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Bioactive Glasses in Periodontal Regeneration

A Systematic Review

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Abstract

Bioactive glasses (BAG) are surface-active ceramic materials that can be used in bone regeneration due to their known osteoconductive and osteoinductive properties. This systematic review aimed to study the clinical and radiographic outcomes of using BAGs in periodontal bone defect regeneration. The selected studies were collected from PubMed and Web of Science databases and included clinical studies investigating the use of BAGs on periodontal bone defect augmentation between January 2000 and February 2022. The identified studies were screened using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A total of 115 full-length peer-reviewed articles were identified. After excluding duplicate articles between the databases and applying the inclusion and exclusion criteria, 14 studies were selected. The Cochrane risk of bias tool for randomized trials was used to assess the selected studies. Five studies compared using BAG with open flap debridement (OFD) without grafting materials. Two of the selected studies were performed to compare the use of BAG with protein-rich-fibrin, one of which also included an additional OFD group. Also, one study evaluated BAG with biphasic calcium phosphate and used a third OFD group. The remaining six studies compared BAG filler with hydroxyapatite, demineralized freeze-dried bone allograft, autogenous cortical bone graft, calcium sulphate β -hemihydrate, enamel matrix derivatives, and guided tissue regeneration. This systematic review showed that using BAG to treat periodontal bone defects has beneficial effects on periodontal tissue regeneration.

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Impact statement:

Bioactive glasses (BAGs) have made a significant stride concerning bone regeneration. This systematic review provides a comprehensive overview of using various forms of bioactive glasses in periodontal bone defect regeneration. A comparison between the use of BAGs with other bone graft materials and bone substitutes is addressed in this review.

Keywords: bioactive ceramics, bone repair, osseous regeneration, intrabony defect, infrabony defect.

Introduction

Periodontitis is an inflammatory disease that affects the teeth-supporting structure, leading to progressive attachment and bone loss around the teeth resulting in pocket formation/recession.¹ Periodontal therapy aims to regenerate the destructed periodontium by forming a new periodontal ligament, cementum, and alveolar bone with the aid of bone graft materials and bone substitutes.² Autogenous bone graft remains the golden standard for bone regeneration as it contains cells responsible for osteogenesis.^{3, 4} However, the limited availability, the need for an extra surgical site, and the uncontrolled remodeling rate are considered the most restricting factors of using autogenous bone.⁵ Therefore, several biomaterials have been used to treat deep intraosseous defects.⁶

Among these grafting materials, bioactive glass (BAG) 45S5, introduced by Hench and co-workers in the late 1960s⁷, has shown osteoconductive and osteostimulatory effects. Different types of bioactive glasses have been developed by varying the chemical composition.⁸ The effects of BAGs are mainly due to ion dissolution that can lead to the formation of the hydroxycarbonate apatite (HA) layer in a short time.⁹⁻¹² Furthermore, ion release is believed to add an osteoinductive property and benefit bone healing by promoting the expression of osteogenic markers, such as alkaline phosphatase, collagen type 1, and osteocalcin.¹³ The reactivity of bioactive glasses can be tailored to meet various clinical requirements by controlling their ion dissolution through changes in the glass composition. Correspondingly, BAGs with antibacterial effects against a wide range of clinically significant microorganisms have been introduced. These effects are attributed to the local increase in the pH and osmotic pressure caused by the dissolution of ions such as Ca^{2+} , and PO_4^{3-} and Si species.¹⁴⁻¹⁸

The chemical composition of the original 45S5 BAG is based on silica, calcium oxide, sodium oxide, and phosphorus pentoxide.⁷ After BAG is soaked in physiological fluid, ion exchange with the medium leads to hydroxyapatite layer deposition. This layer plays a crucial role in favoring the migration and adhesion of bone-forming cells. BAGs are manufactured in various forms, such as porous scaffolds, nanoparticles, granules, and putties.^{19, 20} The scaffolds and filler particle forms have gained particular interest in periodontal regeneration due to their adaptability and antibacterial and osteogenic properties.²¹ Moreover, BAG can be deposited on metallic surfaces such as dental implants to improve their biological behavior.²² There are many clinical and radiological studies supporting the application of BAG in treating bony defects related to advanced periodontal destruction.²³⁻³⁶

This review aims to address the use of BAGs in the regeneration of bone defects related to periodontitis or peri-implantitis by evaluating their clinical and radiographical outcomes compared to non-augmented defects or defects augmented using other grafting materials.

Materials and Methods

Research question

The research question was designed based on the PICO structure, which stands for Population (or Patient or Problem) - Intervention - Comparator – Outcome. In intrabony defects related to periodontitis and peri-implantitis (P), what is the effect of bone augmentation using BAG (I) compared to non-grafted defects or defects grafted using other bone graft materials or bone substitutes (C) on probing depth (PD), clinical attachment level (CAL), and radiographic bone fill (RBF) (O)?

