Review Article

HISTOLOGIC AND HISTOMORPHOMETRIC ANALYSIS OF SINUS FLOOR ELEVATION USING CALCIUM PHOSPHATE MATERIALS: A SYSTEMATIC REVIEW

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ABSTRACT

Teeth loss in the maxillary arch leads to progressive bone atrophy, and enlargement of maxillary sinus cavities can significantly increase the difficulty of the replacement of natural teeth with dental implants. It was decided to clarify and evaluate alloplastic grafts (calcium phosphate ceramics – beta-tricalcium phosphate (β-TCP) and biphasic calcium phosphate (BCP)) after maxillary sinus lifts to see which material retains bone volume better. Interventions included a two-stage sinus floor elevation using β-TCP or BCP as the bone substitute. Comparison groups included a two-stage sinus floor elevation using a different autograft, allograft, xenograft, alloplastic material, or combinations of these substances. In total 8 studies fulfilled all inclusion criteria and underwent systematic review: 6 randomized clinical trials, and 2 cohort studies. Five studies included in this systematic review histologically described the formation of the new bone. Sinuses augmented with β-TCP showed a mean volume of new bone ranging from 26.92% ± 7.26% to 47.6% ± 9.9% and an average residual volume of graft ranged from 30.39% ± 10.29% to 32.25% ± 8.48% in reviewed articles. Sites augmented with BCP (comprising β-TCP and hydroxyapatite) showed an average bone volume ranging from 23.0% ± 8.80% to 43.4% ± 6.1% and the remaining volume of evaluated grafting material ranged from 16.4 ± 11.4% to 32.9% ± 15.6%. Biphasic calcium phosphate and β-tricalcium phosphate could have favourable results in sinus floor elevation procedures. Alloplast can ensure sufficient new bone formation and a stable volume of residual graft particles compared to other graft materials.

Key words: Sinus lift elevation, Calcium phosphate, Histologic analysis, Histomorphometric analysis.

Introduction

Teeth loss in the maxillary arch leads to progressive bone atrophy, and enlargement of maxillary sinus cavities can significantly increase the difficulty of the replacement of natural teeth with dental implants [1]. Nowadays, sinus floor elevation surgical procedure has become increasingly popular procedures before the placement of dental implants in posterior maxillae [2]. The first sinus lift procedure was performed by Tatum in 1976 which modified the Caldwell-Luc technique by preparing a lateral bony window to dissect and elevate the maxillary sinus Schneiderian membrane [3].

There are a lot of bone graft materials that are typically used for bone formation in the maxillary sinuses. In 1989 was clear that the ideal graft should be nontoxic, nonantigenic, noncarcinogenic, strong, resilient, easily fabricated, able to permit tissue attachment, resistant to infection, readily available, and inexpensive [4].

Graft materials in dentistry can be subdivided into four subcategories: autografts, allografts, xenografts, and phytogenic materials [5].

Speaking about autografts there are no histocompatibility and immunogenicity issues, thus they represent the highest degree of biological safety. Cancellous autograft bone contains osteoblasts and progenitor cells with considerable osteogenic potential [5]. Using autograft to maximize bone remodeling performance and healing potential, a combination of cancellous and cortical bone should be used [6]. The best alternative to an autograft is the use of allograft materials. Allografts exhibit good histocompatibility [5]. Xenografts have variable resorption rates, a lack of viable cells and biological components, and the need for tissue treatment processes that enable the retention of osteoinductive cells [7]. Phytogenic material has been shown to possess osteoinductive properties, increased alkaline phosphatase activity, and thus promote bone calcification and remodeling processes [8]. Nowadays, the market can be found synthetic materials which display only osteointegration and osteoconductive properties [9]. In this category of materials, we can find calcium phosphate ceramics (hydroxyapatite (HA), beta-tricalcium phosphate (β-TCP), biphasic calcium phosphate (BCP), bioglass) and others [10]. Moreover, it is noticed that TPC has good osteoconduction, radiopacity allowing monitoring of healing, good resorbability, and low immunogenicity but has poor mechanical properties in particular compressive strength. However, compared with BCP, BCP has osteoinduction and comparatively greater mechanical strengths than either TCP [5]. An animal study showed that the BCP ceramic exhibited similar tissue integration compared to the TCP group [11]. Due to different statements found in the literature, it was decided to clarify and evaluate alloplastic grafts (calcium phosphate ceramics – β-TCP and BCP) after maxillary sinus lift to see which material retains better bone volume.

