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| REVIEW

Bone formation in sinus augmentation with different xenograft particle sizes: systematic review and meta-analysis

Formação óssea em levantamento de seio maxilar com diferentes tamanhos de partículas de enxerto xenográfico: revisão sistemática e meta-análise

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ABSTRACT

The commercial bovine bone mineral most commonly used is available in two particle sizes and studies have demonstrated contradictory results regarding bone formation volume using small or large particles. The aim of this systematic review and meta-analysis was to compare the bone formation volume and residual bovine bone volume in sinus floor augmentation using small and large particles. The following outcome measures were assessed: bone formation volume (%) and residual bovine bone particles volume (%) assessed by histomorphometric analysis. The initial screening resulted in 236 records. After removal of duplicated articles and analysis of titles, abstracts and full texts, three articles were included in the meta-analysis. The bone formation volume and residual bovine bone volume did not differ between small and large particles, with low heterogeneity of studies. The particle size of bovine bone mineral did not influence bone formation percentage; small and large particles of bovine bone graft presented similar residual bone mineral; more randomized clinical trials should be performed to completely confirm that bovine bone mineral particle size does not affect the result of sinus floor augmentation.

Indexing terms: Bone substitutes. Biomaterials. Implantodontology. Sinus floor elevation.

RESUMO

O enxerto ósseo bovino comercial mais comumente utilizado está disponível em dois tamanhos de partícula, que tem demonstrado resultados contraditórios em relação à formação óssea usando partículas pequenas ou grandes. O objetivo desta revisão sistemática e meta-análise é comparar o volume de formação óssea e o volume de enxerto residual em levantamento de seio usando partículas

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pequenas e grandes. Os seguintes dados foram comparados: volume de formação óssea (%) e volume residual de partículas de enxerto (%) dados por análise histomorfométrica. A seleção inicial resultou em 236 artigos. Após remoção de artigos duplicados e análise dos títulos, resumos e textos completos, três artigos foram incluídos na meta-análise. Os volumes de formação óssea e de enxerto residual não diferenciam entre os tamanhos de partícula pequeno e grande, com baixa heterogeneidade dos artigos. O tamanho de partícula de enxerto ósseo bovino não influencia o percentual de formação óssea; partículas de enxerto ósseo bovino pequenas e grandes apresentaram enxerto residual similar; mais ensaios clínicos randomizados deveriam ser realizados para confirmar que o tamanho de partícula de enxerto não afeta os resultados de levantamento de seio maxilar.

Termos de indexação: *Substitutos ósseos. Biomateriais. Implantodontia. Levantamento de seio maxilar.*

INTRODUCTION

Maxillary sinus floor augmentation is the best strategy to obtain sufficient bone height for implant placement. To facilitate bone formation, a graft is placed to fill the newly formed space between residual crest bone and the Schneiderian membrane. The graft interacts with surrounding tissue and growth factors recruit undifferentiated mesenchymal cells that differentiate and deposit bone matrix within the graft [1-4]. Recent studies demonstrate that new bone formation is influenced by several factors such as smoking, periodontal disease, partial or total edentulism, and the type of bone graft [1-4].

A variety of bone substitutes have been used with different clinical outcomes [5-7]. The type of graft affects the rate of resorption and replacement by bone tissue during the remodeling process and may consequently influence the stability of implants in the long term [8]. The ideal bone graft is defined as a biomaterial that adequately interacts with the residual bone for enough time to allow osteoconductive and osteoinductive processes that result in bone formation and remodeling [9]. Although autogenous bone is the gold standard for grafts [10] due to its osteogenic, osteoconductive, and osteoinductive potential, mineral xenografts such as deproteinized bovine bone are well-documented and the most commonly used [11] because of their large availability and absence of donor site morbidity. Besides, implants placed in maxillary sinuses filled with deproteinized bovine bone have shown high survival rate [12]. Therefore, bovine bone mineral has been considered a safe and predictable graft material for sinus augmentation.

The deproteinized bovine bone is obtained by the removal of the organic component of the bone and maintenance of the hydroxyapatite, thus preventing rejection after graft placement [13]. Bone substitute materials vary regarding porosity and structure. The commercial bovine bone mineral most commonly used (Bio-Oss®) is available in two particle sizes: 0.25-1 and 1-2 mm. Two grams of small and large particles have a volume of 4 and 6 cm3, respectively. Despite several studies, results regarding bone formation volume using either particle size of bovine bone mineral are contradictory [10,11], which hinders evidence-based decision making.

