characterized by posterior atrophy of the upper jawbone so that they were eligible for a maxillary sinus lift surgery, using lateral approach technique. After a period of soft and bone tissues healing, patients underwent implant surgery.

Table 2. Characteristics of the included studies.

Author year	Type of study and follow-up	Location	Population, lift sinus, number of implants (mean age, age range)	Gender	PRF preparation	Intervention	Evaluations
Zhang *et al*., 2012 [24]	RCT, prospective Follow up: 6 months Number of checks: 1 week 1 month 3 months 6 months	Department of Implant Dentistry, Peking University, School and Hospital of Stomatology, Beijing, China	10 patients 11 sinuses N° implants not specified Test group: 6 sinuses of 6 patients (mean age: 43.5 years; Range: 30–49) Control group: 5 sinuses of 5 patients (mean age: 46.2 years; Range: 37–53)	2 F 8 M	300 g for 10 min (Choukroun protocol)	Test group: Bio-Oss and L-PRF combined + PRF membrane, which covered the side window Control group: Bio-Oss alone, and covered with mucous membrane (without using membranes) Side access riser	Clinical Radiographic Histological Histomorphometric Number of biopsies: 6 in the test 5 in control (4% formalin at 4 °C) Prepared with Donath technique
Bolukbasi *et al*., 2015 [25]	Single center retrospective study Follow up: 6 months	Istanbul University Faculty of Dentistry Istanbul, Istanbul, Turkey	25 patients 32 sinuses 66 implants Test group: 17 sinuses Control group: 15 sinuses	15 F 10 M	400 g for 12 min (Choukroun protocol)	Test group: PRF membrane (placed over the membrane—"over the membrane") + PRF and Bio-Oss mixed + PPP used as "Wetting" of the graft + all covered by a PRF membrane Control group: Collagen membrane inside + Bio-Oss alone inside + collagen membrane to close the vestibular window Raise according to technique of Boyne, James and Tatum	Clinical Radiographic Histological Histomorphometric

Table 2. Continued.

Author year	Type of study and follow-up	Location	Population, lift sinus, number of implants (mean age, age range)	Gender	PRF preparation	Intervention	Evaluations
Nizam *et al*., 2018 [26]	RCT, split mouth 6 months after elevation: Biopsies + implant insertion Prosthetic load 6 months after implant placement Follow up 12 months after loading	Department of Periodontology, School of Dentistry, Ege University, İzmir, Turkey	13 patients 26 sinuses 58 implants Average age: 49.92 ± 10.37	4 F 9 M	400 g for 12 min (L-PRF and L-PRF membrane) Dohan/Choukroun protocol	Test group: L-PRF and Bio-Oss mixed + collagen membrane to close the window Control group: Bio-Oss alone + collagen membrane to close the window Elevation with lateral approach	Clinical Radiographic Histological Histomorphometric Biopsies: After 6 months of healing Prosthetic load: After 6 months of osteointegration, and follow-up 12 months after prosthetic loading
Pichotano *et al*., 2019 [27]	RCT, split-mouth Follow up: 8 months	Department of Diagnosis and Surgery, São Paulo State University (Unesp), School of Dentistry, Araraquara, São Paulo, Brazil	12 patients 24 sinuses Age: 43–63 years	6 F 6 M	300 g for 10 min (PRF membrane) (Dohan protocol)	Test group: Mixture of membranes of PRF and DBBM (proportion: For each membrane of 4–5 mm cut into fragments, 0.5 g of DBBM was mixed) + collagen to cover the window and implants at 4 months Control group: DBBM alone + collagen to cover the window and implants at 8 months Elevation with lateral approach	Clinical Radiographic Histological Histomorphometric

Table 3. Clinical evaluation data comparison.