Materials and Methods

A systematic review of the literature was performed between April 3, 2017, and April 3, 2022, according to the PRISMA selection criteria. The research was conducted independently by all authors in electronic databases, including PubMed Medline, Science Direct, Wiley Online Library, The Cochrane Library, and references of relevant studies. Databases were searched using the query: (β-TCP OR beta-tricalcium phosphate OR biphasic calcium phosphate) AND sinus AND (lift OR augmentation) AND (histomorphometric OR histomorphometry).

The protocol for the review was registered prospectively in the PROSPERO, registration number: CRD42022316448.

Interventions included a two-stage sinus floor elevation using β-TCP or BCP as the bone substitute. Comparison groups included a two-stage sinus floor elevation using a different autograft, allograft, xenograft, alloplastic material, or combinations of these substances.

This systematic review included studies in which the patients were augmented maxillary sinus using BCP or β-TCP and the percentage of newly-formed bone and the percentage of a residual bone substitute were histomorphometrically evaluated from bone biopsies obtained during implantation.

Clinical studies with humans published less than 5 years ago, written in the English language, and describing histomorphometric assessment of native bone and bone graft changes after maxillary sinus lift were analyzed in this systematic review. All meta-analyses, systematic and narrative reviews, letters to the editor, case reports or case series, animal, in vitro studies, or those with incomparable results, were excluded.

The PICO criteria for the present review were as follows:

- Patients: Patients for whom lateral maxillary sinus floor augmentation is indicated
- Intervention: Open sinus floor elevation.
- Comparison: Two-stage sinus floor elevation using a different graft material: BCP, β-TCP, autograft, allograft xenograft, or alloplastic material, or combinations of these substances.
- Outcome: Histomorphometric and histological analysis of newly formed bone and residual graft particles after sinus floor elevation using different grafting materials focusing on results of BCP or β-TCP.

The titles and abstracts after applying pre-established selection criteria first were analyzed, followed by the full-text review and analysis of complete articles. Any disagreements between reviewers over the inclusion of studies in the systematic review were resolved by discussion until a consensus was reached.

Quality assessments were also evaluated in included studies. The tool used for randomized controlled trials: RoB 2 tool: A revised Cochrane risk of bias tool for randomized trials [12], a tool used for observational studies: ROBINS-I Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) [13].

The important data (publications date, augmented sinuses or patients, used bone substitute materials, time until histologic, histomorphometric evaluation, main results, and outcomes) were independently extracted and collected from included articles.

Results and Discussion

Study selection

The literature research resulted in a total of 654 publications. After applying pre-established eligibility criteria, 184 articles were left for screening. After excluding publications with inappropriate titles or content, for full-text assessment 21 articles were involved. Finally, 8 of them fulfilled all inclusion criteria and underwent systematic review **(Figure 1)**.

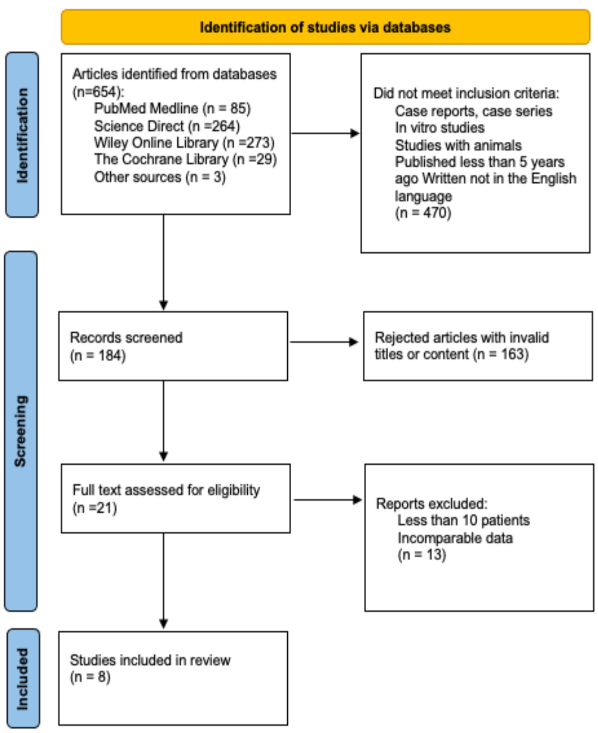

Figure 1. PRISMA flow diagram.

