CATÓLICA
FACULDADE DE MEDICINA DENTÁRIA
VISEU

SINUS LIFT ASSOCIATED WITH SECOND GENERATION OF AUTOLOGOUS PLATELET CONCENTRATES: A SYSTEMATIC REVIEW

Dissertação apresentada a Universidade Católica Portuguesa
Para obtenção do grau de Mestre em Medicina Dentaria

Por:
Ada Isis Pelaez Otero

Viseu, 2021

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SINUS LIFT ASSOCIATED WITH SECOND GENERATION OF AUTOLOGOUS PLATELET (L-PRF) CONCENTRATES FOR BONE GAIN: A SYSTEMATIC REVIEW

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Co-orientador: Gustavo Fernandes

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Happiness is your dentist telling you it won't hurt and then having him catch his hand in the drill.

Johnny Carson

Acknowledgments

To my mother and father, who, thanks to their advice and words of encouragement, have helped me to grow as a person, always giving me strength, affection, and wise advice. I love you both so much

My grandmothers Lucrecia and Eva for giving me so much love, support and for always being there for me in one way or another. For teaching me how to be a strong woman and fight for what I want.

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ABSTRACT

Introduction. The purpose of this systematic review was lift to analyze the available literature of clinical studies involving sinus lifting and comparing the efficiency of 2nd autologous platelet concentrates (APC) generation related to its effects in bone gain and to clarify the regenerative efficacy of APC in sinus lift procedure, whether alone or as a coadjutant to other bone graft materials.

Material and methods. This systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (1) with the focused question being determined according to the Population, Intervention, Comparison and Outcome, Follow-up (PICO) strategy. The protocol for this systematic review was registered on PROSPERO. The focused question for the present review was as follows: "In clinical studies with patients needing a maxillary sinus lift (P), does the use of ACPs either alone (I) or in conjunction with other biomaterials (C) improve the clinical outcome associated with bone gain and density (O), with at least 3 months of follow-up? An electronic search was conducted by two reviewers (A.I.P. and G.V.O.F.), independently, either electronic as manual search, through MEDLINE (PubMed), Science Direct, and Scopus databases with a platform-specific search strategy combining terms such as "*sinus floor elevation*", "*sinus augmentation*", "*platelet-rich fibrin*", "*second generation"*, or *"PRF"*, and variables.

Results. A total of 443 articles were obtained from the electronic database search, 67 on PubMed, 129 on Science Direct, and 247 on Scopus. An additional publication was considered from the manual search through the references of the included articles. After a full-text review, a total of 16 articles met all the criteria and were included in this review.

Conclusion. Through the use of APCs in sinus augmentation the time required for bone graft maturation may be significantly reduced thus allowing sooner implant insertion, however overall long-term bone development did not show any significant difference.

Keywords*:* *Sinus floor elevation, Sinus augmentation, Platelet-Rich Fibrin, Second generation, PRF*

RESUMO

Introdução. O objetivo desta revisão sistemática é analisar a literatura disponível em estudos clínicos envolvendo levantamento do seio e comparar a eficiência da 2ª geração de concentrados autogolos plaquetarios APC relacionada aos seus efeitos no ganho ósseo e esclarecer sua eficácia regenerativa no procedimento de levantamento do seio, seja sozinho ou como coadjuvante de outros biomateriais.

Material e métodos. A questão em foco para a presente revisão foi a seguinte: "Em estudos clínicos com pacientes que precisam de elevação do seio maxilar (P), o uso de ACPs, isoladamente (I) ou em conjunto com outros biomateriais (C), melhora o resultado clínico associado com ganho e densidade óssea (O), com no mínimo 3 meses de seguimento ? Uma busca eletrónica foi conduzida por dois revisores (A.I.P e G.V.O.F), de forma independente, tanto electrónica quanto manual, por meio de bancos de dados MEDLINE (PubMed), ScienceDirect e Scopus com uma estratégia de busca específica da plataforma combinando termos como "elevação do assoalho do seio", "Aumento do seio", "fibrina rica em plaquetas", "segunda geração" ou "PRF" e variáveis.

Resultados. Um total de 443 artigos foi obtido a partir da busca em banco de dados eletrónico, 67 no PubMed, 129 no Science Direct e 247 no Scopus. Uma publicação adicional foi considerada a partir da pesquisa manual nas referências dos artigos incluídos. Após a revisão do texto completo, um total de 16 artigos preencheram todos os critérios e foram incluídos nesta revisão.

Conclusão. Através do uso de APCs no aumento do seio, o tempo necessário para a maturação do enxerto ósseo pode ser significativamente reduzido, permitindo a inserção mais rápida do implante, no entanto, o desenvolvimento ósseo geral a longo prazo não mostrou nenhuma diferença significativa.

Palavras-chave*: Elevação do seio maxilar, Fibrina Rica em Plaquetas, Segunda geração, PRF.*

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APC	Autologous Platelet Concentrate
CGF	Concentrated Growth Factor
DBBM	Deproteinized bovine bone matrix
FDBA	Freeze-dried bone allograft
ISQ	Implant Stability Quotient
L-PRF	Leucocyte –Platelet Rich Fibrin
PRF	Platelets Rich in Fibrin
PRGF	Platelet-rich in growth factors
RFA	Resonance Frequency Analysis
PRP	Platelet-rich plasma
PDGF	Platelet-derived growth factor
IGF	Insulin-like growth factor
VEGF	Vascular endothelial growth factor
TGF-β	Transforming growth factor-beta

1. INTRODUCTION

After tooth removal, resorption of the alveolar ridge arises, which is particularly noticeable in the maxilla, due to the thin cortical-type bone found. Consequently, the maxillary sinus tends to pneumatize, increasing in volume, hampering the implant positioning, and, in many cases, this happens a short period after tooth extraction. [2,3] This insufficient amount of bone makes it almost unmanageable to place an implant in the edentulous space, therefore reducing the possibilities of rehabilitation. [4] Thus, the need for reconstruction and elevation of the maxillary sinus arose, as soon as dental implants became a common procedure for dental rehabilitation.

Tatum was the first author to describe the lateral window technique in 1975 [3], being the first surgeon to perform a sinus lift augmentation in order to prepare the site for implant placement. Nonetheless, sinus elevation has been not an easy task, mostly due to the anatomical variations that may be present on the patient, such as a deviated septum or twisting of the uncinate process, since this may compromise the sinus integrity, due to drainage lessening [4], differences in the Schneiderian membrane, with a prevalence of 68% and the variations of bone thickness, which may allow perforations of the aforementioned membrane, and affect the integrity of the surgery. [3,4]

Few years after Tatum's description, Boyne and James were among the first surgeons to report an autogenous graft for sinus augmentation. After those procedures, the search for a good regenerative option has never stopped. [3] Thereby, several grafting techniques and procedure modifications have been done, to improve outcome, reduce patient discomfort, and improve biocompatibility. [5] More than a few graft materials have been commonly used in maxillary sinus augmentation, most frequently xenografts, since they are widely available, biocompatible, have a low degradation profile, and limited osteoconductive potential. [3,5,6] Besides, allograft and alloplastic are also used but may have certain unfavorable characteristics, which are not present in the xenografts, making the latest the main biomaterial in grafts used for sinus lift. [2,4]