The aim of this systematic review and meta-analysis was to compare the volume of newly formed bone and of the residual bovine bone in sinus floor augmentation when using small and large particles sizes. Our hypothesis was that the smaller spaces among the small particles would inhibit bone formation compared to the larger particles.

METHODS

Design of the study and search strategy

This systematic review was structured following the PRISMA checklist. All available randomized controlled clinical trials were considered for evaluation. No time (year of publication) and language restrictions were implemented. A comprehensive search of the literature was conducted in the MEDLINE (1950–March 10, 2020) (via PubMed), SCOPUS (1966– March 10, 2020), and Cochrane Library (1800– March 10, 2020) databases. The search strategy was composed of MeSH terms and free text words as follows:

#1 xenograft OR deproteinized bovine bone mineral OR bovine bone mineral OR Bio-Oss OR mineralized bone replacement graft OR bovine particulate graft OR bovine particulate xenograft OR bovine particles OR bovine bone

#2 particle size OR size OR large OR small

#3 sinus OR maxillary sinus lift

#4 bone formation OR new bone OR bone augmentation OR tissue augmentation OR volume gain

#1 AND #2 AND #3 AND #4

The reference lists of the relevant review articles and eligible studies were also searched. A first selection was made based on titles and abstracts. The full text of all articles meeting the inclusion criteria (as described below) or of which the abstracts were not clear were obtained. A second selection was made based on the full text analysis performed by two reviewers (B.G., F.W.D.) independently. In case of disagreement, consensus was reached by discussion, and if necessary a third reviewer (R.L.) was consulted.

Criteria for a paper to be included in the study were:

- Bilateral maxillary sinus floor augmentation;
- Split-mouth design;
- Use of deproteinized bovine bone mineral xenograft;
- Comparison of two particle sizes.

Exclusion criteria were:

- Any animal model;
- Absence of a follow-up period of at least 1 month;
- Absence of bone formation analysis;
- Case report, review, technique description, or manual.

Outcome measures

The following outcome measures were assessed:

- Bone formation volume (%) by histomorphometric analysis;
- Residual bovine bone particles volume (%) by histomorphometric analysis.

Risk of bias of individual studies

Quality assessment of the included trials was done by 2 independent reviewers (B.G. and F.W.D.) using the Cochrane Collaboration tool for assessing the risk of bias. The assessment criteria were sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other possible sources of bias.

For each aspect of the quality assessment, the risk of bias was scored following the recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (http:// handbook.cochrane.org). Each entry was judged as "yes" (low risk of bias), "no" (high risk of bias), or "unclear" (either lacking information or uncertainty over the potential for bias).

Data extraction

The outcome measures were independently extracted by two reviewers (B.G. and F.W.D.) and recorded in a data spreadsheet. Again, agreement was reached by discussion and if necessary, a third reviewer (R.L.) was consulted.

Despite few selected studies, a meta-analysis was carried out due to the low (or none) heterogeneity among studies and considering the different weighting of individual study findings.

Statistical analysis

Data from eligible studies were continuous and inverse variance was used as statistical method. The effect size was obtained by the mean difference. Subsequently, as the number of studies was small, a fixed effect model was used to compare bone formation and residual bovine bone mineral. Only studies classified as having "low" or "unclear" risk of bias were included in the meta-analysis. Heterogeneity was assessed using the Cochran Q test and I2 statistics; 95% confidence intervals were calculated. The meta-analysis was performed using 'Review Manager' version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014).

RESULTS

Additional information was requested from the authors of a study to obtain details of the study design for complete risk of bias judgment [11]; the study was then classified as low bias risk regarding blinding.

The initial database screening resulted in 236 records. The removal of duplicates resulted in 174 articles, and after exclusion of unrelated articles by scanning the titles and abstracts four articles were selected for full text evaluation of eligibility. One paper was excluded due to absence of bone formation analysis [10], resulting in three articles for data extraction (figure 1).

