Review Article

Biomaterial selection for bone augmentation in implant dentistry: A systematic review

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Abstract

In the present study, a systematic review was conducted to evaluate the biomaterials and their effectiveness for bone augmentation in implant dentistry. The databases of Cochrane Library, Google Scholar, PubMed (National Center for Biotechnology Information), and Scopus were searched for published studies between 2006 and March 30, 2018. We only included clinical studies in this research. Due to a lack of quantitative evidence and the vast heterogeneity of the biomaterials, implant surgery sites, implant types, follow-up periods, and various implant placement techniques (1-stage or 2-stage), we could not manage to do a meta-analysis on the 13 included studies. Several techniques can result in vertical bone augmentation. Complications can be seen in vertical bone augmentation and especially in the autogenous bone grafting; however, some biomaterials showed promising results to be practical substitutes for autogenous bone. Bio-Oss and beta-tricalcium phosphate are our second-level candidates for vertical bone augmentation due to their promising clinical results with the least infection and immunologic response risk. The gold standard, however, remains the autogenous bone graft. Further clinical studies in the future with exact report of bone measures are needed to develop new comparisons and quantitative analyses.

Key words: Biomaterial, dental implant, osteoconduction, osteogenesis, osteoinduction, vertical bone augmentation

INTRODUCTION

Augmenting alveolar bone tissue around the dental implants is of great concern due to its critical role in the long-term treatment success.[1] We focused on the vertical alveolar ridge augmentation technique for this study. Due to an increase in peri-implantitis conditions in the past decade, it is crucial to provide the best bone augmenting biomaterial to accomplish the best treatment results. Tissue engineering is one of the most critical and expanding fields, which mainly cooperates with regenerative medicine and has indicated a remarkable potential in clinical dental practice applications. Biomaterials are one of the three basics in tissue engineering, namely cells, scaffolds/biomaterials, and growth/differentiation factors.[2-5] Considering their role, many biomaterials have been applied and suggested to use as an alternative to the autogenous bone which is still the gold standard for bone augmentation.[6] Aside from autogenous, xenogenic, and allogenic grafting materials, other natural and synthetic biomaterials have also been playing critical roles in dental clinical cases.[7] Till today, different types of these biomaterials have established their practical roles in dental clinics mainly based on their ease

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of application and predictable results. To decide which biomaterial to choose, we should consider some factors to mimic the autogenous bone structure, e.g., crystal structure, micro- and macroporosity, and intercrystalline spaces.[8] Chemical, physical, and mechanical properties of the scaffolds should be as similar as possible to that of a natural bone structure.[9,10] A good bone substituting scaffold should be settled by the resident bone cells or undifferentiated mesenchymal cells.[11-13] Various biomaterials have been applied into the bone defects using different surgical techniques. Autogenic, allogenic, xenogenic, and synthetic biomaterials are currently on-the-board options for a dental bone grafting process. Lack of immunological responses and a high-volume augmented bone can be considered as the main advantages of autogenic grafts, while they showed a higher infection rate. Other natural biomaterials such as xenogenic grafts can also be encouraged due to their low-content inflammatory reactions and high longevity.[14] Synthetic biomaterials such as bioactive glasses are also another promising choice for bone augmentation considering their notable neosynthetized bone and low amount of residual graft. We retrieved relevant studies about alveolar bone augmentation in implant dentistry and systematically reviewed them based on the PRISMA protocol. This study aimed to systematically review the biomaterials and their effectiveness for bone augmentation in implant dentistry.

METHODS

Searching and selection of studies

We have searched four databases of Google Scholar, PubMed, Scopus, and Cochrane Library with the keywords, "Biomaterials," "Bone Augmentation," and "Dental Implant." Searching query was modified for each database if needed to achieve most relevant studies. Then, we collected data, based on the relevance to the study topic and the main objective. Any conflicts between the authors were resolved by abstract and full-text reading to determine the criteria which were used in the studies. Twenty-one studies were chosen according to the title skimming and abstract screening, and then the references of these studies were manually searched and checked in Google Scholar. After removing duplicates, we added the relevant ones based on the title and abstract screening. Only clinical trials and case reports were included; the exclusion criteria were as follows: studies which included patients with any systemic disease (e.g., diabetes, cancer, and angina pectoris) and patients older than 65 years of age or younger than 15 years, studies with implant surface modification interventions or maxillary sinus lifting or sinus floor augmentation procedures, non-English language studies, and those reflecting information from before 2006. In the final step, inclusion was according to a consensus between the two authors and 13 studies were chosen for data extraction.