With the objective of developing protocols that promote hemostasis and healing on all the surgical areas, fibrin has been the target of numerous studies. The main goal being to find a biocompatible biomaterial, that promotes and improve the healing process, is readily available and affordable for both patient and professional. [2] The application of fibrin as an

adjunct biomaterial has been proven useful in numerous studies since it can enhance the concentration of growth factors in the surgical area, thus leading to improve healing. [2,4,6]

Based on those premises, platelet-rich plasma (PRP) also known as the first generation of blood concentrates was initially exhibited to be successful in the activity of alveolar edge enlargement and promptly spread to the fields of periodontal and oral maxillofacial medical procedure. [6] Nonetheless, it had some barriers: costly, operator-dependent, an astringent within the tube, and extended generation time. [2,5–8]

The second generation for blood concentrates, also known as platelet-rich fibrin (PRF), was developed by Choukroun *et al.* in the early 2000s. This biomaterial has a greater amount of fibrin, platelet, and leucocytes and, either fibrin alone or in combination with different materials, has been utilized as a natural platform for stem or essential cells to regenerate adipose, bone, sensorial, connective tissues, skin, ligaments, and tendons [2,7], thereby, proving fibrin as a flexible natural biopolymer, showing an extraordinary potential in tissue recovery and wound mending. [7] This generation of autologous plasma concentrate did not use anticoagulants or any additional substances inside the tubes. [2,8]

In 2006, Sacco developed a new generation of blood concentrate, also designated as third-generation, known as concentrated growth factor (CGF). This new concentrate is rich in fibrin and growth factors similar to PRF, which also are proved to help in cell proliferation and differentiation, inducing bone and tissue formation, as well as having pro-angiogenic properties. [8]

The 2nd and 3rd generations existent in the literature suggested that the blood harvested must be instantly centrifuged. Afterward, three layers are acquired: at the bottom, red blood corpuscles (RBC); at the top, platelet-poor plasma (PPP); and between them, a fibrin clot (PRF). This PRF clot contains a thick fibrin fiber arrange where platelets and leucocytes are snared and it can serve as a system for other sorts of cells. Its affluence in leucocytes and platelets comes about in a steady discharge of growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF). [2,5–7,9–11]

However, even though it has been proved that both concentrates have a good release potential of growth factors and cytokines, there is not a clear agreement in the literature as of CGF certainly being that much improved as to be called 3rd generation, and it is seen being used interchangeably by clinicians with similar results. [6–8,11,12]

APC has proved to be useful in sinus lift surgery, helping with the release of cytokines, thus accelerating neovascularization and controlling the inflammatory process. Correspondingly, the high concentration of growth factors, leukocytes, and platelets present on PRF matrices, help in the development of new bone. [4,7]

The uses of PRF alone as a biomaterial for sinus floor elevation have been reported. Aoki *et al.* (2016) used PRF alone, since it has therapeutic properties and serves to preserve the sinus membrane during subsequent placement of the implant and reduced the likelihood of sinus infection (9). The authors were able to demonstrate that PRF clot alone, increased significantly a new bone formation histologically. [9] Other researchers have described similar outcomes, by means of an average improvement of implant the site with the use of autologous platelet concentrate (APC), by itself but not as much when combining with other biomaterials. [3–5,8,9,11,12]

Since PRF, is easily available, there is no need for a secondary surgical site and is not costly, it could be a good option as a sole biomaterial or adjunctive with bone graft for the maxillary sinus lift procedure. Thus, the purpose of this systematic review is to analyze the available literature involving clinical studies of sinus lifting and comparing the efficiency of 2^{nd}-APC generation related to its effects in bone gain and to clarify the regenerative efficacy of APC in sinus lift procedure, whether alone or as a coadjutant to other bone graft materials.

2. MATERIAL AND METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines[1] with the focused question being determined according to the Population, Intervention, Comparison and Outcome, Follow-up (PICO) strategy. The protocol for this systematic review was registered on PROSPERO, CRD42021236993, provided by the Centre for Reviews and Dissemination/CRD (University of York).

2.1 Focused Question

The focused question for the present review was as follows: "In clinical studies with patients needing a maxillary sinus lift (P), does the use of ACP's either alone (I) or in conjunction with other biomaterials (C) improve the clinical outcome associated with bone gain and density (O), with at least three months of follow-up (T)?

2.2 Information sources and search strategy

An electronic search was conducted by two reviewers (A.I.P. and G.V.O.F.), independently, either electronic as manual search, through MEDLINE (PubMed), Science Direct, and Scopus databases with a platform-specific search strategy combining terms such as "*sinus floor elevation*", "*sinus augmentation*", "*platelet-rich fibrin*", "*second generation"*, or *"PRF"*, and variables (Table 1). An additional manual search was performed over the references of articles that met the inclusion criteria to identify relevant publications. Only articles published in the English language from January 2006 until and including August 2020 were included. If there was any doubt about whether or not something should be included, a third reviewer was consulted (T.B.).

Table 1 – Search strategy carried out and filters applied.

	P – In clinical studies with patients needing a maxillary sinus lift
#1	((“Sinus Floor Augmentation" [mesh Terms]) OR (“Sinus floor elevation) OR (Sinus lift))
	I – does the use of autologous concentrated platelets
#2	((“Platelet-Rich Fibrin” [mesh Terms]) OR (ACP) OR (Second generation; platelet concentrate) OR (L-PRF]))
#3	**C – with or without the addition of another biomaterial**
#4	**O – improve the clinical outcome associated with bone gain and density**
Search combination	(#1 and #2) No combination was done with **#3** and **#4**, since the preponderance of the papers on sinus elevation consider bone gain and density, and the combination with keywords related to outcome would limit further the results.
Filters	English, Humans, January 2006-August 2020, *in vivo, Clinical Studies*

2.3 Inclusion and exclusion criteria

The inclusion criteria for the selection were *in vivo* clinical studies published in the English language from January 2006 up to August 2020, which included histological and/or radiological evaluation, and only second generation of APC or superior was used either alone or in conjunction with others biomaterials.

The exclusion criteria were articles that did not meet the inclusion criteria, *in-vitro* studies, animal studies, and clinical studies with associated with complications, abstracts, posters, editorial letters, systematic/narrative review, and meta-analyses. Duplicate articles were also excluded, and the remaining articles were screened first by title and then by abstract, to evaluate if inclusion/exclusion criteria were met.

3. RESULTS

A total of 443 articles were obtained from the electronic database search, 67 on PubMed, 129 on Science Direct, and 247 on Scopus. An additional publication was considered from the manual search through the references of the included articles. Of the 443 articles initially establish and after careful screening of title and abstract a total of 32 studies were considered for full-text evaluation of the inclusion and exclusion criteria.

The title screening of the PubMed results lead to 22 articles to be posteriorly evaluated by abstract; six articles were excluded for not meeting the inclusion criteria. After abstract assessment, a total of 16 articles were considered by full-text to perform this systematic review. Title screening on the results obtained from ScienceDirect resulted in 8 titles to be posteriorly evaluated by abstract after abstract evaluation only 6 titles were selected for full-text analyses and 9 out of the 247 found on Scopus, due to studies either being duplicated or not meeting the inclusion criteria (Fig.1). After a full-text review, a total of 15 articles met all the criteria and were included in this review. Due to not meeting exclusion criteria, detailed in Table 2, 18 full-text studies were excluded.