Studies design and characteristics

In this systematic review, 8 studies were included: 6 randomized clinical trials [14-19], 2 cohort studies [20, 21].

All studies included focused on new bone formation after lateral sinus augmentation using alloplastic graft. Three of them evaluated the effects of β-TCP alone [17, 19, 21] and five clinical trials have assessed the effects of BCP (comprising β-TCP and hydroxyapatite) [14-16, 19, 20]. This review also includes studies evaluating the effects of additional substances such as PRP, PRF [17, 18], or enamel matrix proteins (EMD) [16] on new bone formation after sinus augmentation with an alloplastic graft. The study's design and characteristics are shown in **Table 1**.

Table 1. Studies design and characteristics.

No.	Author, year, and reference	Study design	Patients (augmented sinuses)	Time until histologic and histomorphometric evaluation (months)
1.	Sokolowski *et al.*, 2020, [14]	RCT	20 (20)	3, 6
2.	J.S. Oh *et al.*, 2019, [15]	RCT	56 (60)	6
3.	J. C. Nery *et al.*, 2017, [16]	RCT	10 (20)	6
4.	Comert Kilic *et al.*, 2017, [17]	RCT	26 (26)	6
5.	R. S. Pereira *et al.*, 2017, [21]	CS	20 (33)	6
6.	I. C. Cinar *et al.*, 2020, [18]	RCT	20 (20)	6
7.	R. D. Kraus *et al.*, 2020, [19]	RCT	51 (51)	6
8.	R. Kolerman *et al.*, 2019, [20]	CS	13 (26)	9

RCT - randomized clinical trial, CS – cohort study

Quality assessment

Risk of bias evaluation with the RoB 2 tool found that 4 of 6 included randomized studies characterized as low risk, and 2 had some concerns [14-19]. Results of the risk of bias in randomized studies are shown in **Figure 2**.

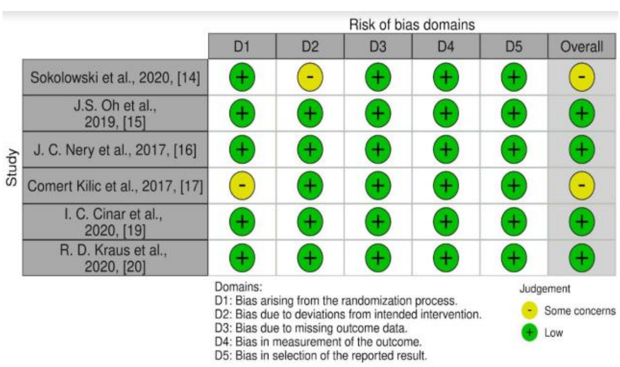

Figure 2. Risk of bias assessment using RoB 2 tool.

Assessing the risk of bias of included publications using the ROBINS-I tool for non-randomized studies is shown in **Figure 3**. Both involved studies were found to be a moderate risk of bias [20, 21].

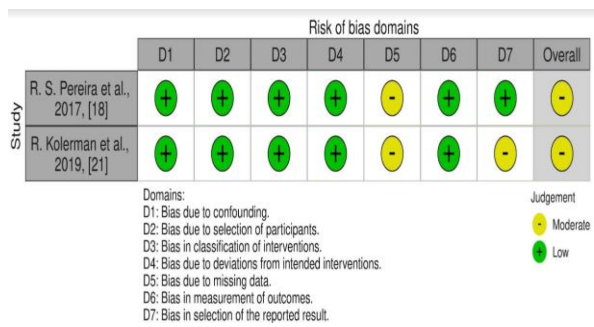

Figure 3. Risk of bias assessment using ROBINS-I tool.

Histology

Five studies included in this systematic review histologically described the formation of the new bone [15-18, 20].

The newly formed bone was in close contact with the partially resorbed graft particles although a demarcation line was separated between the rest of the native bone and the grafted sites. Histologically vital bone was composed of lamellar and woven bone with osteocytes in the lacunae [15-18]. Osteoblasts were also observed near the distinctive contours of the newly formed bone [17]. Only a few inflammatory cells, mostly macrophages or lymphocytes, and multinucleated giant cells were observed in a few studies without signs of acute inflammation [16-18, 20]. In a clinical trial by S. Comert Kilic *et al*. [17], sufficient angiogenesis was declared around the newly formed bone, but in sites grafted with β-TCP and P-PRP a denser network of capillaries was detected compared to β-TCP alone or β-TCP mixed with PRF. In this study was also noted that a lower density of osteoprogenitor cells and a higher density of inflammatory cells were found in β-TCP mixed with the PRF group ($P < 0.05$) [17].

