Clin Oral Invest
DOI 10.1007/s00784-014-1376-1

REVIEW

Evaluation of the bone regeneration potential of bioactive glass in implant site development surgeries: a systematic review of the literature

Andreas L. Ioannou · Georgios A. Kotsakis · Tarun Kumar · James E. Hinrichs · Georgios Romanos

Received: 17 April 2014 / Accepted: 20 November 2014

Abstract
Objectives The aim of this systematic review was to assess the efficacy of bioactive glass (BG) in bone regeneration for implant site development procedures.
Material and methods The following specific question was formulated with reference to Population, Intervention, Control, Outcomes (PICO): "In persons that undergo bone regeneration surgeries for implant site development, what histological outcomes does the use of BG yield, alone or in combination with AB, compared to positive or negative controls?".
Results The 1st phase of screening yielded 400 titles and abstracts. A total of 12 studies reporting on the use of bioactive glass were scrutinized for inclusion in the final analysis and 5 studies were selected for qualitative synthesis of the results. Data were divided into two categories: ridge preservation (n=2) and sinus augmentation (n=3).
Conclusions Within the limitations of this review, it can be concluded that (1) the combination of BG with AB chips in a 1:1 ratio is an efficacious treatment modality for direct sinus augmentation, with histological results comparable to 100 % AB. (2) When used for ridge preservation, BG yields a high percentage of true bone regeneration. (3) Currently, no reliable controlled studies report histological outcomes from the use of BG in ridge augmentation procedures.
Clinical relevance Clinicians may consider BG bone substitutes as efficacious alternatives for ridge preservation and sinus augmentation surgical procedures. Further controlled clinical studies are warranted to determine if bone-to-implant contact is improved in BG-grafted sites versus controls.

Keywords Bioglass · Bioactive glass · Bone regeneration · Bone substitutes · Dental implants · Systematic review

Introduction

The increasing desire for esthetic implant rehabilitation in contemporary clinical practice has faced clinicians with the challenge of creating adequate bone volume for ideal three-dimensional implant placement [1]. Ridge resorption and pneumatization of the sinus are among the most prevalent factors that may lead to inadequate bone volume at the recipient site [2–6]. The quest for restoratively driven implant placement has given birth to a group of specialized surgical techniques that can be summarized as "implant site development" procedures [7]. The aim of these techniques is to augment bone to enable functional loading of dental implants [8]. Implant site development techniques include ridge preservation following tooth extraction, sinus augmentation in the posterior maxilla, and horizontal and/or vertical ridge augmentation for large bone defects, among others [9–11].

Bone graft materials that have been utilized in implant site development surgeries include autogenous bone (AB), allograft, xenograft, and alloplastic biomaterials [8, 12–14]. Each graft category contributes to bone regeneration through discrete mechanisms of action. The properties of each biomaterial can generally be characterized as being osteogenic, osteoinductive, or osteoconductive [3, 15]. In spite of the

Andreas L. Ioannou and Georgios A. Kotsakis contributed equally to this work.

A. L. Ioannou · G. A. Kotsakis (✉) · J. E. Hinrichs
Advanced Education Program in Periodontology, University of Minnesota, 515 Delaware Street SE, Minneapolis, MN 55455, USA
e-mail: geo.kotsakis@gmail.com

T. Kumar
Division of Periodontology, Bapuji Dental College and Hospital, Davangere, India

G. Romanos
School of Dental Medicine, Stony Brook University, Stony Brook, NY, USA

Published online: 05 December 2014

availability of various types of bone graft materials, autogenous bone is considered to be the gold standard, owing to its osteogenic potential [16]. Among the remaining categories of bone graft materials, the use of bioactive glass (BG) has been extensively evaluated [17–21]. BG is a group of surface reactive glass-ceramic biomaterials comprised of silica, natrium and calcium oxides, and phosphoric salts [22]. This alloplastic biomaterial was introduced in 1969 to provide a bioinert alloplastic graft that would not elicit an inflammatory response when implanted in living tissues [23, 24]. The benefit of BG in comparison to other alloplastic bone substitute biomaterials is its ability to elicit the response of mesenchymal cells through the ionic dissolution of soluble calcium, silica, and phosphate [25]. Instead of solely having osteoconductive properties, BG leads to osteoproduction as a consequence of the rapid reactions on its surface [24–28].

The efficacy of BG in the treatment of periodontal defects has been previously elucidated in the dental literature; the highest level of evidence supports its use [29]. While the use of BG biomaterials in implant site development surgeries has been extensively documented and new forms of delivery for this type of biomaterial have renewed interest in its use, no systematic reviews of its efficacy for this indication have been performed. Therefore, the aim of this review was to assess the efficacy of BG alloplastic bone substitutes in bone regeneration for implant site development. Assessment of new bone growth as determined histologically was set as the primary outcome. Safety outcomes and implant survival in grafted sites were also assessed.

Materials and methods

PICO question

Prior to initiation of a comprehensive review of the literature, a research question was developed utilizing the Population, Intervention, Control, Outcomes (PICO) principle [30]. "In persons that undergo bone regeneration surgeries for implant site development, what histological outcomes does the use of BG yield, alone or in combination with autogenous bone, compared to positive or negative controls?".

Population Participants in the included trials must have been healthy humans with at least one site where bone regeneration was performed for implant site development. Bone regeneration was defined as formation and growth of new bone based on histological criteria.

Types of intervention The intervention of interest was bone augmentation in procedures such as ridge preservation, ridge augmentation, and sinus augmentation performed for implant site development, with the use of bioactive glass (BG) alone as a bone substitute or in combination with autogenous bone.