Table 2. Excluded studies and reason for exclusions.

Author/Year	Reason for exclusion
Xin *et al., 2020*	Data not clear for evaluation
Silberman *et al.,* 2020	Data does not meet inclusion criteria (focus on perforation)
Mohamadamin Damsaz *et al., 2020*	Review, Data not clear for evaluation
Xie *et al.,* 2019	Full text only available in Chinese
Wang *et al.,* 2019	Data does not meet inclusion criteria (focus on infection)
Chandra *et al.,* 2019	Data does not meet inclusion criteria (maxillary sinus)
Batas *et al., 2019*	Focus on first-generation
Öncü *et al.*, 2017	Data does not meet inclusion criteria (focus on perforation)
Karaca *et al., 2017*	Only the first generation of ACP discussed
Peker *et al.,* 2016	Data does not meet inclusion criteria (animal)
Anitua *et al., 2016*	Report of immediate placement
Taschieri *et al., 2015*	Only the first generation of ACP discussed
Tanaka *et al. 2015*	Data does not meet inclusion criteria
Anitua *et al., 2015*	Data mostly on short implants and first-generation
Troedhan *et al., 2015*	Only anterior maxilla discussed
Amin Rahpeyma, 2014	Only poster/abstract available
Inchingolo *et al., 2010*	Full text not available
Meyer *et al.,* 2009	Full text only available in French

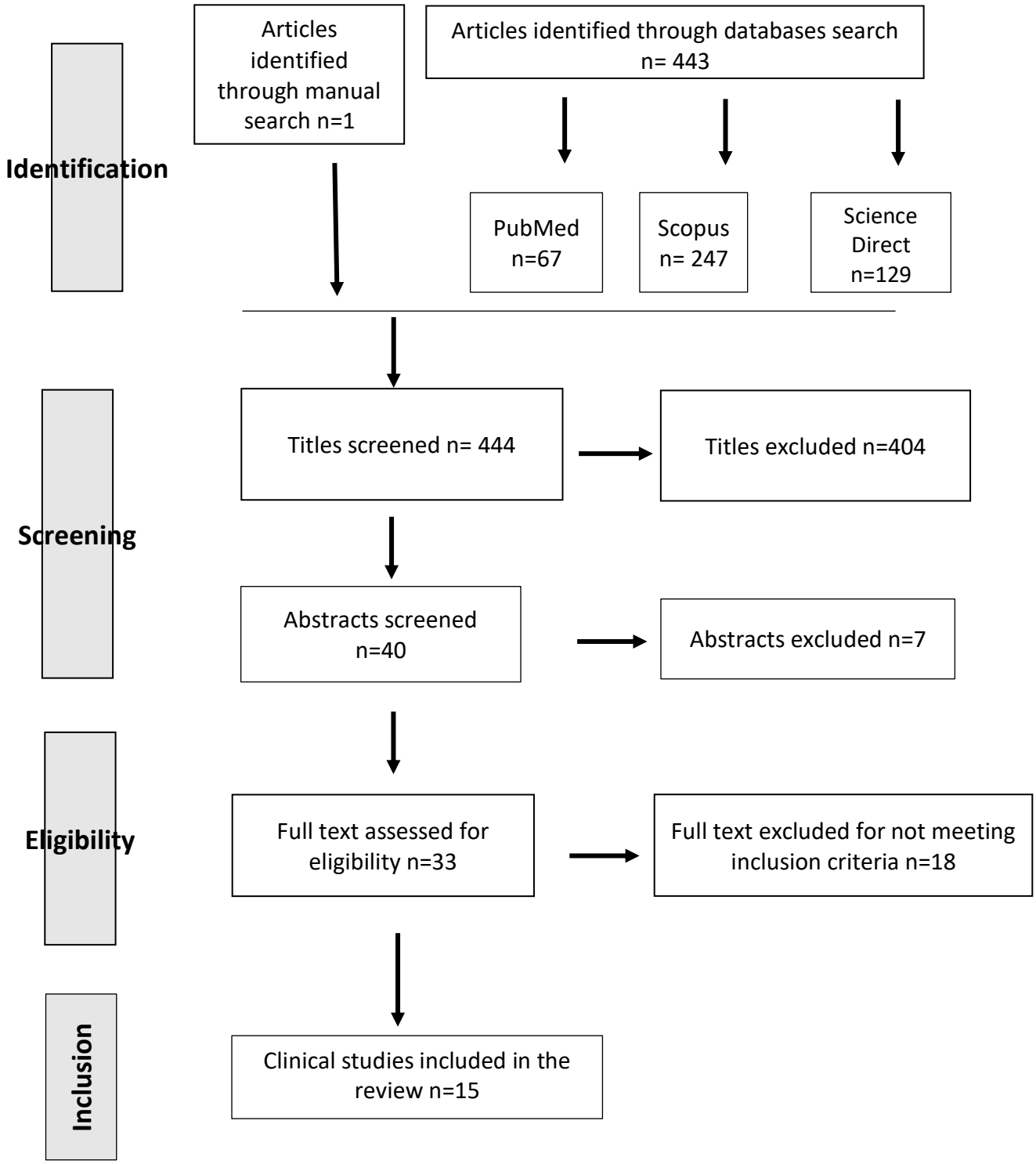

Figure 1. Flow diagram for the search strategy and selection process.

3.1 Studies characteristics

Within the 15 studies selected for inclusion in this review, five were controlled clinical trials [13–16], six were randomized clinical trials [17–23], two retrospective clinical trials[9,24], a clinical histologic study[23], and one case report [25], all of them published between January 2006 and August of 2020 (Table 3).

3.2 Inclusion and exclusion criteria

The inclusion criteria for all studies was based on fit individuals, however, it was not specified at all in two of the 16 studies [14,15] and one of them only reported 6 healthy individuals [20]. All patients were over 18 years old that presented with some sort of edentulism of the maxilla in need of sinus floor elevation, and with a small residual bone height.

Exclusion criteria were not specified in six of the 16 studies [9,15,20,24,25], amount of residual bone height, patients with disorders that may compromise the final results, or with contraindication for implant surgery were the most common contraindications. Perforation of the Schneiderian membrane was a contraindication in one of the studies [16], and the amount of tobacco use was only specified in six of the studies, smokers and ex-smoker were excluded in one of them [18], the current smoking habit was part of the exclusion criteria in four of the studies [17,21–23] and heavy smoking was part of the exclusion criteria in one of them [13] (Table 3). Diabetes was only specified as exclusion criteria in 4 of the studies [23,25–27], alcohol and drug abused were only specified in two of the studies. [13,25]

The amount of residual bone height was referred to as inclusion and exclusion criteria in 8 of the studies. Cho *et al.* denoted reduced residual bone height, which made the placement of implants with a length longer than 8.5 mm impossible, as inclusion criteria and less than 5 mm of residual bone height as an exclusion criterion. Maxillary atrophy with residual ridge < 5mm was part of the inclusion criteria in three of the studies [21–23] and less than 4mm in another two [13,25] and 7 mm or less of residual bone height was a criterion for inclusion of the study of Cömert Kılıç S et al..[19]

Chronic sinus infection and chemotherapy were also considered as exclusion criteria in six of the studies analyzed for this review [19,21,22,25,26], the use of specific drugs such as bisphosphonates was only mentioned as an exclusion criterion in three of the research [21,23,25] and Nizam *et al.*. is the only study that presented the amount of time of being edentulous

specified as exclusion criteria, in this case, edentulous patient of less than one year were excluded from the research.