Histomorphometry

Bone biopsy specimens were taken 6 - 9 months after the sinus lifting procedure [14-21]. The results are presented in **Table 2**.

Table 2. Studies results.

Author, year, and reference	Interventions	Treatment group	Outcomes: Mean (SD) percentage (%) new bone formed	P value*	Mean (SD) percentage (%) residual bone graft	P value*
Sokolowski *et al.*, 2020, [14]	HA or BCP (HA/β-TCP 20:80)	HA	From 14.0 (± 16.9) to 16.4 (± 7.31)	**P < 0.011**	From 36.4 (± 15.1) to 40.0 (± 11.4)	**P = 0.006**
		BCP	From 23.0 (± 8.80) to 34.0 (± 16.9)		From 16.4 (± 11.4) to 32.9 (± 15.6)	
J.S. Oh, *et al.*, 2019, [15]	BCP (HA/β-TCP 60:40) or deproteinized bovine bone mineral	BCP	28.84 (± 7.94)	*P*=0.286	-	
		deproteinized bovine bone mineral	25.13 (± 9.56)		-	
J. C. Nery *et al.*, 2017, [16]	BCP mixed with EMD (BC + EMD) or BCP (HA/β-TCP 60:40)	BCP+EMD	Mean bone area 43.0 (± 9.0)	P=0.94	-	
		BCP	Mean bone area 43.4 (± 6.1)		-	
Comert Kilic *et al.*, 2017, [17]	P-PRP or PRF mixed β-TCP	β-TCP	33.40 (± 10.43)	P > 0.05	30.39 (± 10.29)	P > 0.05
		P-PRP-mixed β-TCP	34.83 (± 10.12)		28.98 (± 7.94)	
		PRF mixed β-TCP	32.03 (± 6.34)		32.66 (± 7.46)	
R. S. Pereira *et al.*, 2017, [21]	β-TCP or β-TCP + autogenous bone graft/ autogenous bone grafts alone	β-TCP	From 44.8 (± 22.1) to 47.6 (± 9.9)	**P = 0.03**	-	
		β-TCP mixed autogenous bone graft	From 32.5 (± 13.7) to 35.0 (± 15.8)		-	
		autogenous bone graft	From 31.0 (± 13.0) to 46.1 (± 16.3)	P < 0.05	-	
I. C. Cinar *et al.*, 2020, [18]	β-TCP/ MPM (comprised of β-TCP+PRF)	β-TCP	26.92 (± 7.26)	**P = 0.003**	32.25 (± 8.48)	**P < 0.001**
		β-TCP mixed PRF	35.40 (± 9.09)		23.13 (± 6.16)	
R. D. Kraus *et al.*, 2020, [19]	BCP (HA/TCP 10:90) or DBBM	BCP	35.9	P > 0.05	25.3	**P < 0.001**
		DBBM	35.4		45.9	
R. Kolerman *et al.*, 2019, [20]	BCP (HA/β-TCP 60:40) or freeze-dried bone allografts	BCP	From 23.5 (± 9.9) to 30.0 (± 11.0)		From 21.9 (± 9.9) to 27.7 (± 6.6)	**P < 0.01**
		freeze-dried bone allograft	From 27.7 (±11.2) to 31.0 (±9.5)		From 7.1 (±6.6) to 9.1 (± 10.3)	

HA- hydroxyapatite; β-TCP - β-tricalcium phosphate; BCP- biphasic calcium phosphate; EMD- enamel matrix proteins; P-PRP- platelet-rich plasma; PRF- platelet-rich fibrin; MPM- mineralized plasmatic matrix; DBBM- deproteinized bovine bone mineral.

Sinuses augmented with β-TCP showed a mean volume of new bone ranging from 26.92% ± 7.26% to 47.6% ± 9.9% and an average residual volume of graft ranging from 30.39% ± 10.29% to 32.25% ± 8.48% in reviewed articles [17, 18, 21].

Sites augmented with BCP (comprising β-TCP and hydroxyapatite) showed an average bone volume ranging from 23.0% ± 8.80% to 43.4% ± 6.1% and the remaining volume of evaluated grafting material ranged from 16.4 ± 11.4% to 32.9% ± 15.6% [14-16, 19, 20].