Author year	Test group	Control group	*p* value
Zhang *et al*., 2012 [24]	T: 1 week, 1 month, 3 months and 6 months Parameters: Inflammation, wound dehiscence, loss of bovine bone particles. No adverse effects	T: 1 week, 1 month, 3 months and 6 months Parameters: Inflammation, wound dehiscence, loss of bovine bone particles. No adverse effects	Not applicable
Bolukbasi *et al*., 2015 [25]	Parameters: At 6 months; Perforation, wound dehiscence, inflammation process No post-surgery complications No post-implant complications: 100% implant survival	Parameters: At 6 months; Perforation, wound dehiscence, inflammation process No post-surgery complications No post-implant complications: 100% implant survival	Not applicable
Nizam *et al*., 2018 [26]	Residual bone height (mm) = 2.45 ± 0.79 At 6 months: Height of regenerated bone (mm) = 13.60 ± 1.09 100% implant survival	Residual bone height (mm) = 2.53 ± 0.61 At 6 months: Height of regenerated bone (mm) = 13.53 ± 1.20 mm 100% implant survival	*p* value > 0.05 *p* value = 0.88
Pichotano *et al*., 2019 [27]	Absence of complications during and after the rise No perforation observed No complications such as: Graft migration, wound dehiscence 100% implant survival at 12 months Resonance frequencies (ISQ) analysis at the time of installation of the system: 60.9 ± 9.35 ISQ at the time of loading: 76.08 ± 5.86 No difference at the time of loading	Absence of complications during and after the rise No perforation observed No complications such as: Graft migration, wound dehiscence 100% implant survival at 12 months Resonance frequencies (ISQ) analysis at the time of installation of the system: 75.13 ± 5.69 ISQ at the time of loading: 75.75 ± 6.14 No difference at the time of loading	*p* value = 0.0014 *p* value = 0.9927

Clinical Results

As reported in Table 3 (Ref. [24–27]), clinical data were collected. In the clinical study of Zhang *et al*. [24], they considered the parameters of inflammation, wound dehiscence, loss of bovine bone particles and demonstrated the absence of adverse effects both in test group and control group.

Bolukbasi *et al*. [25], in their review, considered perforation, wound dehiscence, inflammation process as clinical parameters, concluding that, in both test and control group, post-surgery complications were absent, with a 100% implant survival.

Nizam *et al*. [26] reported quantitative clinical data, considering residual bone height (mm) Height of regenerated bone (mm) in test group and control group which did not have statistically significative differences, with 100% implant survival.

Pichotano *et al*. [27] used the following clinical parameters: Complications during and after the rise, perforation, complications such as graft migration, wound dehiscence demonstrated the total absence of them, with 100% implant survival at 12 months.

Resonance frequency analysis was carried out in the study of Pichotano *et al*. [27] to assess the degree of stability of the implant in two distinct phases (Table 3): After placement and at the time of implant loading. This investigation took place using the Osstell tool (Resonance Frequency Analysis (RFA) device). It was measured using the ISQ (implant stability quotient) parameter. This survey has shown that, after implant placement, the ISQ is significantly higher in the control group 75.13 ± 5.69, compared to the test group 3.59 ± 4.22; $p = 0.0003$. On the other hand, the ISQ parameter, at the moment of loading, has no difference between the two groups ($p = 0.8587$) [27].

Radiological Results

Radiological results are reported in Table 4 (Ref. [24–27]). Radiographic evaluations through orthopantomography (OPG) were carried out in the studies of Zhang *et al*. [24], Bolukbasi *et al*. [25] and Nizam *et al*. [26].

Bolukbasi *et al*. [25] evaluated two parameters: The firs parameter was the relationship between the height of the lifted sinus and the implant, as the ratio between the distance bone level/implant length by bone level (BL/IL by BL), we mean the distance from the most apical point of contact between the implant, the bone, and the fixture's head. For IL, we mean the distance from the apex of the implant head. The interpretation of the relationship between BL and IL is as follows: If greater than or equal to 1, it indicates that the raised sinus covers the apex of the implant; If it is less than 1, the apex of the implant does not cover the floor of the sinus.

The second evaluated parameter was the change in the height of the sinus lift, the Grafted Sinus Eight/Original Sinus Eight (GSH/OSH) ratio. The GSH value represents the distance from the intraoral marginal bone, while the OSH value represents the height of the original breast. This ratio was calculated concerning the areas not supported by the

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Table 4. Radiographic evaluation data comparison.

Author year	Radiographic outcomes				
Zhang *et al.* 2012 [24]	Conclusions: (without quantitative data) Analysis of the quantity and density of mineralized bone tissue, by OPG and Computed Tomopgraphy dental scan Presence, in both groups, of adequate mineralized tissue (bone and bone substitute), both in terms of density and quantity.				
Bolukbasi *et al.* 2015 [25]	T0: 10 days after the sinus lift T1: 10 days post-implant placement T2: 6 months post-implant placement T3: 6 months after prosthetic loading T4: 12 months after loading T5: 24 months after loading	BL/IL T 1.43 1.38 1.37 1.32 1.30 *p* value = 0.022	 C 1.46 1.43 1.37 1.29 1.23	GSH/OSH T 4.26 4.78 4.78 4.39 4.39 4.36 *p* value = 0.093	 C 4.2 4.52 4.75 4.09 3.81 3.67
Nizam *et al.* 2018 [26]	Digital OPG 6 months later: Assessment of bone height (distance between the alveolar ridge and the highest point of regenerated bone in height, measured linearly on the radiographic image) Test group: 13.60 ± 1.09 Control group: 13.53 ± 1.20 *p* value = 0.88 Comparable results between the test group and the control group: Similar radiographic height between the two groups.				
Pichotano *et al.* 2019 [27]	Evaluation using 36 CBCT evaluations of the volumetric graft measurements (cm^3) T1: After the lifting operation. T2: After 4 months for the test group; After 8 months for control.				
	T1 (SD)	Test group	Control group	*p* value	
	T2 (cm^3)	1.68	1.46	0.20	
	T1–T2 (cm^3)	1.10	0.91	0.10	
	Reduction of the graft volume	0.58 (33.14*) (cm^3/%)	0.55 (36.71*) (cm^3/%)	0.78 (0.47*) (cm^3/%)	