TABLE 3. Studies Inclusion and exclusion criteria.

Author/Year	Type of study	Inclusion criteria	Exclusion criteria
Cho *et al., 2020*	Randomized control trial	Any healthy patient over the age of 18 who has edentulism in the posterior maxilla and a decreased RABH, making the placement of implants longer than 8.5 mm unfeasible.	Systemic or local contraindications for implant placement, such as a history of untreated metabolic problems, smoking habits, bruxism, or uncontrolled periodontal disease, as determined on a cone-beam computed tomography (CBCT) scan and a residual bone height of less than 5 mm.
Kempraj *et al., 2020*	Clinical Study	Patients between 20 and 60 years old with severe maxillary atrophy in the sinus region less than 4 mm	Patients with uncontrolled systemic disorders, heavy smoking, alcohol or drug addiction, and uncontrolled periodontal disorders are all at risk.
Pichotano *et al., 2019*	A double-blinded, randomized controlled trial	Patients having a residual bone height of less than 4 mm who needed bilateral sinus floor augmentation for implant placement in the posterior maxillary area (based on CBCT)	Patients with poor general health, smokers or ex-smokers, alcoholics and drug addicts, irradiated patients, pregnancy, and bisphosphonate therapy Immunosuppressive drugs, blood platelet abnormalities, and chronic pain Patients with sinusitis or other pathology in the maxillary sinus, With diabetes that is uncontrolled
Aoki *et al., 2018*	Clinical Retrospective	Maxillary posterior tooth loss, good general health or manage medical conditions, implant placement by sinus floor elevation with PRF alone as the grafting material, informed consent granted, and follow-up visit performed at our	Not specified

		facility following implant installation.	
Pichotano *et al., 2018*	Case clinical report	1 patient split mouth, patient reported no relevant medical history that could compromise bone healing, denied smoking or used of alcohol	Not specified
Nizam *et al., 2018*	Prospective randomized clinical trial	Systemically healthy, age 21 years or older, implant therapy required in bilateral posterior maxilla with a residual bone height of less than 5 mm, and periodontally healthy	Any systemic disease, use of any medications that could interfere with bone metabolism (i.e., corticosteroids, bisphosphonates), smoking, history of maxillary sinusitis or sinus surgery, history of reconstructive or previous implant surgery, and being edentulous for more than a year are all factors to consider.
Cömert Kılıç *et al., 2017*	Randomized clinical trial	Age >20 years, atrophic maxilla, previous posterior tooth loss, residual bone crest height = 7 mm or less on orthopantomographs, and atrophic maxilla.	Had a maxillary sinus infection or hematologic, neurologic, or systemic problems, had radiotherapy or chemotherapy, had inflammatory or connective tissue illness, or had malignant disease in the head and neck region.
Aoki *et al.*, 2016	A Clinical retrospective study	Case 1: good general health and non-smoker Case 2: no systemic pathology, smoker	Not specified
Gassling *et al., 2013*	Randomized controlled study	6 healthy patients	Not specified

Tatullo *et al., 2012*	Randomized clinical trial	A preoperative radiological and tomographic assessment revealed maxillary atrophy with a remnant ridge of less than 5mm. Due to toothlessness, anatomo-functional rehabilitation of the posterior maxilla is required.	Hemo-coagulative diseases Diabetes Incompetence/Immunological deficiency Previous head-neck radiation treatment Normal bone physiology anomalies Bisphosphonate-based treatments Smokers and ex-smokers would both be excluded
Zhang *et al., 2012*	Clinical Study	Not specified	Blood platelet problems, aspirin therapy prior to surgery, viral and metabolic diseases, radiation, and acute and chronic maxillary sinus inflammation are all things to consider.
Toffler *et al., 2010*	Clinical Study	Not specified	Not specified
Choukroun *et al., 2006*	Histologic clinical study	Thrombocyte concentrations in the blood are within normal limits, and there is no history of maxillary sinus irritation. A significant atrophy of the maxilla was discovered during the clinical examination and preoperative radiography.	Patients with immunologic disorders, uncontrolled diabetes, current chemo- or radiotherapy, or a history of drug misuse should not be considered.
Olgun *et al., 2018*	Randomized clinical trial	Age≥18 years Systemically healthy Non-smokers; Full-mouth plaque and bleeding score ≤15% Presence of a residual crest height of <5 mm in the posterior maxilla as detected on X-rays	Infectious and metabolic illnesses; Blood platelet abnormalities Chemotherapy or radiotherapy is still being administered. Chronic sinusitis in the maxillary sinuses is a common occurrence. Antibiotics and/or anti-inflammatory medicines are being taken.

Anitua *et al., 2012*	Clinical Study	All of the patients in the research had severe alveolar atrophy and a class D residual bone height.	Any local or systemic disorders that can make the treatment ineffective. Perforation of the Schneiderian membrane.

3.3 Quality assessment and risk of bias

We used a risk-of-bias evaluation tool to assess the risk of bias in the included randomized controlled trials, as well as for the non-randomized clinical trials in order to perform a methodological quality assessment.

Table 4. Quality assessment risk of bias for non-randomized clinical trials.

	Selection			Comparability		Outcome			Total Score
	Adequate definition of patient cases	Representatives of patient cases	Selection of controls	Definition of controls	Control for important or additional factors (Max of 2X)	Ascertainment of exposure	Was follow-up long enough for outcomes to occur	Adequacy of follow up	
Kempraj et al., 2020	X	X	X	X	XX	X	X	X	**9**
Aoki et al., 2018	X	X	X	X	X	X	X	X	**8**
Pichotano et al., 2018	X			X	XX	X	X	X	**7**
Nizam et al., 2018	X	X	X	X	X	X	X	X	**8**
Aoki et al., 2016	X	X			X	X	X	X	**6**
Zhang et al., 2012	X	X	X	X	X	X	X		**7**
Anitua et al., 2012	X	X	X		X	X	X	X	**7**
Toffler et al., 2010	X	X	X	X	XX	X			**7**
Choukroun et al., 2006	X	X	X	X	XX	X	X	X	**9**

Table 5. Quality assessment risk of bias for randomized clinical trials.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cho *et al*. 2020	+	**?**	**?**	**?**	+	+	+
Pichotano *et al*. 2019	+	+	**?**	+	+	+	**?**
Olgun *et al. 2018*	+	+	**?**	-	+	+	+
Cömert Kılıç *et al*. 2017	+	**?**	**?**	+	+	+	+
Gassling *et al*. 2013	+	+	**?**	+	+	+	**?**
Tatullo *et al*.. 2012	+	**?**	-	-	+	+	+

Table 5 shows the quality of the randomized studies that were included. Risk of bias summary for randomized studies ("+" denotes a low risk of bias; "?" denotes an unknown risk of bias; and "-" denotes a high risk of bias

3.4 Total patients, age, and amount of surgeries

These trials included 354 patients, 431 sinus lift procedures, and 683 implant placements, including patients ranging in age from 18 years old for Cho *et al.* younger's patient to 90 years old for Toffler *et al.* senior's patient. [15,17] Because some studies only reported the youngest or/and oldest patient who had been part of the trial, and others did not report the total number of patients, the mean age of the treatment group could not be computed. These findings will be discussed in greater depth subsequently.