Risk of bias and quality of studies

Both authors independently evaluated the risk of bias for the studies using the Cochrane Collaboration's tool for clinical trials named as grades of recommendation, assessment, development, and evaluation (GRADE) [Supplementary Table 1]. Furthermore, the complications, blinding, source of funding, sample size, and the inclusion and exclusion criteria were assessed for each study. The risk of bias was determined based on these evaluations as "low," "moderate," or "high." Conflicts between the authors were resolved by a consensus. Finally, the overall quality of each study was defined as "high" or "moderate" using the GRADEpro online service. Also, the "importance" of each study was determined by a consensus between authors, based on all of the evaluations in a range from 1 to 9 as defined in the GRADE protocol. The importance of studies was reported as "not important," "important," or "critical" according to their related scores.

Measures of treatment effect

The mean vertical bone augmentation at implant sites and peri-implant marginal bone losses were reported as we did not get enough statistical data to calculate the standard error. The unit of analysis to determine the study quality was the number of implant abutments. Within final studies, we did not find necessary data for the analysis; thus, we sent E-mails to the electronic links or E-mail addresses provided in the studies, but we did not get any response back from them. In the other six studies, weighted mean differences and standard deviations with 95% confidence intervals were used for each study to express the effect measures on continuous outcomes (i.e., vertical bone augmentation and peri-implant marginal bone loss).

Software and applications

The Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. of Cochrane Library was used to create the flow diagram of searching and selecting the studies. The GRADEpro online service was used to create the study quality table. The tables of quantitative and qualitative analysis were created by excel software (Microsoft, Redmond, Washington, 2016), and all of the references were inputted by Endnote (Version X7, Thomson reuters, Canada).

RESULTS

The search results and the number of chosen studies in each step are shown in Figure 1.

Some qualitative [Supplementary Table 2] and quantitative [Supplementary Table 3] data were extracted.

The risk of bias in the included studies was determined by Cochrane's GRADEpro online tool [Supplementary Table 1]. Vertical bone augmentation was considered as the first