Control intervention Randomized control trials that used autogenous bone, allograft, xenograft, or no grafting material (negative control) were included in the search. Since the use of autografts, allografts, and xenografts is considered to be successful in bone regeneration procedures, all the above bone graft types were considered acceptable positive controls.

Outcome measures Histological and histomorphometric outcomes assessing new bone growth were set as primary outcome variables. Safety outcomes and implant survival in sites grafted with BG were set as secondary outcomes.

Based on the above information, the following PICO question was formulated: "In persons that undergo bone regeneration surgeries for implant site development, what histological outcomes does the use of BG yield, alone or in combination with autogenous bone, compared to positive or negative controls?".

Search strategy

A search of two individual electronic databases was performed in duplicate and independently by two reviewers (A.I., G.K.) according to the AMSTAR recommendations for assessing the methodological quality of systematic reviews [31]. The PubMed database of the US National Library of Medicine and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched for scientific articles published between January 1, 1990 and September 30, 2013. Electronic publications ahead of print were considered eligible for inclusion.

The electronic search was performed using the following combination of keywords and MeSH terms: "bioactive glass" or "bioglass" or "glass" and "bone augmentation" or "ridge preservation" or "tooth socket" or "sinus lift" or "sinus augmentation" or "ridge augmentation" and "histological."

In addition to these databases, the following journals were manually searched: *Journal of Periodontology*, *Journal of Clinical Periodontology*, *International Journal of Oral and Maxillofacial Implants*, *International Journal of Periodontics and Restorative Dentistry*, *Journal of Dental Research*, *Clinical Oral Implants Research*, *Clinical Implant Dentistry and Related Research*, and *Implant Dentistry*.

Initial screening included assessment of the titles and abstracts of articles potentially relevant to the PICO question. The reason for exclusion of each article at this phase was recorded. For the second phase of screening, full-text articles of the remaining studies were obtained and scrutinized in light of the inclusion and exclusion criteria of the study. Reasons for exclusion were recorded. References in these articles were further investigated for potentially relevant studies. Both the

electronic and manual searches were performed independently and in duplicate, by two reviewers (A.I., G.K.). If a disagreement between the two reviewers arose that could not be resolved with discussion, the opinion of a senior reviewer (G.R.) would be sought and considered definitive. Inter-reviewer agreement was assessed using Cohen's kappa coefficient [32].

Selection criteria

In order to identify studies relevant to the specific PICO question, the following inclusion and exclusion criteria were set. To be included in this analysis, studies were required to (1) be controlled clinical trials, (2) include human participants, (3) be written in English, (4) report histological and histomorphometric outcomes, (5) include at least 10 sites per group, and (6) use BG alloplastic bone substitute alone or in combination with autogenous bone.

Exclusion criteria were the following:

1. Case series, case reports, or reviews
2. Retrospective studies
3. Animal or in vitro studies
4. Studies published in languages other than English

Data extraction

Pre-specified data elements were identified from individual studies independently by two reviewers (A.I., G.K.) and entered into tables. One table included characteristics for each of the included studies such as country of origin, study design, randomization, masking, and information on the type of intervention and study population characteristics. A second table was used to extract data related to study outcomes. As previously mentioned, the primary outcome variable assessed was the percentage of new bone growth in the grafted sites. Implant survival in the healed sites was also recorded. Adverse events associated with the use of BG were recorded as safety outcomes.

The quality of all studies included in this systematic review was independently assessed by the two reviewers assessed utilizing criteria from the revised CONSORT (Consolidated Standards of Reporting Trials) statement for evaluation of randomized-controlled trials according to the protocol described in a systematic review by Schwarz et al. (2008) [33, 34].

Results

The initial electronic search retrieved 395 scientific articles. Additional manual search of the journals added 5 more articles. After the first phase of evaluation, 388 articles were excluded based on the title and abstract (inter-reviewer agreement: κ=0.885). Reasons for rejection were (1) duplicates (n=1); (2) non-English publications (n=25); 3) irrelevant to the PICO question (n=199); (4) uncontrolled study design (n=19); (5) animal and/or in vitro studies (n=144).

The complete text of the remaining articles was then retrieved for thorough examination. A total of 12 studies reporting on the use of bioactive glass as a bone grafting material were scrutinized for inclusion in the final analysis [8, 18, 20, 21, 35–42]. Cross-search of the reference lists of these articles did not add any studies. In this phase of selection, three articles were excluded due to lack of a control group [20, 36, 37]. Furthermore, three articles were excluded because of a lack of reported histomorphometric data [8, 18, 35]. One article was also excluded because it reported on less than 10 sites in each study group [21]. (Table 1) A total of five studies fulfilled the inclusion criteria and were included in this systematic review [38–42]. (Inter-reviewer agreement: κ= 0.833) (Fig. 1)

Subdivision of included studies

Data were divided into two categories (ridge preservation and sinus augmentation) based on the type of intervention studied. None of the included studies investigated the use of BG biomaterials in ridge augmentation procedures. One of the five studies was a controlled clinical study [41], while four were randomized controlled clinical studies [39, 40, 38, 42]. Three studies were assessed as having a high risk of bias [42, 40, 41], one as having a moderate risk of bias [39], and one as having low risk of bias [38]. (Fig. 2) It has to be noted that all the included studies presented adequate completeness of follow-up and all had comparable group characteristics at baseline. (Table 2)

Ridge preservation

Two studies investigated the use of a BG in ridge preservation procedures [38, 42]. Froum et al. (2002) [38] utilized

Table 1 Studies excluded in the second phase of selection with reasons for the exclusion of each study