Cho *et al.* reported their patient niche as any healthy patient 18 years or older, they had a total of 40 patients 21 males and 19 females, and placed a total of 45 implants in 40 lifted sinuses. [17] Kempraj *et al.*. realized 22 direct sinuses lift in 11 patients, with an age range between 20 and 60 years old, they did not report how many female or male patients they saw and did not report the placement of implants. Pichotano *et al.* (2019) mean patient age was 54.17 ± 6.95 years from 43 to 63 years, comprised of a total of 12 patients that needed bilateral sinus lift, 6 male and 6 female, and placed a total of 38 implants [18], in their 2018 report [25] they had a male patient of 59 years old in need of bilateral sinus elevation and to whom 2 implants were placed.

Aoki *et al.* 2018 had the biggest age range with patients as young as 29 and as old as 82 years old, with a mean age of 57.6 years. They had a sample of 17 females and 17 males for a total of 34 patients who receive a total of 34 sinus lifts and 71 implants were placed. [24] In their 2016 report, they had 2 different patients, a 28-year-old female in need of sinus elevation and implant placement and a 58 years old male with a failed implant, that needed sinus elevation for posterior implant placement. [9]

Nizam *et al.* reported a patient mean age as 49.92 ± 10.37, with a range from 35 to 65 years old, made of nine male patients and four females; they realized a total of 26 sinus lift surgeries and placed a total of 58 implants in those 13 patients described. [21] Cömert Kılıç *et al.* had a total of 26 patients divided between the different test and control groups, with a mean age of 49.92 ± 10.37, two females and seven males in the control group; four females and five males in P-PRP group and three females and five males in PRF group, they performed a total of 26 sinus lift and no implant placement was reported. [19]

Gassling *et al.* reported 12 sinus lift surgeries and a total of 32 implants placed in six patients with a mean age of 61 years old, the number of females or males was not reported [20].

Tatullo *et al.* reported the placement of 240 implants on a total of 60 patients, 48 females, and 12 males, with an age range of 43 to 62 years old, after 72 sinus lift surgeries. [23]

Zhang *et al.* as well as Olgun *et al.* specified the age range of the control and the test group, Zhang *et al.* test group mean was 46.2 and control group was 43.5, while Olgun *et al.* reported it as 53 ± 8.96 and 51 ± 7.94 respectively. Zhang *et al.* realized 11 sinus elevations in 10 patients, two females, and 8 males, and places a total of eleven implants, on the other hand, Olgun *et al.* placed a total of 37 implants, after sinus lift surgery on 18 patients, nine females and nine male. [22,28]

Toffler *et al.* reported the most patients (110), as well as the majority of sinus lift procedures (138). They placed 138 implants in all, with 70 women (92 sites) and 40 men (46 sites). The patients' ages ranged from 34 to 90 (mean age of 58.4 years). [15] Choukroun *et al.* and Anitua *et al.*, on the other hand, did not report the age range or the proportion of female or male patients treated; in fact, Choukroun *et al.* did not even report the number of patients; he reported nine sinus lift surgeries followed by nine implant placements, and five patient and five sinus lift were reported. [16,26]

3.5 Follow-up

The follow-up period and frequency varied between authors, the shorter follow-up being three months and the longer seven years. Aoki *et al.* had an average follow-up time of 3.43 years in one of his studies, from one to seven years [24] and 24 months on other of his studies. Nizam *et al.* and Cömert Kılıç *et al.* had a total follow up time of 18 months [19,21]. Olgun *et al.*, Toffler M *et al.*, Gassling *et al.*, and Cho YS *et al.,* all reported a follow-up period of one year. [15,17,20,22]

A follow-up period of eight months was described by Tatullo *et al.* and Choukroun *et al.*. [23,26] and of six months by Zhang *et al.* [28], Kempraj *et al.* recounted several follow up periods from three months to over two years, Pichotano *et al.* of ten months and Anitua *et al.* of 33 months [13,16,25], as can be seen on Table 6.

Table 6. Follow-up period.

Author/Year	Follow-up
Kempraj *et al., 2020*	3 months over 2 years
Cho *et al., 2020*	1 year
Pichotano *et al.,2019*	4, 8 months, and at implant placement and loading (time not specified)
Pichotano *et al., 2018*	10 months
Olgun *et al., 2018*	1 year
Nizam *et al., 2018*	12 months after implant loading (18 months)
Aoki *et al., 2018*	Average 3.43 years (1-7 years)
Cömert Kılıç *et al., 2017*	18 months 6month after surgery 12 months after loading
Aoki *et al*., 2016	24 months
Gassling *et al., 2013*	1 year follow up after implant placement (17 months)
Zhang *et al.,2012*	6 months
Tatullo *et al., 2012*	8 months
Anitua *et al., 2012*	33 months
Toffler *et al., 2010*	1 year
Choukroun *et al., 2006*	8 months

3.6 Surgical approach and residual bone height.

The most common surgical approach between all of the authors was the lateral window approach, first described by Tatum in the 1970s [16,20,21,23,25–28], modified Caldwell-Luc was only reported by Cömert Kılıç S *et al.*. and the balloon-lift technique is only mentioned by Olgun *et al.*. [19,22]. The other most common surgical approach for sinus lift between the authors was the crestal, trans-crestal and mid-crestal approach [9,13,15,17,18,24] as detailed in Table 7.

Table 7. Surgical approach.

Author/year	Surgical approach	Residual bone height
Kempraj *et al.,* 2020	Mid-crestal incision	Less than 4mm
Cho *et al.,* 2020	Trans-crestal sinus lift	Over 5mm
Pichotano *et al.,* 2019	Lateral window	Less than 4mm
Pichotano *et al*., 2018	Lateral window	Not reported
Olgun *et al.,* 2018	Balloon-lift technique	Less than 5mm
Nizam *et al.,* 2018	Lateral window	2.53 mm
Aoki *et al.,* 2018	54 implants were placed by trans-crestal approach and 15 by the lateral approach	Ranged from 0.56 mm to 9.60 mm
Cömert Kılıç *et al.,* 2017	Modified Caldwell-Luc	Not reported
Aoki *et al.,* 2016	Trans-crestal	Pt#1 2.7mm pt#2 less than 2mm
Zhang *et al.,* 2012	Lateral window	Less than 5 mm
Tatullo *et al.,* 2012	Tatum's technique (lateral window)	Less than 5 mm
Gassling *et al..,* 2012	Lateral window	Less than 5 mm
Anitua *et al.,* 2012	Lateral window	Less than 3 mm
Toffler *et al.,* 2010	Trans-crestal	4 to 8 mm
Choukroun *et al.,* 2006	Lateral window	Not reported

3.6 Membrane perforation and implant failure

Complications such as membrane perforation were only reported by four authors and only two reported implant failures. Kempraj *et al.* reported a membrane perforation, that was healed adding a PRF membrane [13], Cömert Kılıç *et al.* reported five, Toffler M *et al.* described three and Choukroun J *et al.* stated one sinus perforation.(15,19,26)

Toffler M *et al.* reported a total of three implant failures before loading [15], and Aoki N *et al.* reported seven implant failures, all of them when the residual bone height was less than 4 mm [24].