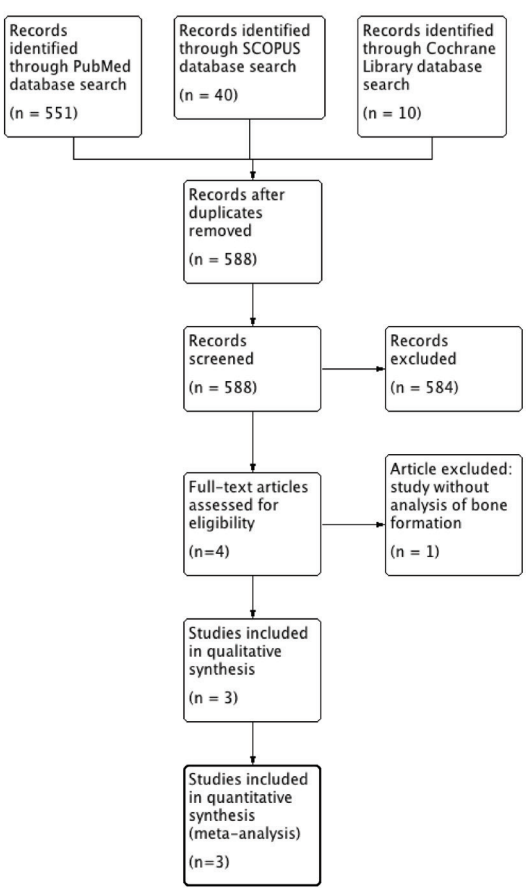

Figure 1. Study flow diagram.

Characteristics of included articles

The characteristics of the selected studies are listed in tables 1 and 2; all of them were clinical trials with a parallel design [11,14,15].

The number of participants included in the studies ranged from 10 [11,15] to 13 [14]; however, in the study by Testori et al. [14], two patients were excluded from analysis due to problems in sample processing, resulting in a sample of 11 [14]. Participants required bilateral maxillary sinus floor elevation for the placement of dental implants, determined by computed tomography scan. Smoked participants [15] and who smoked more than 10 cigarettes a day [11,14] and women who were pregnant were excluded [11,14,15].

In each participant, one side of the maxillary sinus was randomly assigned to be grafted with bovine bone mineral of 0.25–1 mm particle size and the contra-lateral side with bovine bone particles of 1–2 mm (Bio-Oss®, Geistlich Biomaterials Inc., Wolhusen, Switzerland). The access was done by lateral window technique and before soft-tissue closure, the entire window was covered with a resorbable collagen membrane (BioGide, Geistlich Biomaterials Inc., Wolhusen, Switzerland). The follow-up periods were 6 to 9 months [11,14,15]. After the follow-up period, a biopsy of the augmented tissue was retrieved, processed, and analyzed by light microscope and a specific software (histomorphometric analysis), obtaining the percent volume of newly formed bone and residual bovine bone graft. Histologic analyses [11,14,15] were not considered here since the results were descriptive. In addition, micro-CT results were also excluded because only one paper [11] performed this analysis.

Table 1. Summary of the included studies for this systematic review.

Study ID	Study design	Number of participants	Procedure	Test group	Control group	Follow-up period (months)	Outcomes
Chackartchi et al. [11]	randomized clinical trial	10	bilateral sinus floor augmentation	small particles	large particles	6 to 9	morphometric results by micro-CT, histological and histomorphometric outcomes
Testori et al. [14]	randomized clinical trial	13	bilateral sinus floor augmentation	small particles	large particles	6 a 8	histological and histomorphometric outcomes
de Molon et al. [15]	randomized clinical trial	10	bilateral sinus floor augmentation	small particles	large particles	8	histological and histomorphometric outcomes

Table 2. Outcomes in included studies.

Study ID	Groups	Histomorphometric outcomes				Morphometric outcomes by micro-CT			
		Bone formation (%)	Residual bovine bone mineral (%)	Spaces (%)	Soft tissue/hard tissue rate	Increased bone height (mm)	Volume of bone (%)	Bovine bone mineral (%)	Soft tissue (%)
Chackartchi et al. [11]	Small particles	34.6±8.1	28.0±6.5	37.4±4.1	-	-	14.6±12.0	22.9±8.3	62.5±14.9
	Large particles	33.7±8.3	27.1±3.9	39.1±8.5	-	-	8.0±4.2	23.1±6.2	68.9±4.1
Testori et al. [14]	Small particles	18.8±4.7	21.7±10.5	-	59.6±9.9	-	-	-	-
	Large particles	26.8±9.6	20.0±9.0	-	53.2±11.5	-	-	-	-
de Molon et al. [15]	Small particles	36.1±9.6	32.4±8.6	-	-	7.9±2.1	-	-	-
	Large particles	36.7±5.8	38.0±6.9	-	-	9.2±1.3	-	-	-

Risk of bias assessment

The assessment of the risk of bias is presented in figure 2. All included articles had unclear or low risk of bias.