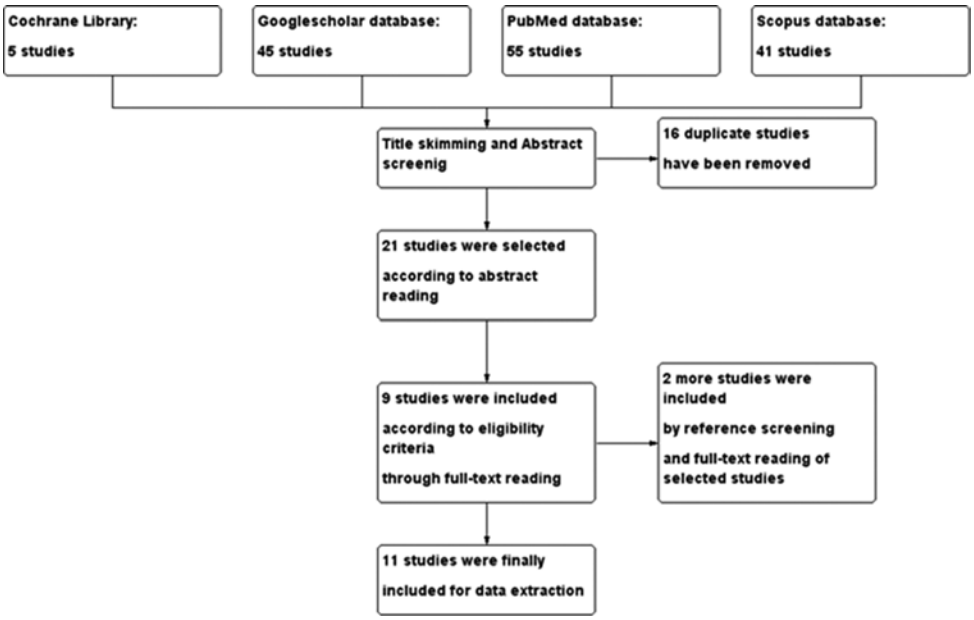

Figure 1: Study selection flow chart

continuous outcome and the second continuous outcome was peri-implant marginal bone loss. Due to a lack of evidence, the measurement of effect size and heterogeneity assessment was not accomplished and no meta-analysis could be done.

DISCUSSION

We aimed to systematically review the biomaterials and their effectiveness for bone augmentation in implant dentistry. Between the included studies, three articles have used autogenous bone fragments. Autogenous bone grafts exhibit three main features as being osteogenic, osteoconductive, and osteoinductive.[7,15]

Iliac crest bone and bovine anorganic bone were used in two different groups of patients in a randomized controlled trial. The residual graft in the xenograft group (bovine bone) was significantly more than the autogenous bone. The main advantage of the xenograft over the autogenous graft was reported as its less invasiveness.[16] Also, a mixture of autogenous bone and anorganic bovine bone in association with micro-titanium mesh were used for bone augmentation in another case series.[17]

We observed that a mixed xenograft material (Bio-Oss) with autogenous bone and a collagen or titanium mesh membrane as a part of GBR technique can provide an adequate bone augmentation during 6 months after grafting without any specific bone resorption in the follow-up periods.[18]

Bio-Oss was the most common material being used in our data and showed some promising results comparable to autogenous bone grafts in every study.[19] Some of the best characteristics featured about this material can be listed as follows: adequate new bone formation, low reabsorption rate, osteoconductive characteristics, and compensation for the natural bone resorption caused by remodeling.[19] Bio-Oss has also been applicated in sinus floor elevation,[20] extraction socket filling,[21] and treatment of periodontal defects.[22]

Another randomized clinical trial has used autogenous demineralized dentin matrix (AutoBT) from the extracted tooth in comparison with anorganic bovine bone (Bio-Oss) for bone augmentation. Their work showed that AutoBT exhibits osteoconductivity and biocompatibility comparable to Bio-Oss.[23]

Beta-tricalcium phosphate (β-TCP) scaffold materials are eminent as bone substitutes according to their biocompatibility, practically extensive availability, ease of sterilization, long shelf life, and low infection risk.[24] β-TCP exhibits a good balance among absorption, degradation, and new bone formation and can also sustain its structural stability by discharging a large quantity of calcium (Ca2+) and sulfate (SO42−) ions, which are crucial inorganic salts for new bone formation.[25,26]

β-TCP granule-scaffolds with sizes of 1 mm and 1–2.5 mm can also improve the proliferation of BMSCs and promote the expression of osteogenic genes and osteogenesis-related proteins.[12]

Two case series studies had used β-TCP and bioactive glass as the filling biomaterials. Autologous bone marrow-derived mononuclear cells (BMMNCs) were combined with β-TCP, and the role of BMMNCs in reducing early absorption

of β-TCP alloplasts in the implant sites was asserted.[24] Bioactive glass provided adequate bone height for implant placement without any complications for implant stability and peri-implant tissue health.[27] The most important aspect here was the "osteostimulation" effect of bioactive glass.[14,28]

Our data also showed the effectiveness of xenogeneic biomaterials alone to augment the bone defects. Porcine-derived bone and flexible equine bone sheets without membranes have also yielded insufficient bone augmentation for implant placement with no significant resorption of the graft material during a 3-year follow-up period.[29,30]

Cecchetti *et al*.[31] showed enough bone preservation after tooth extraction using deproteinized bovine bone mineral to conduct an implant-supported treatment.

The limitations of our systematic review were the heterogeneity in the implant sizes, the different timing of implant placement, the technique of placement (1-stage or 2-stage), and also lack of studies using a single type of scaffold to specifically evaluate its effect. The included studies have used different antibiotic regimens before and after bone grafting for their patients which could possibly affect the bone augmentation results. Various sites of implant placement and different characteristics of bone regions in the maxilla and mandible were the most important limiting factors in our study, and we did not sort our results based on the implant placement locations due to their wide heterogeneity.