Study	Reason for exclusion
Stavropoulos et al. [20]	No control group
Canullo and Dellavia [36]	No control group
Clozza et al. [37]	No control group
Kotsakis et al. [8]	No report of histological data
Yilmaz et al. [18]	No report of histological data
Camargo et al. [35]	No report of histological data
Galindo-Moreno et al. [21]	Less than 10 sites in each group

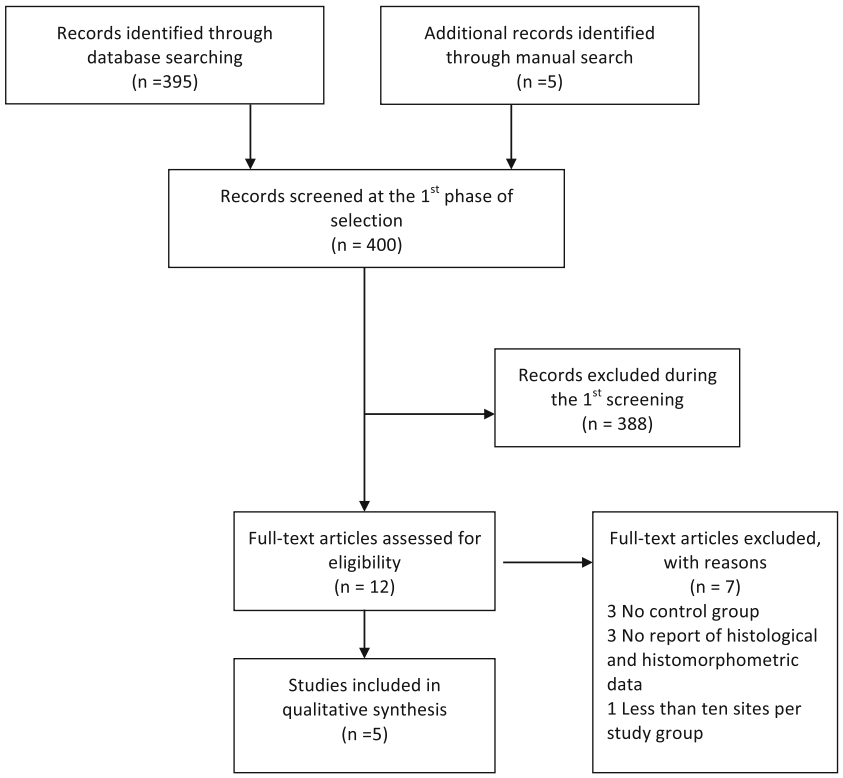

Fig. 1 Flowchart of the stages of the present systematic review based on PRISMA guidelines

particulate bioactive glass and found that when employed in ridge preservation procedures, BG resulted in more new bone formation than did areas grafted with demineralized freeze-dried bone allograft (DFDBA). More specifically, new bone formation was found in 59.5 % of areas grafted with BG, in contrast to DFDBA and un-grafted areas that exhibited 34.7 and 32.4 % new bone growth, respectively [38]. In the same study, the percentage of residual bone graft was 5.5 % when BG was used, while it was 13.5 % in sites grafted with DFDBA at 6 to 8 months post-surgery [38]. Mahesh et al. (2013) [42] investigated ridge preservation using a pre-mixed putty formulation composed of BG particles embedded in a binder (NovaBone Dental Putty, NovaBone Products, LLC, Alachua, FL). They found that 6 months post-grafting, BG showed histologically more new bone and less residual bone graft in comparison with an anorganic bovine xenograft (positive control) [42]. The use of putty BG resulted in 47.15 % new bone formation and 17.40 % residual grafting material [42]. The particulate bovine xenograft resulted in 22.20 % new bone formation in the regenerated sockets, with 25.60 % residual grafting material identified [42]. The authors also noted that while at 4 months post-grafting, both biomaterials showed comparable amounts of residual bone graft in the sockets, at the 6-month point, the putty BG had a significantly

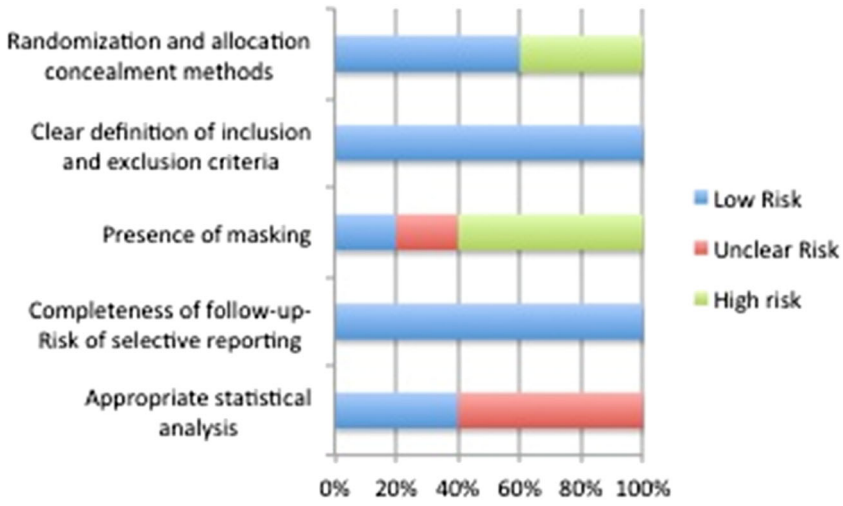

Fig. 2 Risk of bias graphical presentation of included studies based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions

Table 2 Presentation of main characteristics for studies included after the second phase of selection