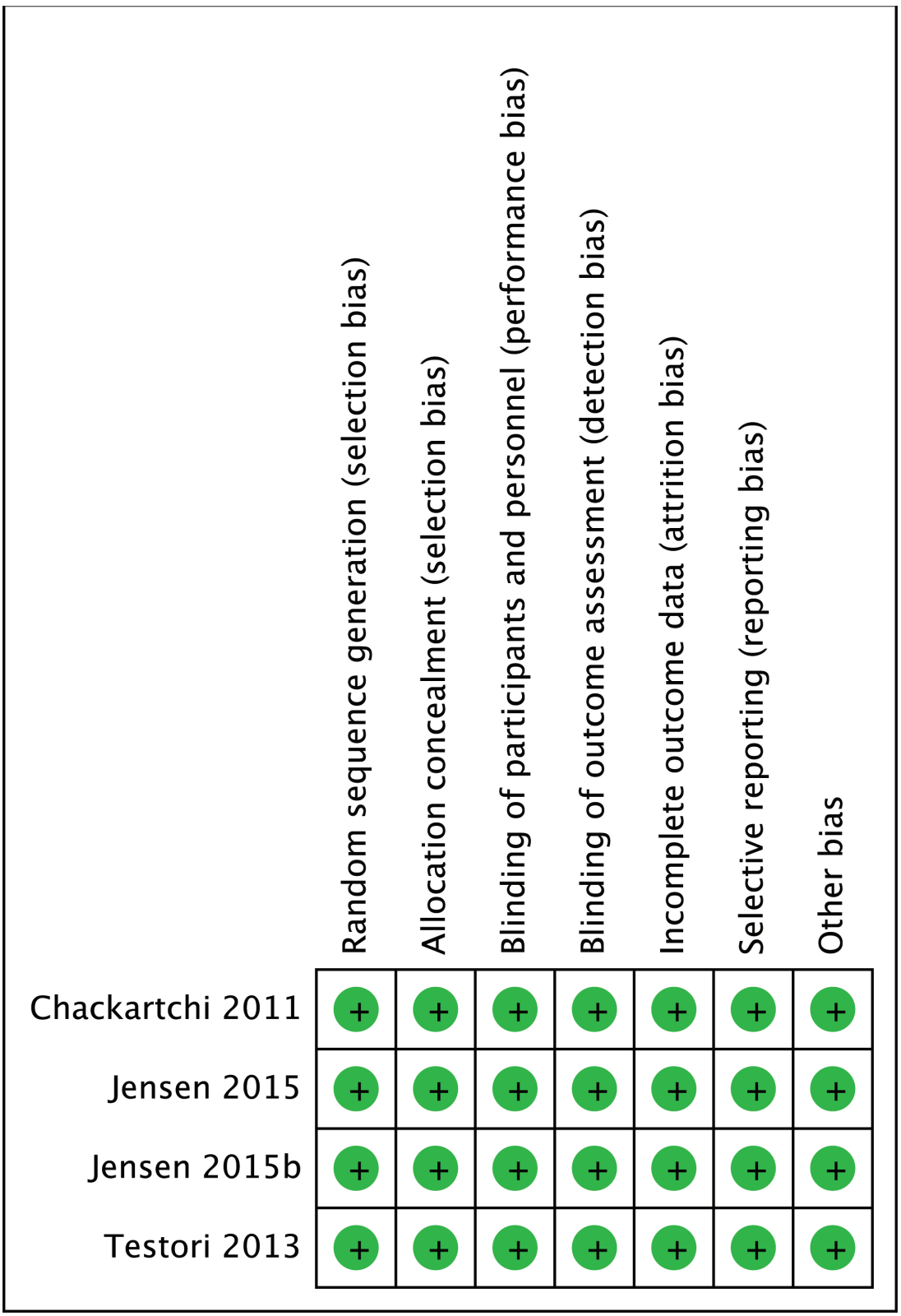

Figure 2. Summary of the risk of bias assessment according to the Cochrane Collaboration tool. Empty square indicates an unclear risk.