CONCLUSIONS

Several biomaterials have been used for bone augmentation in implant dentistry, but there are not enough predictable results to show one or more of them as an alternative to the autogenous bone. In general, after the autogenous grafts, we can introduce the Bio-Oss and β-TCP as the most trusted and widely used biomaterials in the xenogenic and synthetic biomaterial categories of grafting materials in dentistry, respectively. These two can give predictable, sustainable, and adequate new bone formation with the least infection rates in implant placement cases, which is the current goal of vertical bone augmentation in dentistry.

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Conflicts of interest
There are no conflicts of interest.

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Supplementary Table 1: Quality assessment of the included studies

Quality assessment							№ of participants in each group		Effect		Quality	Importance
№ of implant abutments	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	biomaterials	placebo	Relative (95% CI)	Absolute (95% CI)		
b-TCP/autologous BMMNCs (follow up: 12 months)												
17	Case series	not serious	not serious	not serious	not serious	No blinding, relative low sample size	3	-	-	68.48%	High	IMPORTANT
Bioactive glass (follow up: 24 months)												
5	Case series	not serious	not serious	not serious	not serious	no blinding, reporting bias risk, low sample size	3	-	-	-	Moderate	NOT IMPORTANT
xenograft material/bone fragments from traumatic site (GBR) (follow up: range 6 months to 48 months)												
10	Case series	not serious	not serious	not serious	not serious	No blinging, relative low sample size	3	-	-	-	Moderate	IMPORTANT
Prehydrated Corticocancellous Bone Graft (GBR) without autogenous bone (follow up: 24 months)												
1	Case report	not serious	not serious	not serious	not serious	No blinding, low sample size	1	-	-	-	Moderate	NOT IMPORTANT
collagen sponge/nonresorbable high-density PTFE membrane (follow up: 12 months)												
2	Case report	not serious	not serious	not serious	not serious	No blinding, low sample size	1	-	-	49.3%	Moderate	NOT IMPORTANT
Titanium Mesh/Combination of Autogenous Bone and Anorganic Bovine Bone (follow up: 24 months)												
44	Case series	not serious	not serious	not serious	not serious	No blinding	16	-	-	28.27%	Moderate	CRITICAL
Flexible Heterologous Cortical Bone Sheet (follow up: 36 months)												
49	Case series	not serious	not serious	not serious	not serious	No blinding	18	-	-	-	Moderate	CRITICAL
Deproteinized Bovine Bone Mineral/free gingival graft (follow up: 6 months)												
1	Case report	not serious	not serious	not serious	not serious	No blinding, low sample size	1	-	-	-	Low	NOT IMPORTANT
Iliac crest vs. bovine anorganic bone (follow up: 16 months)												
38	randomized clinical trial	not serious	not serious	not serious	not serious	-	5	5	-	MD 1.51 mm higher (7.07 lower to 10.09 higher)	High	CRITICAL
Xenogenic bone blocks (Bio-Oss) (follow up: 9 months)												
18	Case series	not serious	not serious	not serious	not serious	No blinding	9	-	-	50.5%	High	IMPORTANT
Autogenous demineralized dentin matrix from extracted tooth vs anorganic bovine bone (follow up: 6 months)												
33	randomized clinical trial	not serious	not serious	not serious	not serious	-	21	12	-	mean 5.38 mm higher (2.65 higher to 4.75 higher)	High	CRITICAL
Assessment of vertical ridge augmentation in anterior aesthetic zone using onlay xenografts with titanium mesh versus the inlay bone grafting technique: A randomized clinical trial												
40	randomized clinical trial	not serious	not serious	not serious	not serious	-	8	8	-	mean percentage of vertical bone gain: 20.7% in control group and 31.6% in study group	High	CRITICAL
Long-term outcomes of implants placed after vertical alveolar ridge augmentation in partially edentulous patients: a 10-year prospective clinical study												
82	prospective clinical study	not serious	not serious	not serious	not serious	-	41	-	-	-	Moderate	NOT IMPORTANT