3.7 Biomaterials used

All of the studies used PRF as the main biomaterial, some only used PRF, while others compared the effectiveness of using only PRF or PRF combined with other biomaterials such as Bio-Oss®, β-TCP, or freeze-dried bone allograft.

The most common adjunct biomaterial used by the researchers was Bio-Oss® (Geistlich Pharma AG, Wolhusen, Switzerland). The study made by Kempraj *et al.* was the only one that compared sinus augmentation with only PRF and PRF+Bio-Oss®[13], Bio-Oss®+PRF compared to Bio-Oss® alone was preferred by five authors. [16,18,21,23,28]

A mixture of Bio-Oss® plus cortilocancelous bone and PRF, for the study group, and cortilocancelous bone+Bio-Oss®+collagen membrane for the control group were the biomaterials preferred by the study of Gassling *et al.* [20] and Pichotano *et al.* 2018 compared the use of collagen membrane with a PRF membrane and Bio-Oss®, versus only using a collagen membrane and Bio Oss in the control group. [25]

Choukroun *et al*. and Cömert Kılıç *et al.* did not use Bio-Oss® as a bone substitute material but freeze-dried bone allograft was the preferred biomaterial by the first and PRF+ β -TCP compared to PRP+β-TCP and β-TCP alone was preferred by the latter. [19,26]

Four of the authors preferred not to use any type of bone substitute but just PRF membranes as their preferred biomaterial; of those authors, only Cho *et al.* compared the use of PRF versus saline water in the sinus augmentation procedure. [9,15,17,24] (Table 8).

Table 8. Biomaterials applied within the studies.

Author/Year	PRF alone	PRF + Bone substitute	Only Bone Substitute
Kempraj *et al., 2020*	YES	PRF+BIO-OSS®	N/A
Cho *et al., 2020*	YES	N/A	N/A
Pichotano *et al., 2019*	NO	PRF+BIO-OSS®	Bio-Oss®
Pichotano *et al., 2018*	NO	PRF+BIO-OSS®+COLLAGEN MEMBRANE	BIO-OSS®+COLLAGEN MEMBRANE
Olgun *et al., 2018*	YES	N/A	N/A
Nizam *et al., 2018*	NO	PRF+BIO-OSS®	BIO-OSS®
Aoki *et al., 2018*	YES	N/A	N/A
Cömert Kılıç *et al., 2017*	NO	PRF+β-TCP / PRP + β -TCP	β -TCP ALONE
Aoki *et al*., 2016	YES	N/A	N/A
Gassling *et al., 2013*	NO	PRF+CORTILOCANCELOUS BONE+BIO-OSS®	CORTILOCANCELOUS BONE+BIO-OSS® + COLLAGEN MEMBRANE
Zhang *et al., 2012*	NO	PRF+BIO-OSS®	BIO-OSS®
Tatullo *et al., 2012*	NO	PRF+BIO-OSS®	BIO-OSS®
Anitua *et al., 2012*	NO	PRF+BIO-OSS®	BIO-OSS®
Toffler *et al., 2010*	YES	N/A	N/A
Choukroun *et al., 2006*	NO	PRF+FREEZE-DRIED BONE ALLOGRAFT	FREEZE-DRIED BONE ALLOGRAFT

N/A = not available.

3.7.1 PRF as the sole biomaterial

PRF was employed as the only grafting material in five trials [9,15,17,22,24] for a total of 232 lift surgeries in 204 patients, the authors chose the crestal approach, and 293 implants were inserted in the enhanced areas. PRF membranes were inserted into the sinus cavity to fill the space; the average residual bone height at T0 was 5.45 mm, spanning from 0.56 to 9.6 mm. The average of new bone development with PRF alone cannot be stated since Aoki et al. 2018 and 2016 did not address it.

Aoki *et al*. 2018 reported a total of seven implant failures, but exclusively in patients with a residual bone height of less than 4 mm at T0 [24]. Toffler *et al*. also reported three implant losses, all of which occurred before the loading phase, in areas that had a sinus floor elevation with a gain of 3 to 4 mm but had an initial residual bone height of 4 mm, and all the implants were replaced 16 weeks later with no further complications observed, and PRF was used as the grafting material. [15]

During the recovery process, no major complications were identified. Clear sinus membrane perforations were identified in 5 cases (3.5%) [15] and were easily repaired using PRF membranes.

3.7.2 PRF with allograft

Only Choukroun *et al.* [26] research used PRF combined with demineralized freeze-dried bone allograft (DFDBA). In nine sinuses, 29 sinus lifts were executed using the lateral approach. They fill three sinuses that acted as a control group; with DFDBA granules (Phoenix, TBF, Mions, France). The allograft/PRF mixture was used to fill the remaining six sinuses, and PRF membranes were employed to cover the sinus membranes. For implant placing, stage 2 surgery was executed, and samples were taken 4 months after surgery for the experimental group and 8 months following surgery for the control group. Perforation of the Schneiderian membrane occurred in one case, but it was easily repaired using PRF.[26]

In the allograft/PRF group, histomorphometric examination revealed that there was 65 percent vital new bone and 35 percent inert bone in the bone trabecular areas after four months. The proportion of vital new bone and inert bone in the bone trabecular areas was 69 percent vital new bone and 31 percent inert bone in the control group after eight months. [26]

The control group (FDBA alone) and the test group (FDBA+PRF) seemed to have similar bone structures, as per histomorphometric assessment. Nonetheless, the healing times of the two groups were not the same, 4 versus 8 months, it seems when PRF is combined with FDBA to perform sinus floor augmentation, bone regeneration appears to be enhanced, enabling implant insertion after only 4 months of recovery. [26]

3.7.3 PRF with Xenografts

PRF was used in combination with Bio-Oss® (Geistlich Pharma AG, Wolhusen, Switzerland) in nine studies with a total of 124 patients and 191 sinus lift surgeries, the lateral approach was the preferred surgical access method, performed by seven of the researchers [16,18,20,21,23,25,28] and only Kempraj *et al.* performed a mid-crestal surgical approach [13], a total of 381 implants were placed in 157 of those elevated sinuses since Kempraj *et al.* did not perform any implant surgery. [13]

In all trials, a radiographic examination was done using panoramic radiography or a CT scan to assess bone development. No major complications were identified during the recovery process and only Kempraj *et al.* reported a perforation of the Schneiderian membrane which they solve by placing a PRF membrane and then waited three months in order to elevate the sinus again. [13]