The addition of autologous platelet concentrates to the β-TCP graft showed controversial results **(Table 3)**. In the randomized control trial of S. Comert Kilic *et al*. [17], involving 26 patients was found no statistically significant differences between β -TCP, P-PRP-mixed β -TCP, and PRF-mixed β-TCP groups in terms of mean percentages of bone regeneration, residual grafting particles and soft-tissue area (P > 0.05). I. C. Cinar *et al.* [18] established statistically significant differences in percentages of newly formed bone and remaining graft material between groups of the β-TCP and β-TCP mixed with PRF (P < 0.05). However, no statistically significant difference was found in the evaluation of soft tissue areas between these two groups (P > 0.05).

The effect of EMD as an adjunct to BCP was not statistically significant compared to graft material alone on new bone formation, residual graft, or soft tissue formation 6 months after lateral sinus augmentation (P > 0.05) [16].

Table 3. Results in studies with additional biomaterials.

Author, year, and reference	Patients (n)	Measurement	β-TCP	β-TCP + PRP	β-TCP + PRF	β-TCP + EMD	P
Nery, J.C *et al*., 2017 [16]	10	New bone (%)	43.4% ± 6.1%	-	-	43.0% ± 9.0%	0.94
		Other materials (%)	35.3% ± 9.0%	-	-	35.5% ± 8.2 %	0.97
		Soft tissue (%)	21.3% ± 6.8%	-	-	21.5% ± 5.3%	0.96
Comert Kilic S *et al*., 2017 [17]	26	New bone (%)	33.40% ± 10.43%	34.83% ± 10.12%	32.03% ± 6.34%	-	0.825
		Residual graft (%)	30.39% ± 10.29%	28.98% ± 7.94%	32.66% ± 7.46%	-	0.686
		Soft tissue (%)	36.21% ± 10.59%	36.19% ± 13.94%	35.31% ± 10.81%	-	0.985
Cinar IC *et al*., 2020 [18]	20	New bone (%)	26.92% ± 7.26%	-	35.40% ± 9.09%	-	**0.003**
		Residual graft (%)	32.25% ± 8.48	-	23.13% ± 6.16%	-	**<0.001**
		Soft tissue (%)	40.83% ± 8.86%	-	41.48% ± 8.41%	-	0.817

Two studies histomorphometrically compared results after maxillary sinus augmentation using BCP and deproteinized bovine bone mineral [15, 19]. Studies indicate that more newly formed bone was in the BCP group, but the difference is not statistically significant (P < 0.05) [15, 19]. However, R.D. Kraus *et al*. [19] found that statistically significantly less graft material remained and more nonmineralized tissue formed in augmented sites 6 months after the sinus lift procedure using BCP compared to deproteinized bovine bone mineral (P < 0.001).

The only study included compared BCP, β-TCP mixed with autogenous bone graft, and autogenous bone graft alone [21]. There was a statistically significantly more new bone observed in the β-TCP group compared with β-TCP mixed with autogenous bone graft group (P = 0.03) [21]. No other statistically significant differences were revealed in this study.

Allograft and alloplastic materials were histomorphometrically examined in a study by R. Kolerman *et al.* [20]. In this study the new bone formation fractions in groups of freeze-dried bone allograft and BCP were similar, however, it was found that there were statistically significantly more residual graft particles in the BCP group (P < 0.01) [20].

A clinical study by A. Sokolowski *et al*. [14], comparing HA and BCP indicates that statistically significantly more new bone is formed using the BCP as a bone substitute for maxillary sinus augmentation (P < 0.011). However, also significantly lower percentages of residual BCP were noted than of HA after 6 months postoperatively (P = 0.006) [14].

In this systematic review was found that sinuses augmented with β-TCP hold a mean volume of new bone ranging from 26.92% ± 7.26% to 47.6% ± 9.9% and an average residual volume of graft ranged from 30.39% ± 10.29% to 32.25% ± 8.48% [17, 18, 21]. It is also stated that sites augmented with BCP (comprising β-TCP and hydroxyapatite) showed an average bone volume ranging from 23.0% ± 8.80% to 43.4% ± 6.1% and the remaining volume of evaluated grafting material ranged from 16.4 ± 11.4% to 32.9% ± 15.6% in included studies [14-16, 19, 20].