* is referred to the unit of measurement of the values, in brackets, of reduction of the graft volume.

plant. If this ratio is greater than or equal to 1, the floor of the sinus is above the original sinus height. After this radiographic evaluation, this study concluded that there are no non-statistically significant radiographic differences [25].

Nizam *et al.* [26] showed a similar radiographic height of bone in the regenerated area between the test group and the control group.

In the study of Pichotano *et al.* [27] the interpretation of the radiographic investigations, through Cone Beam Computed Tomography (CBCT), did not reveal statistically significant differences in bone volume between the two groups (Table 4), demonstrating a p-value > 0.05.

Histological and Histomorphometric Results

As regards the histological data (Table 5, Ref. [24–27]), samples of both groups were similar in the included studies, characterized by the absence of significant signs of inflammation with areas of newly formed trabecular bone, connective tissue with enlargement, residual biomaterial, vascularization of the connective tissue, gaps, osteoblasts, osteoclasts, lymphocytes and polimorphonuclear leukocytes (PMN), connective tissue consisting of fibroblasts in the wound area and similar degree of vascularity and inflammation between the two groups [25]; Zhang *et al.* [24] demonstrated absence of significant signs of inflammation, Bio-Oss particles distributed evenly, formation of new bone tissue, active formation of fiber-intertwined trabecular bone, active reabsorption of Bio-Oss and, in some areas, the presence of residual Bio-Oss and signs of slight resorption in the area of bone formation.

Finally, Nizam *et al.* [26] and Pichotano *et al.* [27] demonstrated that both test group and control group showed overlapped clinical results.

Regarding the histomorphometric data (Table 6, Ref. [24–27]), Zhang [24] and Nizam [26] calculated the percentage of new bone formed, the percentage of residual bone substitutes and the percentage of contact length between the newly formed bone surface and the bone. They concluded that, concerning the above data, no statistically significant differences were found between the two groups.

At the same way, Bolukbasi *et al.* [25] and Pichotano *et al.* [27] both evaluated newly formed bone and biomaterials residual, demonstrated the absence of statistically significant differences between test group and control group.

Table 5. Histological evaluation data comparison.

Author Year	Histological characteristics of biopsy specimens (biopsy according to the Donath technique)
Zhang *et al*., 2012 [24]	Similar between the test group and the control group
	Absence of significant signs of inflammation.
	Bio-Oss particles distributed evenly.
	Formation of new bone tissue: Fiber-intertwined trabecular bone active formation of fiber-intertwined trabecular bone.
	Active reabsorption of Bio-Oss.
	In some areas, presence of Bio-Oss still intact, and signs of slight resorption (presence of osteoclasts).
	In the area of bone formation, there was the greatest number of vessels.
	In areas away from the sinus floor: Fibrous tissue poor in blood vessels.
Bolukbasi *et al*., 2015 [25]	Presence of:
	Areas of newly formed trabecular bone.
	Connective tissue with enlargement.
	Residual biomaterial.
	Vascularization of the connective tissue, gaps, osteoblasts, osteoclasts, lymphocytes and polimorphonuclear leukocytes (PMN).
	Connective tissue consisting of fibroblasts in the wound area.
	Similar degree of vascularity and inflammation between the two groups.
Nizam *et al*., 2018 [26]	Presence of newly formed bone tissue and residual graft material, connected together by a direct bond.
Pichotano *et al*., 2019 [27]	Overlapping results, albeit at different times: At 4 months in the test group; At 8 months in the control group.

The only significant difference between test group and control group was demonstrated by Pichotano *et al*. [27] in the timing of healing, which was earlier in the test group because the evaluation of clinical, radiological, histological and histomorphometric results was carried out in the test group 4 months before than the control group, achieving the same results in both ones.