The exact amount of bone gain was not reported by all of the researchers, some relied only in the x-ray images to demonstrate that a significant amount of volume had been gain after the surgical procedure.[21,23,25] The authors that reported a higher amount of bone gain were Anitua et al., with a test group bone gain varying from 20% to 30% versus just an 8% gain in the control group [16], Kempraj *et al*. also reported a significant difference between the control (PRF alone 6.545 mm) group and the test group of PRF+Bio-Oss® that reported an average gain of 12.636 mm. [13]

3.7.4 PRF with synthetic bone graft

PRF was used in conjunction with beta-tricalcium phosphate (β-TCP) in one of the includes studies[19], it included a total of 26 patients, divided into 3 groups, the control group was composed of nine patients, another 9 in the PRP plus β-TCP group and 8 patients were

included in the PRF group, PRF was prepared by the using the procedure described by Choukroun, and the was mixed with the β-TCP particles by hand, then this mixture was placed in the study group for sinus augmentation, the lateral window was covered after surgery with a membrane of collagen in all groups. [19]

All patients were called for follow-up and implantation six months after the sinus elevation, and bone biopsies were harvested at that point, the composition and distribution of histologic features in the P-PRP, PRF, and control groups biopsies were remarkably similar. [19] all of them displayed a large amount of new bone development as well angiogenesis around the β-TCP units, also a high amount of inflammatory cells were found in the PRF group when compared with the control or P-PRP, the amount of new bone formation in the PRF group was 32.03 % resulting in a slightly less development than when mixed with PRP. [19]

3.8 New bone formation

The amount of new bone formation was not reported in six of the studies. [9,21,23–25] All other studies reported the amount of bone gain in different ways; some reported the amount of new bone formation as a percentage and others by the number of millimeters of bone gain. The highest amount of bone gain of 33% was reported by Cömert Kılıç *et al.*, however, he did not report a difference between the control and the test group. [19] Anitua *et al.* reported the second-highest amount of bone gain of 20-30% in the test group, much better than the amount of new bone formation that was reported for the control group of only 8%. [16] Kempraj *et al.* reported the highest amount of bone gain when PRF was used in aggregation with BIO-OSS®, with an average bone gain of 12.636 mm, compared to the mean of 6.545 mm obtained when PRF was used by itself [13]. A mean increase of 3.5 mm of bone was reported by Toffler *et al.* when using only PRF. [15] All other studies reported a similar amount of bone gain between the control and the test group (Table 9).

Table 9. Description of the amount of newly formed bone.

Author	New bone formation
Kempraj *et al.., 2020*	PRF alone mean: 6.545 mm PRF+ Bio-Oss® 12.636 mm
Cho *et al.., 2020*	2.5mm ± 1.2mm (PRF) 1.7±1.0 mm (Saline)
Pichotano *et al.., 2019*	PRF+ DBBM 2.35mm^2 DBBM 1.58 mm^2
Pichotano *et al.., 2018*	Not reported
Olgun *et al.., 2018*	Test 16.58 mm (1.05) % Control 17.28 mm (2.53) %
Nizam *et al.., 2018*	Not reported
Aoki *et al.., 2018*	Not reported
Cömert Kılıç *et al.., 2017*	Mean of 33% in all groups
Aoki *et al.*., 2016	Not reported
Gassling *et al.., 2013*	PRF mean 17% Collagen 17.2%
Zhang *et al.., 2012*	Test group 18.35% ± 6.62% Control group 12.95% ±5.33%
Tatullo *et al.., 2012*	Not reported
Anitua *et al.., 2012*	20-30% Test group 8% Control
Toffler *et al.., 2010*	Mean increase 3.5 mm (3.4-5mm)
Choukroun *et al.., 2006*	Test group: 65% vital new bone 35% inert bone (4M) Control group: 69 % vital new bone 31% inert bone (8M)

3.9 Implant stability quotient (ISQ)

Implant stability quotient was only reported by four of the research included in this review [18,22,23,25], this measurement may be taken in two ways, using implant resistance (Periotest, Avtec Dental, Mount Pleasant, SC, USA) or resonance frequency analysis (RFA). [29] This measure is important to evaluate the stability of the dental implant and could be measure from 1 to 100, however, a range of 55 to 85 is considered suitable to declare implant stability and comprehensive development of osseointegration. [25,29]

Pichotano *et al.* reported the ISQ value in both of their research. [18,25] the method to analyze the implant stability rate was the RFA device (Osstell; Integration Diagnostics, Gothenburg, Sweden), and it was done straight away after implant placement and at the loading phase for both groups. [18,25] In their 2018 study they measure ISQ at 4 months for the

test group and 8 months for the control group, they found an ISQ of 75.13 ± 5.69 in the control group, which was significantly higher than that found on the test group 60.90 ± 9.35; nonetheless, at the time of loading the ISQ value of the test group had incremented significantly to 76.08 ± 5.86, reducing the previous difference, they reported at that time of loading no significant difference between both groups. [25]

Pichotano *et al.* 2019, followed a similar procedure to measure the ISQ, they used the same type of RFA device (Osstell; Integration Diagnostics, Gothenburg, Sweden). [18] An initial ISQ mean in the study group was reported as 69.5 at 4 months after sinus elevation and an ISQ value of 77 was on the control group at the initial measurement at 8 months after the initial surgery. A second measurement was taken at the loading phase which resulted in an ISQ average of 81.5 in the study group, which demonstrated a significant boost when compared with the initial measurements, and of 75.75 in the control group, demonstrating a similar result than on the initial ISQ. [18]

Olgun *et al.* only measure the ISQ three months after implant placements, also using the RSA technique (Ostell ISQ, Gothenburg, Sweden). [22] They reported an ISQ value of 68.50 in the test group and 66.37 in the control group, showing no significant difference between the groups. [22]

Tatullo *et al.* also used the resonance frequency analysis to assess the implant stability rate[23], and the results were 37.2 in the early protocol group, 106 days after sinus lift, 36.8 in the intermediate protocol group, 120 days after sinus lift, and 39.1 in the late protocol group, 150 days after sinus lift, showing no significant difference between the test and control groups. [23]

3.10 Albrektsson's implant success criteria

None of the articles included in this systematic literature review acknowledged Albrektsson's implant success criteria. [30] Meant for maxillary implants, this determination is based on 1-, 5-, and 10-year follow-ups and a subsequent success rate of none complications reported and 100 percent success rate during the first year, 85 percent success rate after five years, and at least an 80 percent survival rate after ten years. However, the results reported by Aoki *et al.* met the criterion partially, since they reported a cumulative survival implant rate of 85.7 % at 7 years [24], but the ten-year results are still missing.

4. DISCUSSION

The goal of this study was to see how the second generation of APC affected open maxillary sinus augmentation surgeries. The findings of this literature review revealed that just a few clinical investigations have been conducted. Furthermore, given the diversity of the identified research in terms of surgical technique, grafting material, implant placement time, protocol, sample characteristics, biopsy, implant placement healing time, and follow-up period, meta-analysis was not possible.