Study	Country	Intervention	Study design	Randomization	Masking	Population characteristics	Conflict of interest	Quality assessment
Ridge preservation								
Froum et al. [38]	United States	Ridge preservation	Randomized controlled clinical study	Simple random sampling	Single-blinded (histologist)	19 Non-smoker, patients presenting for extraction of teeth for prosthetic or periodontal reasons	Non-declared, study funded by corporate sponsor	Low
Mahesh et al. [42]	India—Greece	Ridge preservation	Randomized controlled clinical study	Simple random sampling. Computer-generated randomization list	Non-reported	19 patients, presenting with 20 single-rooted teeth that were scheduled for extraction	Non-declared, partial material support reported	High
Sinus augmentation								
Tadjoedin et al. [39]	Netherlands	Sinus lift	Randomized, controlled, split-mouth study	Simple random sampling	Non-reported	10 patients with maxillary edentulism and bilateral sinus pneumatization with a residual sinus floor of less than 3 mm in height	Non-declared, study funded by two corporate sponsors	Moderate
Turunen et al. [40]	Finland	Sinus lift	Controlled, split-mouth study	Non-reported	Non-reported	17 patients (women/men:16/1; mean age: 50, range 39–70 years) for bilateral sinus floor augmentation. 15 patients had totally edentulous maxilla, 1 had maxillary canines, and 1 still had maxillary incisors and canines	Non-declared	High
Scarano et al. [41]	Italy	Sinus lift	Controlled clinical study	Non-reported	Non-reported	94 patients(52 to 68 years (mean 61)), maxillary partial (unilateral or bilateral) edentulism involving the premolar/molar areas, and the presence of 3–5 mm crestal bone between the sinus floor and alveolar ridge	Conflict declared by 4 of the authors. Study partially funded by National funding agency (Italy)	High

less percentage of residual graft and a greater amount of bone regeneration [42]. Overall, the percentage of new bone growth in sockets grafted with BG ranged from 47.15 to 59.5 % with 5.5 to 17.40 % residual graft after 4–8 months of healing [38, 42]. (Table 3)

Sinus augmentation

The remaining three studies investigated the use of BG in sinus augmentation surgery [39–41]. Tadjoedin et al. (2000) [39] performed bilateral sinus lift surgery in 10 patients. One side received autogenous bone, and the other side was grafted with a 1:1 mixture of autogenous bone and BG. After 6 months, the areas grafted with the autogenous/BG mixture exhibited 38.07 % new bone formation and 6.95 % residual graft material [39]. The contralateral positive control sides showed 43.65 % new bone and 5.47 % residual grafting material [39]. In one of the 10 patients, the sites were re-entered at 16 months following sinus surgery. In the side grafted with the autograft/BG mixture, new bone formation was estimated at 44.48 % and residual material at 3.81 % [39]. In the side grafted solely with autogenous bone, the percentage of new bone formation was 45.07 %, and the fraction of residual grafting material was 4.07 % [39].

Turunen et al. (2003) [40] augmented the posterior compartment of 17 maxillary sinuses with a 1:1 mixture of BG granules and AB chips harvested from the iliac crest. The anterior part of the same sinus and the contralateral sinus served as positive controls. Control sites were filled with AB chips alone. At 5–8 months, new bone was found in 26 % of the test sites and 25 % of the control sites [40]. At 12–15 months, the percentage of new bone had increased to 29 % in the test sites but remained at 25 % at the control sites [40]. Residual grafting material was only reported for the test group: 34 % at 5–8 months and 31 % at 12–15 months [40]. One adverse event associated with the sinus augmentation was noted in a single patient. Infection of the autograft donor site and both sinus cavities developed 1 week post-surgery. The infection was treated with systemic antibiotics. Three weeks post-operatively, 2–3 ml of the infected bone was removed carefully from the posterior part of the osteotomy opening of both the sinuses [40]. As a result, the most posterior implant in the control group had to be inserted into the planned biopsy area, precluding the biopsy procedure. In another patient, seroma of the donor site was also noted that was not associated with the sinus procedures [40]. No clinical complications during the clinical follow-up period occurred in other patients.

Scarano et al. (2006) [41] compared the histological and histomorphometrical data after maxillary sinus augmentation with nine different biomaterials in 94 patients. The biomaterials employed included bioactive glass, autogenous bone, DFDBA, calcium carbonate, polymer of polylactic and polyglycolide acids, bovine-derived bone and peptide, calcium sulfate, bovine deproteinized bone/xenograft, and hydroxyapatite. This was the only study identified that evaluated BG as the sole grafting biomaterial in a sinus. The BG test areas exhibited 31 % new bone and 18 % residual material at 6 months [41]. In the areas grafted with autologous bone, the percentage of new bone was 40.1 %, while the various types of biomaterials used in this study yielded high percentages of new bone formation ranging from 29 % for DFDBA to 39 % for calcium carbonate and bovine xenograft, respectively [41]. The authors reported that a total of six implants failed, including one that was inserted in a sinus augmented with calcium carbonate, one with autologous bone, one with DFDBA, two with BG, and one with hydroxyapatite [41]. There was not any association between the type of graft and implant failure. No further complications were reported in this study. Overall, the percentage of new bone growth in sinuses grafted with BG ranged from 26 to 38.07 % with 18 to 34 % residual graft after 4–15 months of healing [38, 42]. (Table 3)

Discussion

Autogenous bone grafting was almost exclusively employed for bone regeneration during the dawn of implant dentistry, but patient demands for minimally invasive surgeries have led to the use of bone substitutes such as BG for oral surgical procedures [16, 43, 29]. To the authors' knowledge, the present systematic review is the first to evaluate the efficacy of BG for bone regeneration in such procedures. Using a systematic methodology, comprehensive evaluation of controlled studies that assessed the outcomes of ridge preservation and sinus lift surgery, utilizing BG as a grafting material was performed.