Discussion

Findings from the Review: The Advantages of Considering Multiple Points of View

This systematic review evaluated the potential of Choukroun's L-PRF/PRF basing on the study selection, and in particular on the investigation methods used to evaluate the effectiveness of the PRF from four different points of view: Clinical, radiographic, histological, and histomorphometric. Indeed, the choice of the coexistence of the four types of evaluations in individual studies derives from the desire to compare works that would create an evaluation framework as complete as possible within the same population. Among these four elected studies, three appear to be of the randomized clinical trial (RCT) type [24,25,27]: Specifically, prospective RCT [24] and RCT with split-mouth method [25,27]; Thanks to the method of random allocation, these studies eliminate accidental bias or bias during the early phase of planning the study protocol, and also create study groups which can be compared more accurately, both on a qualitative and quantitative point of view [39]. The fourth study under review is a retrospective study [35]. As regards the study design, Bolukbasi *et al*. [25] provided a retrospective study, with a greater limit than the remaining studies, being more subject to systematic errors [39], as they depend on previously collected data, with a limited margin of reliability. Furthermore, unlike prospective studies, retrospective studies cannot estimate the incidence of a possible "new event".

Regarding the follow-ups, they range from a minimum of 4 months to a maximum of 8 months from the maxillary sinus lift operation, with some follow-ups extended to 12 months after the prosthetic load; Therefore, the follow-ups are relatively short. Regarding the results, in most of the studies, no statistically significant data was shown on the possible efficacy of PRF, except in Pichotano *et al*. [27], in which significant data is linked to the timing. Unlike other included studies, Pichotano *et al*. [27] carried out an earlier follow-up in the test group (at 4 months) than in the control group (at 8 months), not finding statistically significant differences in the two samples, but underlining the achievement of the same positive result, in the group test, at a distance of less time, compared to the control group. Furthermore, in this study, the clinical evaluation of implant survival is carried out using the Osstell tool to quantitatively assess the stability of implant-bone interface and calculate the ISQ index [27].

As regards the histological and histomorphometric data, the same parameters were examined in all the studies [24–27].

From a radiographic point of view, there was no homogeneity in the analysis tools used. Specifically, Zhang *et al*. [24] used OPG and CT dental scans to evaluate the quantity and density of mineralized bone tissue. Bolukbasi *et al*. [25] used OPGs to carry out measurements, which included calculating two indices, BL/IL and GSH/OSH. Furthermore, Nizam *et al*. [26] performed digital OPGs, for the evaluation of the height of the bone. Radiographic measure-

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Table 6. Histomorphometric evaluation data comparison.

Included studies	Test group	Control group	*p* value
Zhang *et al*., 2012 [24]			
Newly formed bone	18.35 % ± 5.62%	12.95 % ± 5.33 %	0.138
Biomaterial residues	19.16% ± 6.89%	28.54% ± 12.01 %	0.141
New bone-bone substitute contact	21.45% ± 14.57 %	18.57% ± 5.39 %	/
Bolukbasi *et al*., 2015 [25]			
Newly formed bone	35.0 ± 8.60 %	32.97 ± 9.71 %	0.61
Fibrous connective tissue	30.63 ± 7.53 %	33.94 ± 9.15 %	0.34
Biomaterial residues	33.05 ± 6.29 %	33.79 ± 8.57 %	0.87
Nizam *et al*., 2018 [26]			
Newly formed bone	21.38% ± 8.78%	21.25% ± 5.59%	0.96
Residual bone graft	25.95% ± 9.54%	32.79% ± 5.89%	0.06
Bone graft in contact with the newly formed bone tissue	47.33% ± 12.33	54.04% ± 8.36%	0.16
Fibrous connective tissue	52.67% ± 12.53%	45.96% ± 8.36%	0.16
Pichotano *et al*., 2019 [27]			
Newly formed bone (percentage increase)	44.58% ± 13.9%	30.02% ± 8.42%	0.0087
Biomaterial residues	3.59% ± 4.22 %	13.75 % ± 9.99 %	0.0111
Fibrous connective tissue	26.60% ± 11.13%	30.64 % ± 12.46%	0.3767

ments carried out by Pichotano *et al*. [27] on CBCT are the least invasive and the most accurate type of evaluation of bone volumes.