Biomaterials are employed as space maintainers and bone scaffolds during sinus lift to enhance healing, in the sub-sinus area, bone renewal occurs and the popular consensus is that several biomaterials could be used in the sinus lift procedures as a result of the high osteogenic potential of the Schneiderian membrane's. [31]

Choukroun's PRF is a simple and low-cost technique that can be employed in daily practice.[2,3,16,23,28] This is the simplest and most cost-effective technique for creating autologous fibrin membrane or platelet concentrate. [2,8] The systematic use of this biomaterial during sinus lift, even without bone substitute, appears to be a highly attractive choice, particularly for the Schneiderian membrane protection.[2,5,8,10,12,16,18,23,31]

Concentrated growth factor (CGF) is considered as the third generation of autologous material[7], which is composed of a denser fibrin matrix, thus is richer in growth factors. However, it was not included in this systematic review due to the fact that during the selection process we did not come across any human studies that comply with the inclusion criteria and specifically reported the use of CGF for maxillary sinus augmentation.

This may be due to the reality that, indeed, in spite of the fact that it has been demonstrated that both concentrates have a great discharge potential of growth factors and cytokines, there is not a clear understanding within the literature as to CGF certainly being that much progress as to be called 3rd generation, and it is seen being utilized interchangeably by clinicians with comparable results. [6–8,11,12,32]

Biomaterials such as L-PRF can be used either as a single graft material or combined with other materials.[8,16,18,21,23,25,26] In clinical practice, the BIO-OSS® (DBBM) + L-PRF combination is frequently used since BIO-OSS® is biocompatible and has osteoconductive qualities, and various studies have shown that it has a high clinical success rate with satisfactory results.[14,16,18,21,23] However, because Bio-Oss® lacks osteogenic and osteoinductive qualities, as well as the fact that maturation can take up to eight months, the

implant placement limitation is established,[13,18,26] as a result, it is critical to include additional biomaterial that can act as a scaffold, allowing osteogenic cells from the maxillary sinus to migrate to the graft, permitting bone neoformation. [2,10,14,21,23]

Another advantage of the mixing of L-PRF and Bio-Oss® is the existence of a fibrin network in the L-PRF minimizes the dispersion of DBBM particles, resulting in a reduction in the amount of grafting material required to reestablish the height of the maxillary ridge when Bio-Oss® + L-PRF is used. [14,18,21]

Choukroun *et al.* used PRF in conjunction with a freeze-dried bone allograft (FDBA) to increase the sinus floor. Histological assessments suggested that sufficient new bone growth was seen in their study. Furthermore, the blended graft material has the potential to speed up the healing process. According to histomorphometric analysis, the control group (FDBA alone) and the test group (FDBA+PRF) had similar bone characteristics. Despite the fact that the two groups' healing durations were not equal (4 vs. 8 months), it indicates that when PRF is paired with FDBA to perform sinus floor augmentation, bone regeneration appears to be improved, allowing implant insertion after only 4 months of recovery. [26] Similar results were obtained by Pichotano *et al.* and Tatullo *et al.* for the two authors; they found a faster maturation of the bone graft, which predicts a shorter healing time before implant placement, as well as a 100 percent implant survival rate, after four months of healing. [23,25]

PRF membrane by itself also provides excellent results, but mostly when the sinus to be elevated has a residual bone height of more than 4 mm since most of the implant failures reported were in maxillary sinuses whose initial residual height was below those parameters. [24] Thus, the use of PRF alone for the maxillary sinus augmentation could not be adequate is the amount of bone that needs to be gained is over 3 to 4 mm [17] since the sinus membrane may collapse the PRF plug [13], hence the recommendation of adding other biomaterials to the PRF in those cases. [13,17] Another factor to be taken into consideration if a PRF membrane is going to be used without any other biomaterial, could be the immediate implant placement to act as a tent pole [15,24], this could help to maintain the elevated sinus membrane into the desired position. Then again, the most important factor for implant survival rate when using PRF either alone or in conjunction with another biomaterial is the initial residual bone height, since this may change the final prognosis. [5,10,15,24]

When it comes to bone gain or new bone formation, almost all of the literature agrees that there is no significant difference in the amount of bone formation when PRF is used by itself than when PRF is used with other biomaterials [13,14,18–20,22,26], but Anitua *et al.*. that reports an increase of 20%-30% in the study group versus an eight percent in the control group. [16]

Based on the literature we can say that the use of PRF surpassed the benefits of the use of the first generation of ACPs, as reported by Batas *et al..,* whose study demonstrated that adding platelet-rich in growth factors (PRGF), first-generation, with Bio-Oss® grafting for maxillary sinus floor augmentation did not improve bone growth 6 months after surgery when compared to DBB grafting alone, they reported PRGF as an adjuvant to Bio-Oss® for maxillary sinus lift does not appear to enhance or interfere with bone development inside the human sinus 6 months after surgery, except for enhanced handling during the procedure. [27]

The main reason for a maxillary sinus lift is to be able to rehabilitate the area with implants, either immediately or at a second stage surgery and a significant factor that should be used by the professional in choosing a simultaneous over a delayed implant placement is the quantity of residual crestal bone [5,10,15,24] in the posterior maxilla as it relates to establishing primary implant stability, that is why the ISQ quotient is important, however, this was only reported in 4 studies. [18,22,23,25] similar ISQ quotients were reported by all of the authors ranging from 60 to 75 [18,22,25], but Tatullo *et al.* who reported an average ISQ of 35 for all the different groups. [23] Tatullo *et al..* reported results are not consistent with the literature since we should only state that implant stability has been achieved if we have at least an ISQ in the range of 55 to 85. [18,29]

A direct comparison of published reports was difficult due to the wide range of study design, inclusion and exclusion criteria, patient age and gender, smoking habits, implants placed or not, follow-up intervals, use or non-use of a PRF or collagen membrane to cover the graft, and amount of residual bone height between the sinus floor and alveolar crest. This demonstrates the difficulty experienced when attempting to draw findings from non-controlled trials, due to the inclusion of many other confounding variables that may impact the success of the sinus lift treatment.

As a result, it was impossible to isolate all of these distinct variables in this literature systematic review. The quantity of bone development after surgery and ISQ were explored as the main outcomes in this research since they are easy to determine, although long-term

success is more valuable yet involves particular criteria to be determined. Regrettably, these criteria varied considerably between investigations.

5. CONCLUSION

Several types of research have shown that sinus augmentation treatments are very predictable, with many trials showing 100% success. The type of graft material used, PRF alone or in combination with other biomaterials, as well as the amount of residual alveolar height, can all have an impact on this type of surgery. It may be concluded that the highest risk of surgical failure or implant failure after a sinus lift augmentation can be seen in patients with a residual alveolar height of 4 mm or less.

The use of PRF either alone or in conjunction with another biomaterial has been demonstrated in the literature to be effective to reduce the amount of time needed for new bone formation, and thus, the amount of time needed for implant rehabilitation of the edentulous area. It could be agreed that the healing period can be reduced to almost half when PRF is used in the maxillary sinus lift elevation surgery.

More high-level evidence studies are needed to assess PRF's performance, either alone or in combination with other bone substitutes, in the maxillary sinus elevation surgery, and to assess the impact of other variables on the survival of implants placed in the grafted maxilla.

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