Data sources

A thorough literature search of electronic databases was performed, including PubMed-MEDLINE and Web of Science. The keywords used in the search are indicated in table (1)

Eligibility criteria

A literature search was performed on published studies with BAG application on intrabony defects between January 2000 and February 2022. The published studies met the following criteria: (1) type of study (in vivo clinical study); (2) type of intervention (Placement of BAG in periodontal or peri-implant bone defect); (3) control (either non-grafted or using other bone graft material or bone substitutes); (4) principal outcomes (changes in the PD, CAL, and RBF)

Inclusion and exclusion criteria

Clinical studies and case report series investigated the effect of BAG on the treatment of periodontal diseases with intrabony defects were screened. Review articles, animal studies, articles not written in English, or their full text was not available were excluded.

Study selection

Three reviewers separately examined the titles and abstracts. If necessary, full-text articles were also reviewed when the abstracts did not provide enough information to decide. Two reviewers evaluated the full texts of the remaining articles and established inclusion and exclusion criteria based on the PICOS strategy. The identified studies were screened using Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. If there was disagreement, a third reviewer was consulted. After the full-text screening, important information was extracted, and the potential articles were selected (Fig 1). Cochrane risk of bias tool for randomized trials was used to assess the selected articles (table 2).

Data extraction

Two reviewers independently obtained data from eligible studies after reading their full text. The following variables were extracted from each study: 1) year of publication; 2) study design (randomized split-mouth design, randomized parallel trial); 3) type of bone defect; 4) Number of participants in the treatment and control groups; 5) the number of bone defects per treatment and control groups; 6) treatment and control interventions; 7) study outcomes (PD, CAL, and bone fill); 8) setting and country of intervention; and 9) trial duration.

Results

The leading search was conducted from January 2000 to February 2022 and resulted in 53 articles from PubMed and 62 articles from the Web of Science: a total of 115 articles. Twenty-nine duplicate articles were removed by an automated tool (EndNote, Find Duplicate). Based on the exclusion and inclusion criteria, additional 53 articles were excluded after screening their titles and abstracts.

Based on the full-text screening of 33 articles, 19 articles were excluded; review article (n = 1); inadequate control group (n = 2); bone defect was not due to periodontal disease (n = 1); omission of intrabony defect in baseline and follow up (n = 1); BAG is mixed/used with another material and/or BAG is used in both test and control groups (n = 10); less than 10 bone defects in the test group (n = 2); duplicate study (n = 1) and non-English study (n = 1). A total of 14 studies were left in the analysis.²³⁻³⁶ All studies evaluated patients with intra- or infra-bony defects except one study, which had patients with furcation defects. Six of the 14 studies were randomized split-mouth designs, and the remaining eight were randomized parallel trials (Table 3)

Five studies compared BAG to open flap debridement (OFD)^{26, 30, 33, 35, 36}, while seven studies used active controls, including nanohydroxyapatite (HA)²³, platelet-rich fibrin (PRF)²⁵, demineralized freeze-dried bone allograft (DFDBA)²⁷, autogenous cortical bone graft (ACBG)²⁸, calcium sulphate β -hemihydrate (CaSO₄)²⁹, enamel matrix derivative (EMD)³², and bioresorbable membrane (GTR).³⁴ Two studies compared two test groups to OFD; one used BAG and biphasic calcium phosphate (Ca(PO₄)₂)³¹, and the other used BAG and PRF.²⁴ Five of the included studies used Perioglas®^{24, 26-28, 32, 33}, three studies used Novabone® Putty^{23, 25, 29}, two studies utilized Biogran®^{3,5 36}, and the remaining studies did not specify the manufacture of the BAG used.^{30, 31, 34} In terms of the investigated parameters, all studies investigated the effect of the intervention on PD, CAL, and hard tissue fill. One study did not include post-operative PD measurements.³⁶ All studies evaluated the healing of intrabony defects except studies conducted by Koduru et al.²³ and Chacko et al.²⁶ used infrabony defects.

The studies compared the use of BAG against OFD showed a statistically significant PD reduction, CAL gain, and intrabony defect fill in both experimental and control groups compared to baseline measurements. Comparison of post-operative study outcomes varies between studies.^{26, 30, 33, 35, 36} Chacko et al.²⁶ demonstrated a significant PD reduction in BAG treated group compared to OFD alone. However, this was not related to CAL gain and intrabony defect fill since no significant difference was reported in both 6- and 9-month periods. The study conducted by Satyanarayana et al.³⁰, over 12 months of observation time, reported a significant PD reduction in sites with more than 7 mm, CAL gain, and intrabony defect fill in the BAG-treated group than in OFD alone. Also, in the study by Park et al.³⁵, more significant results where PD reduction and CAL gain were reported in sites that exceeded 7 mm, and more RBF in sites with defect depth exceeded 4 mm. Besides, in Rosenberg et al.³⁶, a significant CAL gain and intrabony defect fill were also seen in the BAG-treated group compared to OFD alone over 6-month observation time. On the other hand, Dybvil et al.³³ reported that the use of BAG in combination with OFD provided no significant benefit over OFD alone over a 12-month study period.