The Combined Use of PRF and DBBM did not Influence the Maxillary Sinus Lift Outcomes

Previous reviews conclude that there is no beneficial adjuvant effect in using PRF in sinus lift procedures; In particular, as reported in review of Ali *et al*. (2015) [40], PRF did not show benefits, compared to natural blood clot, neither have a beneficial effect on the process of maturation of DBBM. At the same time, the recent review of Damsaz *et al*. (2020) [41] demonstrated the absence of advantage or disadvantage in the use of PRF. In the other recent review of Ortega-Mejia *et al*. (2020) [32] it was concluded that the use of PRF in combination with other biomaterials does not give particular advantages.

The outcomes of this work, beyond adding new scientific evidence, aimed to justify the results that emerged through histological, histomorphometric, and clinical analyzes of the use of autologous and heterologous grafts. Indeed, also the study selection was the most possible complete, the data did not show any significant difference between the use of PRF and the use of combination of PRF and bone grafts in maxillary sinus lift interventions. The evaluation and classification of graft materials are mainly based on evaluating the graft materials' conductive and inductive capacity. Graft conductivity is the ability to represent an optimal substrate for developing the different phases of tissue healing, mediated by an inflammatory process inducing cell migration. Cellular induction is a phenomenon in which one cell, or a group of cells, changes the behavior, in terms of shape, mitotic activity and differentiation of another cell, or group of cells [42,43]. Furthermore, inductivity activates the metabolism and proliferation of undifferentiated and pluripotent mesenchymal cells to stimulate the differentiation pathway [40]. As highlighted by recent evidence, PRF shows these inductive properties, by promoting bone morphogenetic protein 2 (BMP2) expression, in oral fibroblast, through the activation of TGF-β signaling pathway. Autologous platelet concentrates show both conductive and inductive potentials, and the inductive potential discriminant does not explain why a difference between the various biomaterials has never been reached. Specifically, an in vitro study evaluated the reactions to different types of dentin derivatives and Bio-Oss in fibroblasts of the human periodontal ligament (HPLF) [28]. Their results were obtained using a bio-morphological analysis, carried out with a scanning electron microscope (SEM) with the aid of a colorimetric assay (XTT), and a confocal microscope (CLSM). As regards the Bio-Oss effects, SEM images show fibroblasts' different reactions when exposed to Bio-Oss, assuming a spheroidal appearance, characterized by a significant increase in volume, compared to the flat morphology, assumed in reaction to the other groups, represented by the dentinal derivatives. Moreover, the confocal microscopy data evaluated the state of the nuclei, the expression of constituents of the cytoskeleton, such as actin, vinculin, and integrin, and the state of cell proliferation. As regards fibroblasts exposed to Bio-Oss, it was observed that they had a stronger expression of vinculin and integrin 24 h after exposure. The same result was obtained for actin at 72 h and 7 days. As regards the state of activity of the cell nuclei, Ki67, a marker of proliferation, revealed that even in the sample with Bio-Oss, there was an important expression of the dye, suggestive of active cell proliferation. Through this study, it was possible to highlight the active inductive capacity of Bio-Oss towards HPLF. Common bone substitute applied

in bone regeneration, Bio-Oss is free of inductive factors; Anyway, this bone substitute may sustain the surrounding environment in tissue regeneration, due to its morphological features [44,45]. These data could represent an important key for interpreting the results included in this systematic review and previous studies on this topic [46,47].

Future Perspectives

In this perspective, the reason why a statistically significant difference between the use or not of PRF as a graft has never been detected, could be investigated. The main speculation is that PRF is an added value, due to its conductive and inductive properties, to obtain a good yield of the regeneration process mediated by Bio-Oss. However, this hypothesis can be viewed in a scaled-down way, as some results support the alleged intrinsic inductive properties of Bio-Oss, which could reduce the real effectiveness of the presence of PRF as an adjuvant factor to Bio-Oss.

Regenerative materials are not the only factors that influence the process of bone regeneration, which depends on the type of bone defect and the type of histology of the specific anatomical districts.

Finally, further new studies are needed, focusing on a more extensive evaluation, including clinical, radiological, histological and histomorphometric results, in order to have adequate data to produce a meta-analyses, so that it would be possible to investigate the potential of platelet concentrates in sinus lift techniques in comparison with other biomaterials, and to evaluate again the real inductivity properties of Bio-Oss help to confirm or not its greater predictability.

Limitations

The included studies are characterized by a positive approach of evaluating the outcomes which is a full examination, but they used different quantitative methods of assessment about radiological evaluation, using different radiological instruments, as OPT or CBCT or dental scan, without approaching this kind of evaluation through the same quantitative instruments of interpretation of abovementioned radiological exams, so that it is not possible to compare data with an higher degree of precision, in order to highlight the advantages or disadvantages of using PRF in maxillary sinus augmentation.