In a randomized clinical trial evaluating xenograft influence on new bone formation after 6-8 months after sinus lift procedure is stated that vital bone formation consists from 18.77% ± 4.74% to 38.5% ± 17% and larger graft particles lead to better results [22, 23]. The portion of the remaining graft is also indicated in a randomized clinical trial by Stacchi C *et al*. [23], which consists of 22.3% ± 12%. Compared to the received results of calcium phosphate ceramics, xenograft shows a lower proportion of new bone formation and a higher proportion of augmentation dissolution.

The histomorphometric analysis by Xavier SP [24] evaluated residual native bone and graft particle proportion 6 months after sinus augmentation. Results of the autogenous bone and frozen allograft bone showed 36.09% and 34.93% of residual graft particles, and 8.27% and 8.26% of newly formed bone respectively [24].

The systemic review by Pesce *et al*. [25] evaluated the volumetric change of different biomaterials. After 6 months a volumetric contraction of 7.30 ± 15.49% was assessed for xenograft, 27.82 ± 15.58% for the alloplastic, 30.23 ± 1.61 for the allograft, 26.68 ± 11.03% for a mix of autogenous and alloplastic, and finally, the autogenous graft resorbed the most up to 41.71 ± 12.63%. It is observed that xenograft is characterized as a good space maintainer and a very slowly resorbable graft [26, 27]. Alloplast material could be also defined as a sufficient bone volume maintainer. Stumbras *et al*. [28] found that the greatest amount of newly formed bone was in sinuses augmented with autologous bone.

Platelet concentrates appear to enhance the osteoinductive properties of bone by increasing the volume of newly formed bone. Wiltfang *et al*. [29] compared mixed grafts of β-TCP and PRP with β-TCP alone in sinus augmentation, and they found the average bone formation of 38% with the β-TCP plus PRP and 29% with the β-TCP. PRF mixed with deproteinized bovine bone and deproteinized bovine bone alone in sinus augmentation were compared by Zhang *et al*. [30]. Six months after sinus-floor augmentation the new bone formation using PRF mixed with deproteinized bovine bone and deproteinized bovine bone was 18.35% ± 5.62% and 12.95% ± 5.33%, respectively, while the percentage of residual bone substitute in the deproteinized bovine bone group was 28.54% ± 12.01% and in PRF mixed with the deproteinized bovine bone group was 19.16% ± 6.89% [30]. These results suggest that additional application of autologous platelet concentrates improves viable bone formation. Although there are conflicting findings showing that the use of platelet concentrates has a positive effect on new bone formation, it is agreed that the growth factors released by platelets reduce inflammation, reduce the risk of complications and promote bone vascularization. Also, as alternative plasma rich in growth factors (PRGF) can be used to increase bone regeneration, the amount of newly formed bone and vascularization [31].

A sinus floor elevation study by Kim H-W *et al*. [32], analyzing allograft and xenograft showed similar results. The evaluation of bovine bone showed 34.9% of new bone, 19.8% of residual graft, and 45.3% of connective tissue. Allografts provide 40.3% of new bone, 2.7% of residual graft, and 57.0% of connective tissue.

An in vivo study by Harel N. *et al*. [33] investigated the effect of β-TCP and HA ratios on osteoconductivity and stated that a 20:80 ratio promoted more newly formed bone than other mixture ratios (80:20, 70:30, and 30:70 ratios). However, the ratio of HA and β-TCP of 60:40 provided the greatest amount of new bone, less connective tissue, and fewer remaining graft particles after 6 months compared with the other groups [34]. More studies analyzing the difference in proportion should be conducted.

In a study by Koch F.P. *et al*. [35] that investigated recombinant human growth and differentiation factor-5 (rhGDF-5) coated onto β-TCP on the support of bone formation after sinus augmentation, it was found that bone regeneration was similar and rfGDF-5 did not enhance the amount of newly formed bone.

The included publications are heterogeneous (6 randomized clinical trials, 2 cohort studies). Most studies are characterized by small sample sizes (augmented sinuses range from 20 to 51). These limitations prevent the accurate comparison of results and reduce their reliability.

Although biphasic calcium phosphate and β-tricalcium phosphate provide potentially beneficial results, more clinical studies individually analyzing and histomorphometrically comparing different grafting materials are needed to enhance the understanding of its effectiveness in sinus floor elevation procedures.

Conclusion

Biphasic calcium phosphate and β-tricalcium phosphate could have favorable results in sinus floor elevation procedures. Alloplast can ensure sufficient new bone formation and a stable volume of residual graft particles compared to other graft materials.

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