Published studies that reported various primary outcomes following the use of BG in sinus augmentation and ridge preservation procedures were available [39, 40, 38, 21, 18, 20, 36, 37, 35, 42, 41]. No controlled studies reporting histological outcomes of ridge augmentation procedures with the use of BG were available in the literature during the search. Only studies that reported histological and histomorphometric data were included [37–42, 36]. The decision to include histological and histomorphometric data as outcomes of interest in the present review was made as those seemed to be the most appropriate surrogates for true bone regeneration. Studies excluded from this review reported on clinical outcomes including dimensional alterations of grafted sites and short-term implant success data [8, 18, 35]. Albeit clinically important, these outcomes lack information on the true regenerative potential of a bone graft biomaterial. Inclusion of controlled, histological studies enabled direct comparison of the physiologic behavior of BG to grafts harvested from living donors.

Taodjedin et al. (2000) [39] indicated that a 1:1 mixture of autogenous bone/BG particles seems a promising alternative

Table 3 Outcomes assessment of the included studies

Study	Group allocation									Follow-up
	Test group (bioactive glass)	Histomorphometric data	Implant survival	Test group (other)	Histomorphometric data	Implant survival	Control group	Histomorphometric data	Implant survival	
Ridge preservation										
Froum et al. [38]	Placement of bioactive glass and flap advancement for primary closure (particles size: 300 to 355 μm)	New bone: 59.5 % RBG: 5.5 %	Not reported	Placement of DFDBA and flap advancement for primary closure (particles size: 250 to 500 μm)	New bone: 34.7 % RBG: 13.5 %	Not reported	Flap advancement for primary closure without the placement of a bone graft (negative control)	New bone: 32.4 %	Not reported	6–8 months
Mahesh et al. [42]	Extraction with a flapless technique and immediately grafting with calcium phosphosilicate putty	New bone: 47.15 % RBG: 17.40 %	Not reported	No secondary test group		Not reported	Extraction with a flapless technique and immediately grafting with particles of bovine xenograft	New bone: 22.20 % RBG: 25.60 %	Not reported	4–6 months
Sinus augmentation										
Tadjoedin et al. [39]	Direct sinus lift using the lateral window approach under general anesthesia. 1:1 mixture of autogenous bone particles (from iliac crest) and BG particles size: 300–355 μm	New bone: 38.07 % RBG: non-reported	Not reported	No secondary test group		Not reported	Autogenous bone particles (size: 0.5–3 mm) harvested from the iliac crest (positive control)	New bone: 43.65 % RBG: non-reported	Not-reported	4–6 months
Turunen et al. [40]	The posterior part of 17 maxillary sinus was augmented with a 1:1 mixture of BG granules (800–1000 μm) and AB chips harvested from the iliac crest	At 5–8 months new bone: 26 % RBG: 34 % At 12–15 months new bone: 29 % RBG: 31 %	Not reported	No secondary test group		Not reported	The anterior parts of the same sinus and the contralateral sinus, serving as a control (AB group), were filled with AB chips alone.	At 5–8 months new bone: 25 % RBG: non-reported At 12–15 months new bone: 25 % RBG: non-reported	Not reported	5–8 months and 12-15 months
Scarano et al. [41]	Direct sinus lift using the lateral window approach with immediate implant placement. BG grafting material was mixed with venous blood and carefully packed in the sinus cavity, especially in the posterior and anterior parts. The remaining sinus space around the implants was completely packed with the graft material.	New bone: 31 % RBG (residual bone graft): 18 %	2 failed implants. Mean follow-up was 4 years (range 2–7).	Multiple secondary test groups	DFDBA new bone: 29 % RBG: 34 % Calcium carbonate new bone: 39 % RBG: 22 % Polymer of polylactic and polyglycolide acids new bone: 33 % RBG: 3 % Bovine-derived bone and peptide new bone: 37 % RBG: 37 % Calcium sulfate new bone: 38 % RBG: 13 % Bovine deproteinized bone new bone: 39 % RBG: 31 %	3 failed implants: 1 in the calcium carbonate group, 1 in the DFDBA group, and 1 in the hydroxyapatite. Mean follow-up was 4 years (range 2–7).	Direct sinus lift using the lateral window approach with immediate implant placement. Autologous bone was mixed with venous blood and carefully packed in the sinus cavity, especially in the posterior and anterior parts. The remaining sinus space around the implants was completely packed with the graft material.	New bone: 40.1 % Residual non vital bone fraction: 18 %	1 failed implant. Mean follow-up was 4 years (range 2–7).	6 months

Table 3 (continued)

Study	Group allocation						Follow-up		
	Test group (bioactive glass)	Histomorphometric data	Implant survival	Test group (other)	Histomorphometric data	Implant survival	Control group	Histomorphometric data	Implant survival
					Hydroxyapatite new bone: 32 % RBG: 34 %				

to autogenous bone alone. BG particles in combination with autogenous bone were found to yield a bone percentage higher than that found in the non-atrophic maxilla of control patients. New bone formation increased rapidly within 2 months, from 29 % at 4 months to 38 % at 6 months, while bone formation in the autogenous bone group increased only slightly with time [39]. Therefore, there may be an indication for increased healing time in sites grafted with BG. Turunen et al. (2004) [40] also showed that BG granules can be used together with AB chips for sinus floor augmentation procedures, decreasing the need for harvested autograft. Their study included an interesting design, with the authors filling one compartment of a sinus cavity with autogenous bone chips and the remaining compartment with a 50–50 combination of autograft chips and BG particles. The contralateral sinus also served as positive control in each patient. Results showed that vital bone percentage in both groups was directly comparable at 21–34 weeks (BG: 25.7 %, autogenous: 25.1 %) and at 49–62 weeks (BG: 28.8 %, autogenous: 25.1 %) [40]. Histological analysis consistently showed residual BG particles in intimate contact with vital bone, which was verified by evidence from energy-dispersive x-ray analysis suggestive of bone bonding to the BG particles. When the percentage of bone and BG particles in intimate contact with the bone was calculated, it reached 34 % in the grafted sites [40].