At the same time, outcome measures are not totally overlapped even in clinical, histologic and histomorphometric investigations. As consequence of the strategy of analysis of the included studies, this systematic review is limited to a qualitative interpretation of result, so that the summary of evidence is reduced.

Another limitation is about to the criteria of inclusion of only studies written in English.

Conclusions

No advantages, much less disadvantages, were highlighted in the application of the PRF in combination with Bio-Oss, the gold standard of grafting material. However, evidence show PRF could be useful for enhancing the healing process and preventing intra-operative complications such as oro-sinus perforations or post-operative complications.

Availability of Data and Materials

Data will be available upon reasonable request to the corresponding author.

Author Contributions

DG, NS and SBe—designed the research study; DG and NS—performed the research; DT and FR—provided help and advice on the qualitative results; SBi, MP and GV—substantially contribute in acquisition, manuscript draft writing and revisions. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Guarnieri R, Belleggia F, DeVillier P, Testarelli L. Histologic and Histomorphometric Analysis of Bone Regeneration with Bovine Grafting Material after 24 Months of Healing. A Case Report. *J Funct Biomater*. 2018;9(3):48. doi: 10.3390/jfb9030048

[2] Bianchi S, Bernardi S, Perilli E, Cipollone C, Di Biasi J, Macchiarelli G. Evaluation of Effectiveness of Digital Technologies During Anatomy Learning in Nursing School. *Appl Sci*. 2020;10:2357.

[3] Al-Moraissi EA, Alkhutari AS, Abotaleb B, Altairi NH, Del Fabbro M. Do osteoconductive bone substitutes result in similar bone regeneration for maxillary sinus augmentation when compared to osteogenic and osteoinductive bone grafts? A systematic review and frequentist network meta-

analysis. *Int J Oral Maxillofac Surg*. 2020;49(1):107–120. doi: 10.1016/j.ijom.2019.05.004

[4] Whyte A, Boeddinghaus R. The maxillary sinus: physiology, development and imaging anatomy. *Dentomaxillofac Radiol*. 2019;48(8):20190205. doi: 10.1259/dmfr.20190205

[5] Derjac-Aramă AI, Sarafoleanu C, Manea CM, Nicolescu MI, Vrapciu AD, Rusu MC. Regenerative potential of human schneiderian membrane: progenitor cells and epithelial-mesenchymal transition. *Anat Rec (Hoboken)*. 2015;298(12):2132–2140. doi: 10.1002/ar.23276

[6] Candotto V, Gallusi G, Piva A, Baldoni M, Di Girolamo M. Complications in sinus lift. *J Biol Regul Homeost Agents*. 2020;34(1 Suppl. 1):139–143.

[7] Raponi I, Giovannetti F, Buracchi M, *et al*. Management of orbital and brain complications of sinusitis: A practical algorithm. *J Craniomaxillofac Surg*. 2021;49(12):1124–1129. doi: 10.1016/j.jcms.2021.09.005

[8] Giovannetti F, Raponi I, Priore P, Macciocchi A, Barbera G, Valentini V. Minimally-Invasive Endoscopic-Assisted Sinus Augmentation. *J Craniofac Surg*. 2019;30(4):e359–e362. doi: 10.1097/SCS.0000000000005365

[9] Upputuri PK, Sivasubramanian K, Mark CS, Pramanik M. Recent developments in vascular imaging techniques in tissue engineering and regenerative medicine. *Biomed Res Int*. 2015;2015:783983. doi: 10.1155/2015/783983

[10] Bernardi S, Macchiarelli G, Bianchi S. Autologous Materials in Regenerative Dentistry: Harvested Bone, Platelet Concentrates and Dentin Derivates. *Molecules*. 2020;25(22):5330. doi: 10.3390/molecules25225330

[11] Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). *Trends Biotechnol*. 2009;27(3):158–167. doi: 10.1016/j.tibtech.2008.11.009

[12] Dohan DM, Choukroun J, Diss A, *et al*. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006;101(3):e37–e44. doi: 10.1016/j.tripleo.2005.07.008

[13] Fan Y, Perez K, Dym H. Clinical Uses of Platelet-Rich Fibrin in Oral and Maxillofacial Surgery. *Dent Clin North Am*. 2020;64(2):291–303. doi: 10.1016/j.cden.2019.12.012

[14] Fujioka-Kobayashi M, Miron RJ, Hernandez M, Kandalam U, Zhang Y, Choukroun J. Optimized Platelet-Rich Fibrin with the Low-Speed Concept: Growth Factor Release, Biocompatibility, and Cellular Response. *J Periodontol*. 2017;88(1):112–121. doi: 10.1902/jop.2016.160443