Meta-analysis

Data from three articles were used in the meta-analysis. The bone formation volume using small or large bovine bone particles was not significantly different (-2.99%, 95% CI [-6.91%, 0.94%]) and the data had low heterogeneity (Q = 3.98, P = 0.14, I2 = 50%). The analysis of bone formation is shown in figure 3.

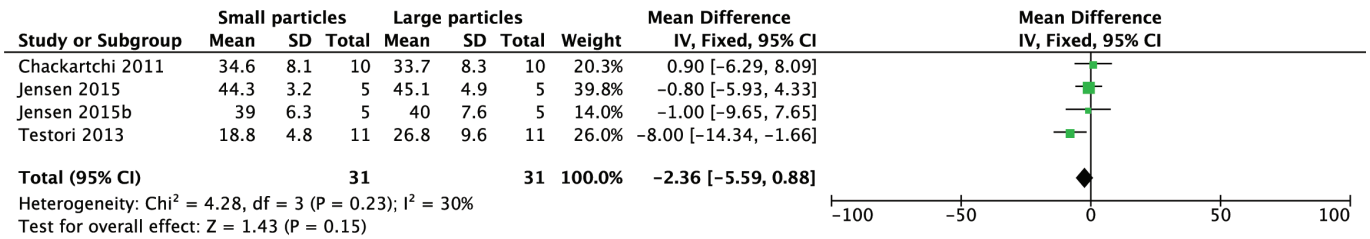

Figure 3. Forest plot of bone formation.

For the residual bovine bone mineral (in percent), the analysis also showed no significant difference between both particle sizes (-0.66%, 95% CI [-4.16, 2.84]) and the data was not heterogeneous (Q = 2.76, P = 0.25, I2 = 27%). The analysis is shown in figure 4.

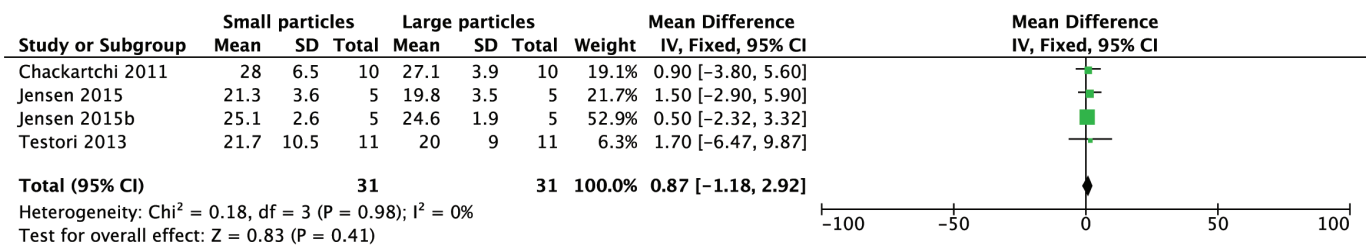

Figure 4. Forest plot of residual bovine bone mineral.

DISCUSSION

Bovine bone mineral of different particle sizes results in a variable graft volume, but the data on the impact of particle size in new bone formation is conflicting. The present systematic review and meta-analysis aimed to elucidate whether particle size could influence the results of the sinus floor augmentation procedure. The results indicate that small and large particles produce similar volumes of new bone and leave similar graft residuals. The included data had no inconsistency of results (heterogeneity) and were from randomized clinical trials with low risk of bias. These factors corroborate the high quality of the produced evidence although few studies on the subject were available in literature.

Smoking habits and history of periodontitis are the main risk factors for sinus floor lift complications and greater bone loss in regenerative techniques due to their effect on inflammation process, osteogenesis, and angiogenesis [4,16]. Nicotine influences the expression of several enzymes and cytokines that play an important role in the regulation of cells, collagen fibrils, and osteoinductive agents, importantly affecting bone formation and remodeling [4,16,17]. Nicotine exposure has also direct effects on blood vessels, producing vasoconstriction and low oxygen flow [4,16,17]. Patients with history of periodontitis can have genetic factors that exacerbate inflammatory reaction

after tissue injury [1]. In addition, the osteoclast activity of these patients is modified by hormones, cytokines, or certain bacterial components [18]. Therefore, the included studies used specific exclusion criteria for smoking and poor oral hygiene of participants.