In ridge preservation surgeries, alloplastic grafting materials are considered to act as osteoconductive, providing a scaffold for bone regeneration in the socket. Beyond that, however, bioactive glass has been shown in vitro to have a positive effect in the stimulation of stem cells that can enhance bone regeneration [44, 29, 45]. Mahesh et al. (2013) [42] performed a clinical study comparing the rate of bone regeneration in post-extraction sockets grafted with either a putty bioactive glass biomaterial or a particulate bovine xenograft. Results showed a significantly greater percentage of bone formation for the bioactive putty and also found an increased rate of bone formation during the 4- to 6-month post-operative period, in comparison with the xenograft [42]. The authors attributed this to the osteostimulative properties of bioactive glass [42, 23]. The clinical implication of the increased rate of bone formation in sites grafted with a putty BG was investigated by Kotsakis et al. (2014) [8]. The authors performed ridge preservation in a xenograft group and a BG group and found that the primary stability for implants placed 5 to 6 months post-extraction in sockets grafted with BG putty was significantly greater than in the xenograft group [8]. Implant survival in the BG putty group was 100 % after 1 year [8]. Thus, there may be merit in exploiting the increased rate of bone regeneration observed in extraction sites treated with BG biomaterials to reduce treatment time. Froum et al. (2002) [38] also noted a positive effect of BG in bone healing in extraction sockets. At 6 to 8 months post-extraction, sites treated with BG demonstrated 59.5 % new bone growth, while

sockets treated with DFDBA had 34.7 % new bone [38]. This difference was partially attributed by the authors to the common histological finding of new bone growth in the internal pores of BG particles [38]. Pore configurations of alloplastic biomaterial scaffolds have been shown to play a major role for new bone formation in vivo. Klein et al. (2009) investigated the visualization and quantification of these pore properties [46]. They found that scaffolds with a high ratio of pores >250 μm might be suitable for larger, voluminous defects, whereas scaffolds with predominantly small (>60 μm) and intermediate (60–250 μm) pores might rather meet the requirements of smaller lesions. Since the bioactive glass that was utilized in most studies had large pores, this could explain the results of Froum et al. (2002) for lesions of the size of an extraction socket.

Overall, the use of BG in implant site development surgeries seems to be safe and effective. No BG-specific adverse events were noted in the included studies. All evaluated BG materials in the included studies appeared to be biocompatible, and there were no reports of allergies or other immunologic reactions, abscess formation, or rejection of the grafting materials. From a histological point of view, BG seems to have the potential to promote bone regeneration, does not evoke an inflammatory infiltrate or fibrous encapsulation, and resorbs in a timely manner, leaving only a small percentage of residual graft in the site after 6 months of healing [26, 42, 38].

The use of BG in combination with autogenous bone offers some advantages in sinus augmentation. BG has osteoconductive properties; it acts as a scaffold that is essential for bone remodeling and it allows the volume of the graft to be at least doubled, avoiding the need to harvest large amounts of autogenous bone [39, 40]. The combined use of BG granules with autogenous bone chips for augmentation of the maxillary sinus floor diminished the amount of bone needed for augmentation and resulted in the same quantity of bone as when autogenous bone chips alone were used [39]. In the only study in which BG was used alone for sinus augmentation, results were very similar to the combination of autogenous bone alone, with the mean bone percentage in the regenerated sites being 38 % [41]. These findings are commensurate with the results of a recent systematic review that investigated the efficacy of bone substitutes as compared to autogenous bone in alveolar bone regeneration, whereby the authors concluded that there is a lack of evidence that autogenous bone is superior to bone substitutes [47].

A limitation of the present review lies in the multiple confounding variables that were identified in the included studies. Variables such as the pre-operative height of the residual bone prior to sinus augmentation, timing of implant placement, number of remaining socket walls prior to grafting, and combination of BG with autogenous bone resulted in a heterogeneity of the included studies that, combined with the small number of studies, did not allow for meta-analysis. Nonetheless, a systematic review is a qualitative evaluation of the literature that yields the highest level of evidence and a meta-analysis based on the currently available information could not be justified. Further research following implant placement in treated and control sockets is warranted to determine if bone/implant contact is improved in BG-filled versus unfilled sockets. Well-designed studies with more sites are indicated to determine if the increased vital bone found in BG-treated sockets translates into more implant/bone contact in humans.

Conclusions

Within the limitations of this review, it can be concluded that:

1. The combination of BG with autogenous bone chips in a 1:1 ratio is an efficacious treatment modality for direct sinus augmentation, with histological results comparable to 100 % autogenous bone. A healing time of at least 5 to 6 months is indicated. The use of BG as the sole biomaterial for sinus augmentation seems promising, yet limited information is available for this indication.
2. When used for ridge preservation, BG yields a very high percentage of true bone regeneration. There may be an added benefit in allowing 6 months for healing instead of 4, in terms of bone regeneration and reduction of the percentage of residual bone graft.
3. Currently, no reliable controlled studies report histological outcomes from the use of BG in ridge augmentation procedures.

Conflict of interest The authors report no conflict of interest to this study.