[15] Ai-Aql ZS, Alagl AS, Graves DT, Gerstenfeld LC, Einhorn TA. Molecular mechanisms controlling bone formation during fracture healing and distraction osteogenesis. *J Dent Res*. 2008;87(2):107–118. doi: 10.1177/154405910808700215

[16] Bornfeldt KE, Raines EW, Graves LM, Skinner MP, Krebs EG, Ross R. Platelet-derived growth factor. Distinct signal transduction pathways associated with migration versus proliferation. *Ann N Y Acad Sci*. 1995;766:416–430. doi: 10.1111/j.1749-6632.1995.tb26691.x

[17] Cromack DT, Porras-Reyes B, Mustoe TA. Current concepts in wound healing: growth factor and macrophage interaction. *J Trauma*. 1990;30(12 Suppl):S129–S133. doi: 10.1097/00005373-199012001-00026

[18] Pierce GF, Tarpley JE, Allman RM, *et al*. Tissue repair processes in healing chronic pressure ulcers treated with recombinant platelet-derived growth factor BB. *Am J Pathol*. 1994;145(6):1399–1410.

[19] Tsay RC, Vo J, Burke A, Eisig SB, Lu HH, Landesberg R. Differential growth factor retention by platelet-rich plasma composites. *J Oral Maxillofac Surg*. 2005;63(4):521–528. doi: 10.1016/j.joms.2004.09.012

[20] Linkhart TA, Mohan S, Baylink DJ. Growth factors for bone growth and repair: IGF, TGF beta and BMP. *Bone*. 1996;19(1 Suppl):1S–12S. doi: 10.1016/s8756-3282(96)00138-x

[21] Feng M, Wang Y, Zhang P, *et al*. Antibacterial effects of platelet-rich fibrin produced by horizontal centrifugation. *Int J Oral Sci*. 2020;12(1):32. doi: 10.1038/s41368-020-00099-w

[22] Dohan Ehrenfest DM, Del Corso M, Diss A, Mouhyi J, Charrier JB. Three-dimensional architecture and cell composition of a Choukroun's platelet-rich fibrin clot and membrane. *J Periodontol*. 2010;81(4):546–555. doi: 10.1902/jop.2009.090531

[23] Zhao R, Yang R, Cooper PR, Khurshid Z, Shavandi A, Ratnayake J. Bone Grafts and Substitutes in Dentistry: A Review of Current Trends and Developments. *Molecules*. 2021;26(10):3007. doi: 10.3390/molecules26103007

[24] Zhang Y, Tangl S, Huber CD, Lin Y, Qiu L, Rausch-Fan X. Effects of Choukroun's platelet-rich fibrin on bone regeneration in combination with deproteinized bovine bone mineral in maxillary sinus augmentation: a histological and histomorphometric study. *J Craniomaxillofac Surg*. 2012;40(4):321–328. doi: 10.1016/j.jcms.2011.04.020

[25] Bolukbasi N, Ersanlı S, Keklikoglu N, Basegmez C, Ozdemir T. Sinus Augmentation with Platelet-Rich Fibrin in Combination With Bovine Bone Graft Versus Bovine Bone Graft in Combination With Collagen Membrane. *J Oral Implantol*. 2015;41(5):586–595. doi: 10.1563/AAID-JOI-D-13-00129

[26] Nizam N, Eren G, Akcalı A, Donos N. Maxillary sinus augmentation with leukocyte and platelet-rich fibrin and deproteinized bovine bone mineral: A split-mouth histological and histomorphometric study. *Clin Oral Implants Res*. 2018;29(1):67–75. doi: 10.1111/clr.13044

[27] Pichotano EC, de Molon RS, de Souza RV, Austin RS, Marcantonio E, Zandim-Barcelos DL. Evaluation of L-PRF combined with deproteinized bovine bone mineral for early implant placement after maxillary sinus augmentation: A randomized clinical trial. *Clin Implant Dent Relat Res*. 2019;21(2):253–262. doi: 10.1111/cid.12713

[28] Bianchi S, Mancini L, Torge D, *et al*. Bio-Morphological Reaction of Human Periodontal Ligament Fibroblasts to Different Types of Dentinal Derivates: *In Vitro* Study. *Int J Mol Sci*. 2021;22(16):8681. doi: 10.3390/ijms22168681