Supplementary Table 2: Qualitative evaluation of the included studies

Author/ date	Pieri et al. 2008	Pang et al. 2016	Bulgin and Hodzic 2015	Aimetti et al. 2017	Cucchi and Ghensi 2014	Cechetti et al. 2014	Ludovichetti et al. 2011	Felice et al. 2009	Gatti et al. 2014	Li et al. 2013	Kim and Leem 2014
Biomaterials	Anorganic bovine bone and autogenous bone (30:70), micro-mesh	Autogenous demineralized dentin matrix (AutoBT), Bio-Oss	BMMNCs, OSferion (β-TCP) granules	Collagen sponge, high-density d-PTFE membrane	Corticocancelous porcine-derived bone, d-PTFE membrane (without autogenous bone)	Deproteinized bovine bone, free gingival graft	Flexible cortical equine bone sheet (without GBR membrane)	Iliac crest bone versus bovine anorganic bone	PerioGlas (bioactive glass) mixed with autogenous bone	Xenogenous bone block (Bio-Oss) onlay graft	Xenograft material and bone fragments from traumatic site, resorbable collagen membrane or titanium mesh
Study design	Case series	Prospective randomized clinical trial	Case series	Case report	Case report	Case report	Case series	Randomized clinical trial	Case series	Case series	Case series
Study sample	16 patients, 44 implant abutments	AutoBT in 21 sites of 15 patients, Bio-Oss in 12 sites of 9 patients	3 patients, 17 implant abutments	1 patient, no implant abutment	1 patient, 1 implant abutment	1 patient, 1 implant abutment	18 patients, 49 implant abutments	10 patients, 20 implant abutments	3 patients, 5 implant abutments	9 patients, 18 implant abutments	3 patients, 10 implant abutments

PTFE: Polytetrafluoroethylene, β-TCP: Beta-tricalcium phosphate, GBR: Guided bone regeneration