References

1. Ishikawa T, Salama M, Funato A, Kitajima H, Moroi H, Salama H, Garber D (2010) Three-dimensional bone and soft tissue requirements for optimizing esthetic results in compromised cases with multiple implants. Int J Periodontics Restor Dent 30(5):503–511
2. Schropp L, Isidor F (2008) Timing of implant placement relative to tooth extraction. J Oral Rehabil 35(Suppl 1):33–43. doi:10.1111/j.1365-2842.2007.01827.x
3. Kotsakis G, Chrepa V, Marcou N, Prasad H, Hinrichs J (2012) Flapless alveolar ridge preservation utilizing the "socket-plug" technique: clinical technique and review of the literature. J Oral Implantol. doi:10.1563/AAID-JOI-D-12-00028.1
4. Hansson S, Halldin A (2012) Alveolar ridge resorption after tooth extraction: a consequence of a fundamental principle of bone physiology. J Dent Biomech 3:1758736012456543. doi:10.1177/1758736012456543

5. Block MS, Kent JN (1997) Sinus augmentation for dental implants: the use of autogenous bone. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 55(11):1281–1286
6. Boyne PJ (2004) Augmentation of the posterior maxilla by way of sinus grafting procedures: recent research and clinical observations. Oral Maxillofac Surg Clin N Am 16(1):19–31. doi:10.1016/j.coms.2003.10.006, v-vi
7. Winkler S (2002) Implant site development and alveolar bone resorption patterns. J Oral Implantol 28(5):226–229. doi:10.1563/1548-1336
8. Kotsakis GA, Salama M, Chrepa V, Hinrichs JE, Gaillard P (2014) A randomized, blinded, controlled clinical study of particulate anorganic bovine bone mineral and calcium phosphosilicate putty bone substitutes for socket preservation. Int J Oral Maxillofac Implants 29(1):141–151. doi:10.11607/jomi.3230
9. Kotsakis GA, Joachim FP, Saroff SA, Mahesh L, Prasad H, Rohrer MD (2014) Histomorphometric evaluation of a calcium-phosphosilicate putty bone substitute in extraction sockets. Int J Periodontics Restor Dent 34(2):233–239. doi:10.11607/prd.1855
10. Barone A, Toti P, Piattelli A, Iezzi G, Derchi G, Covani U (2014) Extraction socket healing in humans after ridge preservation techniques: comparison between flapless and flapped procedures in a randomized clinical trial. J Periodontol 85(1):14–23. doi:10.1902/jop.2013.120711
11. Thoma DS, Jones A, Yamashita M, Edmunds R, Nevins M, Cochran DL (2010) Ridge augmentation using recombinant bone morphogenetic protein-2 techniques: an experimental study in the canine. J Periodontol 81(12):1829–1838. doi:10.1902/jop.2010.100161
12. Toloue SM, Chesnoiu-Matei I, Blanchard SB (2012) A clinical and histomorphometric study of calcium sulfate compared with freeze-dried bone allograft for alveolar ridge preservation. J Periodontol 83(7):847–855. doi:10.1902/jop.2011.110470
13. Sbordone C, Toti P, Guidetti F, Califano L, Pannone G, Sbordone L (2013) Volumetric changes after sinus augmentation using blocks of autogenous iliac bone or freeze-dried allogeneic bone. A non-randomized study. J Cranio-Maxillofac Surg Off Publ Eur Assoc Cranio-Maxillofac Surg. doi:10.1016/j.jcms.2013.03.004
14. Wood RA, Mealey BL (2012) Histologic comparison of healing after tooth extraction with ridge preservation using mineralized versus demineralized freeze-dried bone allograft. J Periodontol 83(3):329–336. doi:10.1902/jop.2011.110270
15. Fu JH, Wang HL (2011) Horizontal bone augmentation: the decision tree. Int J Periodontics Restor Dent 31(4):429–436
16. Misch CM (2010) Autogenous bone: is it still the gold standard? Implant Dent 19(5):361. doi:10.1097/ID.0b013e3181f8115b
17. Margonar R, Queiroz TP, Luvizuto ER, Marcantonio E, Lia RC, Holzhausen M, Marcantonio-Junior E (2012) Bioactive glass for alveolar ridge augmentation. J Craniofac Surg 23(3):e220–e222. doi:10.1097/SCS.0b013e31824de5a4
18. Yilmaz S, Efeoglu E, Kilic AR (1998) Alveolar ridge reconstruction and/or preservation using root form bioglass cones. J Clin Periodontol 25(10):832–839
19. Eldesoqi K, Seebach C, Nguyen Ngoc C, Meier S, Nau C, Schaible A, Marzi I, Henrich D (2013) High calcium bioglass enhances differentiation and survival of endothelial progenitor cells, inducing early vascularization in critical size bone defects. PLoS ONE 8(11):e79058. doi:10.1371/journal.pone.0079058
20. Stavropoulos A, Sima C, Sima A, Nyengaard J, Karring T, Sculean A (2012) Histological evaluation of healing after transalveolar maxillary sinus augmentation with bioglass and autogenous bone. Clin Oral Implants Res 23(1):125–131. doi:10.1111/j.1600-0501.2011.02161.x
21. Galindo-Moreno P, Avila G, Fernandez-Barbero JE, Mesa F, O'Valle-Ravassa F, Wang HL (2008) Clinical and histologic comparison of two different composite grafts for sinus augmentation: a pilot clinical trial. Clin Oral Implants Res 19(8):755–759. doi:10.1111/j.1600-0501.2008.01536.x
22. Hench LL (2006) The story of bioglass. J Mater Sci Mater Med 17(11):967–978. doi:10.1007/s10856-006-0432-z
23. Hench LL, Polak JM (2002) Third-generation biomedical materials. Science 295(5557):1014–1017. doi:10.1126/science.1067404
24. Hench LL, Splinter RJ, Allen WC, Greenlee TK (1972) Bonding mechanisms at the interface of ceramic prosthetic materials. J Biomed Mater Res Symp 5:117–141
25. Hench LL, Wilson J (1986) Biocompatibility of silicates for medical use. CIBA Found Symp 121:231–246
26. Schepers E, de Clercq M, Ducheyne P, Kempeneers R (1991) Bioactive glass particulate material as a filler for bone lesions. J Oral Rehabil 18(5):439–452
27. Xynos ID, Edgar AJ, Buttery LD, Hench LL, Polak JM (2001) Gene-expression profiling of human osteoblasts following treatment with the ionic products of Bioglass 45S5 dissolution. J Biomed Mater Res 55(2):151–157
28. Jell G, Notingher I, Tsigkou O, Notingher P, Polak JM, Hench LL, Stevens MM (2008) Bioactive glass-induced osteoblast differentiation: a noninvasive spectroscopic study. J Biomed MaterRes A 86(1):31–40. doi:10.1002/jbm.a.31542
29. Sohrabi K, Saraiya V, Laage TA, Harris M, Blieden M, Karimbux N (2012) An evaluation of bioactive glass in the treatment of periodontal defects: a meta-analysis of randomized controlled clinical trials. J Periodontol 83(4):453–464. doi:10.1902/jop.2011.110347
30. Richardson WS, Wilson MC, Nishikawa J, Hayward RS (1995) The well-built clinical question: a key to evidence-based decisions. ACP J Club 123(3):A12–A13
31. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 7:10. doi:10.1186/1471-2288-7-10
32. Cohen JA (2001) A coefficient of agreement for nominal scales. Educ Psychol Meas 1960 20(1):37–46. doi:10.1177/001316446002000104
33. Moher D, Schulz KF, Altman D, Group C (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA J Am Med Assoc 285(15):1987–1991
34. Schwarz F, Aoki A, Becker J, Sculean A (2008) Laser application in non-surgical periodontal therapy: a systematic review. J Clin Periodontol 35(8 Suppl):29–44. doi:10.1111/j.1600-051X.2008.01259.x
35. Camargo PM, Lekovic V, Weinlaender M, Klokkevold PR, Kenney EB, Dimitrijevic B, Nedic M, Jancovic S, Orsini M (2000) Influence of bioactive glass on changes in alveolar process dimensions after exodontia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90(5):581–586. doi:10.1067/moe.2000.110035
36. Canullo L, Dellavia C (2009) Sinus lift using a nanocrystalline hydroxyapatite silica gel in severely resorbed maxillae: histological preliminary study. Clin Implant Dent Relat Res 11(Suppl 1):e7–e13. doi:10.1111/j.1708-8208.2008.00141.x
37. Clozza E, Pea M, Cavalli F, Moimas L, Di Lenarda R, Biasotto M (2012) Healing of fresh extraction sockets filled with bioactive glass particles: histological findings in humans. Clin Implant Dent Relat Res. doi:10.1111/j.1708-8208.2012.00463.x
38. Froum S, Cho SC, Rosenberg E, Rohrer M, Tarnow D (2002) Histological comparison of healing extraction sockets implanted with bioactive glass or demineralized freeze-dried bone allograft: a pilot study. J Periodontol 73(1):94–102. doi:10.1902/jop.2002.73.1.94
39. Tadjoedin ES, de Lange GL, Holzmann PJ, Kulper L, Burger EH (2000) Histological observations on biopsies harvested following sinus floor elevation using a bioactive glass material of narrow size range. Clin Oral Implants Res 11(4):334–344