[29] Bolander ME. Regulation of fracture repair by growth factors. *Proc Soc Exp Biol Med*. 1992;200(2):165–170. doi: 10.3181/00379727-200-43410a

[30] Bianchi S, Bernardi S, Mattei A, *et al*. Morphological and Biological Evaluations of Human Periodontal Ligament Fibroblasts in Contact with Different Bovine Bone Grafts Treated with Low-Temperature Deproteinisation Protocol. *Int J Mol Sci*. 2022;23(9):5273. doi: 10.3390/ijms23095273

[31] Zumarán CC, Parra MV, Olate SA, Fernández EG, Muñoz FT, Haidar ZS. The 3 R's for Platelet-Rich Fibrin: A "Super" Tri-Dimensional Biomaterial for Contemporary Naturally-Guided Oro-Maxillo-Facial Soft and Hard Tissue Repair, Reconstruction and Regeneration. *Materials (Basel)*. 2018;11(8):1293. doi: 10.3390/ma11081293

[32] Ortega-Mejia H, Estrugo-Devesa A, Saka-Herrán C, Ayuso-Montero R, López-López J, Velasco-Ortega E. Platelet-Rich Plasma in Maxillary Sinus Augmentation: Systematic Review. *Materials (Basel)*. 2020;13(3):622. doi: 10.3390/ma13030622

[33] Rochira A, Siculella L, Damiano F, *et al*. Concentrated Growth Factors (CGF) Induce Osteogenic Differentiation in Human Bone Marrow Stem Cells. *Biology (Basel)*. 2020;9(11):370. doi: 10.3390/biology9110370

[34] Marchetti E, Mancini L, Bernardi S, *et al*. Evaluation of Different Autologous Platelet Concentrate Biomaterials: Morpholog-

ical and Biological Comparisons and Considerations. *Materials (Basel)*. 2020;13(10):2282. doi: 10.3390/ma13102282

[35] Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. *AMIA Annu Symp Proc*. 2006;2006:359–363.

[36] Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. doi: 10.1136/bmj.b2700

[37] Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71

[38] Study Quality Assessment Tools. 2021. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (Accessed: 15th March 2023).

[39] Lim CY, In J. Randomization in clinical studies. *Korean J Anesthesiol*. 2019;72(3):221–232. doi: 10.4097/kja.19049

[40] Ali S, Bakry SA, Abd-Elhakam H. Platelet-Rich Fibrin in Maxillary Sinus Augmentation: A Systematic Review. *J Oral Implantol*. 2015;41(6):746–753. doi: 10.1563/aaid-joi-D-14-00167

[41] Damsaz M, Castagnoli CZ, Eshghpour M, *et al*. Evidence-Based Clinical Efficacy of Leukocyte and Platelet-Rich Fibrin in Maxillary Sinus Floor Lift, Graft and Surgical Augmentation Procedures. *Front Surg*. 2020;7:537138. doi: 10.3389/fsurg.2020.537138

[42] Langan SM, Benchimol EI, Guttmann A, *et al*. Setting the RECORD straight: developing a guideline for the REporting of studies Conducted using Observational Routinely collected Data. *Clin Epidemiol*. 2013;5:29–31. doi: 10.2147/CLEP.S36885

[43] Xu C, Dinh VV, Kruse K, *et al*. Induction of osteogenesis by bone-targeted Notch activation. *Elife*. 2022;11:e60183. doi: 10.7554/eLife.60183

[44] Kargarpour Z, Nasirzade J, Panahipour L, Mitulović G, Miron RJ, Gruber R. Platelet-Rich Fibrin Increases BMP2 Expression in Oral Fibroblasts via Activation of TGF-β Signaling. *Int J Mol Sci*. 2021;22(15):7935. doi: 10.3390/ijms22157935

[45] Iaquinta MR, Martini F, D'Agostino A, *et al*. Stem Cell Fate and Immunomodulation Promote Bone Regeneration *via* Composite Bio-Oss®/Avitene™ Biomaterial. *Front Bioeng Biotechnol*. 2022;10:873814. doi: 10.3389/fbioe.2022.873814

[46] Zhao R, Yang R, Cooper PR, Khurshid Z, Shavandi A, Ratnayake J. Bone Grafts and Substitutes in Dentistry: A Review of Current Trends and Developments. *Molecules*. 2021;26(10):3007. doi: 10.3390/molecules26103007

[47] Bianchi S, Torge D, Rinaldi F, Piattelli M, Bernardi S, Varvara G. Platelets' Role in Dentistry: From Oral Pathology to Regenerative Potential. *Biomedicines*. 2022;10(2):218. doi: 10.3390/biomedicines10020218