Supplementary Table 3: Quantitative evaluation of the included studies

Biomaterials	Treatment success and failures	Posttreatment evaluation method	Vertical bone augmentation	Bone loss after treatment	Reference
Anorganic bovine bone and autogenous bone (30:70), micro-mesh as the GBR membrane	One of the implants become exposed and was removed, all of the implants were retained after 2 years (100% survival rate and 91.3% success rate)	Clinical examination and CT at baseline and 8 to 9 months after the bone grafting, clinical examinations and PA radiographs at every 6 months till 2 years after the prosthetic loading	Mean vertical bone augmentation equals to 3.71 mm (SD=1.24 mm)	Mean bone resorption around the implants equals to 1.37 mm (SD=0.32 mm), 3 implants showed bone resorption >2 mm	Pieri *et al.*, 2008
Autogenous demineralized dentin matrix (AutoBT), Bio-Oss	No infection or wound dehiscence, ISQ of AutoBT-grafted sites equals to 72.80 (SD=10.81), ISQ of Bio-Oss-grafted sites equals to 70.0 (SD=12.86)	Clinical probing through resin template from graft placement till 6 months postoperative, CT and histomorphometric analysis 6 months after the bone grafting, panoramic radiography after implant placement	5.38 mm in AutoBT (SD=2.65 mm), 6.56 in Bio-Oss (SD=3.54 mm) at 6 months postextraction	Not mentioned	Pang *et al.*, 2016
BMMNCs (autologous cell source) andOSferion (β-TCP) granules	No adverse tissue reaction, infection or delayed healing, good peri-implant health within 12 months after bone graft	Panoramic radiography at 1 and 12 monthsafter operation	15.3 mm mean bone augmentationat 12 months	Not mentioned, all patients maintained good peri-implant health and oral hygiene	Bulgin and Hodzic, 2015
Collagen sponge, high-density d-PTFE membrane	No signs of infection, preserved keratinized tissue, no implant complications	CBCT at 12 months after the bone grafting, clinical examination, histologic analysis, and CT at 12 months after implant placement	The overall mean percentage of newly formed bone equals to 49.3% (SD=4.7%)	No implant was placed	Aimetti, *et al.*, 2017
Corticocancelous porcine-derived bone and d-PTFE membrane (without autogenous bone)	Uneventfully healing with no clinical signs of soft-tissue inflammation, no recession, and no membrane exposure, complete maintenance of peri-implant without any signs of bone resorption	Biopsy and histomorphometric analysis (optical microscope) at 9 months after the bone grafting, follow-up PA radiographs at 1, 12, and 24 months after prosthesis delivery (15 days after implant abutment surgery)	Adequate bone for implant placement and to support the functional loading of the implant	Complete maintenance of bone level and no signs of bone resorption in all of the follow-ups	Cucchi and Ghensi, 2014
Deproteinized bovine bone and free gingival graft	Successful implant placement and favorablesoft tissue preservation	Radiographic evaluation on Tc scans and PA radiographs3 months after the bone grafting, clinical examination of implantat 6 months after implant placement	Adequate bone volume in height and in width, allowing an implant placement	Notmentioned	Cechetti *et al.*, 2014
Flexible cortical equine bone sheet (without GBR membrane)	All of the implant abutments were judged to be successful throughout the study (Albrektsson and Zarb criteria)	Panoramic radiography and clinical evaluation after implant placement at 1 week, 1 month, 6 months and then yearly for at least 3 years	Adequate bone volume to reconstruct the correct ridge profile and to ensure successful implant outcomes	Not mentioned, stable PD at all of the follow-ups (2-3 mm)	Ludovichetti *et al.*, 2011
Iliac crest bonevs. bovine anorganic bone	Two implants could not be placed in one patient at the autogenous bone group (graft failure),1 implant in the Bio-Oss group failed after loading, after implant loading, one peri-implantitis occurred at the autogenous bone group	Clinical and radiographic examination at 3 and 6 weeks and 3 months after the bone grafting, biopsy and histological analysis at 4 months after the bone grafting, PA radiographs at the implant placement time, and at 1 year after that	31.2% in autogenous bone (SD=6.9%), 27.3% in Bio-Oss (SD=7%), at 4 months after the bone grafting	0.82 mm peri-implant marginal bone loss in autogenous bone (SD=0.59), 0.59 mm peri-implant marginal bone loss in Bio-Oss (SD=0.4)	Felice *et al.*, 2009
PerioGlas® (Bioactive glass) and autogenous bone	All of the implant abutments were reliable and lasting throughout the study	Panoramic radiography immediate postoperative, and at 6, 12, 18, and 24 months after bone graft, a biopsy at 6 months after the bone grafting and then histomorphometric analysis and SEM microscopy, clinical examination of implant abutments at follow-up sessions	Adequate bone volume tosupport the implants placement	Maintained bone volume during all of the follow-ups	Gatti, *et al.*, 2014
Xenogenous bone block (Bio-Oss) onlay graft	No inflammation, no implant complications	Clinical examination and panoramic radiographs at 1 day, 1 month, and 6 months after the bone grafting, bone tissue segments harvested and histological analysis at 9 months after the bone graft, CTs at 6 months after the bone grafting, PA radiographs at 12 months after placing the final prosthesis	The level of bone augmentation was measured in height ranged from 4.1 to 6.0 mm	0.5 mm peri-implant marginal bone loss (SD=1.00 mm)	Li *et al.* 2013
Xenograft material and bone fragments from traumatic site, resorbable collagen membrane or titanium mesh as the GBR membrane	Successful placement of all the implant abutments, and progressed through the follow-up periods without complications	Cases 1, 2, and 3: CBCT at 6 months after the bone grafting; Cases 1 and 2: panoramic radiograph and clinical examination at 4 and 1 year (s) after implant placement, respectively	Adequate bone volume for implant placement	No specific bone resorption during all of the follow-ups	Kim and Leem, 2014

CT: Computed tomography, PA: Posteroanterior, PD: Progressive disease, SD: Standard deviations, GBR: Guided bone regeneration, CBCT: Cone-beam computed tomography, ISQ: Implant stability quotient