40. Turunen T, Peltola J, Yli-Urpo A, Happonen RP (2004) Bioactive glass granules as a bone adjunctive material in maxillary sinus floor augmentation. Clin Oral Implants Res 15(2):135–141
41. Scarano A, Degidi M, Iezzi G, Pecora G, Piattelli M, Orsini G, Caputi S, Perrotti V, Mangano C, Piattelli A (2006) Maxillary sinus augmentation with different biomaterials: a comparative histologic and histomorphometric study in man. Implant Dent 15(2):197–207. doi:10.1097/01.id.0000220120.54308.f3
42. Mahesh L, Kotsakis G, Venkataraman N, Shukla S, Prasad H (2013) Ridge preservation with the socket-plug technique utilizing an alloplastic putty bone substitute or a particulate xenograft: a histological pilot study. J Oral Implantol. doi:10.1563/AAID-JOI-D-13-00025
43. Trombelli L, Heitz-Mayfield LJ, Needleman I, Moles D, Scabbia A (2002) A systematic review of graft materials and biological agents for periodontal intraosseous defects. J Clin Periodontol 29(Suppl 3):117–135, discussion 160–112
44. Xynos ID, Hukkanen MV, Batten JJ, Buttery LD, Hench LL, Polak JM (2000) Bioglass 45S5 stimulates osteoblast turnover and enhances bone formation in vitro: implications and applications for bone tissue engineering. Calcif Tissue Int 67(4):321–329
45. Varanasi VG, Owyoung JB, Saiz E, Marshall SJ, Marshall GW, Loomer PM (2011) The ionic products of bioactive glass particle dissolution enhance periodontal ligament fibroblast osteocalcin expression and enhance early mineralized tissue development. J Biomed Mater Res A 98(2):177–184. doi:10.1002/jbm.a.33102
46. Klein M, Goetz H, Pazen S, Al-Nawas B, Wagner W, Duschner H (2009) Pore characteristics of bone substitute materials assessed by microcomputer tomography. Clin Oral Implants Res 20(1):67–74
47. Al-Nawas B, Schiegnitz E (2014) Augmentation procedures using bone substitute materials or autogenous bone—a systematic review and meta-analysis. Eur J Oral Implantol 7:S219–S234