One of the included studies found that large particles favored bone formation, which was justified by the authors as being due to the small sample size [14]. However, the present systematic review and meta-analysis, which included all the participants involved in the three studies, found no difference in bone formation with different particle sizes (figure 3). For an adequate osteoconduction and osseointegration that result in bone formation, biological processes need to occur between host cells and the biomaterial. The similar results obtained from small or large graft particles might be explained by the particles' similar micro porosity, with pore sizes around 100 μm, which allow bone cells attachment, permeation of osteoinductive agents, and bone ingrowth [2,3]. Pores that are too small favor an osteochondral growth, which is undesirable [2]. An adequate pore size also promotes reliable function in terms of mechanical strength of the graft [3]. Another important point is the interconnecting porous structure, recommended to be from 80 to 90%, allowing reliable vascularization of the graft; the grafts used in the included studies (Bio-Oss® small and large particles) were within the recommendation [2,3]. To the best of our knowledge, clinical studies comparing different sizes of particles are only available for Bio-Oss® deproteinized bovine bone.

No difference was found also regarding residual bovine bone mineral (figure 4). After its placement in the sinus, the graft is degraded providing space and creating the conditions for new bone formation. This degradation process depends on graft composition. The calcium/phosphate ratio of porcine bone mineral is 2.22±0.08, of bovine bone mineral is 2.31±0.09 [19], and is 1.67, 1.5, and 1.0 for hydroxyapatite, tricalcium phosphate, and bioactive glass, respectively [3,20]. The small quantity of phosphate in bovine bone mineral allows the slow dissolution of the graft [19], which is an advantage of the material. A high solubility could restrict the regenerative capacity leading to inadequate osteoconduction and clinical failure since dissolution, precipitation, and ion exchange need to be accompanied by absorption and attachment of biological molecules [20,21]. Because the two tested bone grafts differed only in particle size and had the same composition, the volume of residuals found was similar with both materials.

During the remodeling process, the bovine bone mineral is slowly resorbed by osteoclasts and replaced by bone tissue. However, knowledge on the exact duration of graft degradation is unclear. Previous study reported a degradation rate of 4 to 10% per year [22]. Another study [23] showed that degradation of inorganic bovine bone lasts for 3 years while other studies [24,25] found residual graft after 10 years. However, long-term residual bovine particles were embedded in mature bone [25] and did not affect implant osseointegration [26]. During the first months, the degradation rates of large and small particles seem similar [25,27]. The bone formation also presents comparable rate in the initial periods (up to 9 months) [25,27]. In the period after placement in the sinus, the graft particles interact with the host bone cells, which is followed by the processes of inflammation, angiogenesis, osteoconduction, osteoinduction, initial bone formation, and remodeling [25]. Therefore, the time-points used in the present meta-analysis are supported by the literature.

In a meta-analysis, homogeneity refers to a mathematical compatibility between the results of each individual study. Another important aspect of the present review are only randomized clinical trials were included and the low risk of bias of the studies [28]. Due to an adequate homogeneity and low risk of bias of the included articles, the meta-analysis could be carried out even with a small number of studies. It can be concluded that clinicians' indication of particle size for sinus floor augmentation is based in few randomized clinical trials.

The need for experimental models evaluating novel materials and techniques for sinus floor augmentation has increased in recent years due to the increased demand for implant supported prosthesis even in compromised maxillary posterior areas. Although physiological functions and bone metabolism of pigs and humans sinuses are similar, anatomical aspects of animals and humans are different [29-31]. Besides, there are few studies using animal models to be considered in a systematic review, which would increase heterogeneous. For those reason, we excluded studies using animal models in the present meta-analysis.

CONCLUSION

Within the limitations of this study, it is concluded that: (1) the particle size of bovine bone mineral has no influence in bone formation volume; (2) small and large particles result in similar residual bone mineral; (3) more randomized clinical trials should be performed to confirm that particles sizes of bovine bone mineral have no influence in sinus floor augmentation.

Collaborators

B Genari, study design, review of articles, analysis and interpretation of the data, writing and review of manuscript. R Cantarelli, study design, interpretation of the data, writing and review of manuscript. AS Ramos Neto, study design, interpretation of the data, writing and review of manuscript. EB Silva, study design, interpretation of the data, writing and review of manuscript. FW Degrazia, study design, review of articles, analysis and interpretation of the data, writing and review of manuscript.

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