Pandit et al.³¹ compared OFD to two experimental groups, BAG and Ca(PO₄)₂. Their study reported a statistically significant reduction in PD and CAL and bone defect fill in all experimental groups compared to baseline measurements. Intergroup comparison showed a statistically significant reduction in PD was observed for BAG and Ca(PO₄)₂ treated groups compared to OFD alone in 3 and 6 months. At 3 months, PD reduction in the BAG group was significantly more than in the Ca(PO₄)₂ group. However, during 6 months observation period, the Ca(PO₄)₂ showed significant PD reduction. The CAL gain and bone defect resolution were significantly higher for both experimental groups compared to OFD alone.³¹ In Yajamanya et al.²⁴, which compared PRF and BAG to OFD over a 9-month observation period, a significant PD reduction, CAL gain, and more PRF were observed in all groups. After 3 months, PRF and

BAG groups showed a significantly lower PD and CAL gain than the OFD group. Also, a statistically significant intrabony defect fill was observed for PRF and BAG groups compared to OFD over a 6-months observation period.²⁴

All studies comparing the post-operative outcomes of BAG to different bone grafts and bone substitutes showed significant PD reduction, CAL gain, and intrabony defect fill compared to baseline measurements. However, the clinical and radiological outcomes vary between the grafting materials used. The studies by Koduru et al.²³, Sumer et al.²⁸, Mandlik et al.²⁹, Leknes et al.³², and Mangel et al.³⁴ used BAG and compared it to HA, autogenous cortical bone graft, CaSO₄, EMD, and GTR, respectively. All studies reported no significant difference in intergroup comparison over the studies period. In contrast, Katuri et al.²⁷ study, in which BAG was compared to DFDBA, showed no significant difference in PD reduction or CAL gain, but more intrabony defect fill was observed at 6 months in the BAG-treated sites. However, when observation time was extended to 12 months, significant PD reduction, CAL gain, and intrabony defect fill were observed for the DFDBA sites.²⁷ One study by Biswas et al.²⁵ compared BAG to PRF in managing Glickman's grade II furcation defects in mandibular molars. The study reported that defect augmentation using BAG led to more vertical and PD reduction, more CAL gain, and better bone fill improvement compared to PRF. However, this difference was not related to the horizontal probing depth reduction.²⁵

Discussion

This systematic review aimed to investigate the outcome of using bioactive glasses in clinical periodontal regeneration over the past 22 years. Fourteen articles were found to meet the established inclusion criteria. Animal studies and clinical studies investigating the antimicrobial effects of BAGs were not included in this review. The BAGs were tested against various materials, including ACBG, DFDBA, GTR, EMD, PRF, and various bone substitutes. In some studies, BAGs were mixed with other materials or combined with GTR membranes. Those studies were also excluded from the review because the regenerative effect cannot be solely related to the BAG. The BAG compositions used in the included studies appeared to be biocompatible, and there were no reports of adverse effects, such as allergies or other immunologic reactions, rejection of the graft material, or abscess formation. All studies included in this review evaluated the treatment outcome of intrabony defects except two studies^{23, 26} in which the healing of infrabony defects was evaluated. Intrabony defect means the defect is inside the wall, referred to as a 3-wall bone defect, while other forms of angular bone defects are termed infrabony defects.³⁷

In this review, the clinical and radiographical outcomes of using BAGs were evaluated against OFD without the additional use of graft materials. The parameters evaluated were PD, CAL, and radiographic bone level changes. In all studies,^{26, 30, 33, 35, 36} there was evidence to support that OFD can be effectively used for intraosseous defects therapy and using a graft material seemed to enhance the treatment outcome. These observations are mostly related to deep and narrow intrabony defects that have the property of self-maintaining space, as indicated by other studies.^{38, 39} Furthermore, the results support the hypothesis that sites with larger preoperative PD and CAL tend to result in more significant PD reduction and CAL gain. Other studies conducted by Renvert et al.⁴⁰ and Pihlstrom et al.⁴¹ also supported this notion, and they attribute it to more gingival recession and clinical attachment gain are expected in deep sites. However, the results from Chacko et al.²⁶ study were not in line with the other studies^{30, 35, 36} and showed no significant difference in the CAL gain between using BAG and OFD alone. Also, Dybvik et al.³³ study agreed with Chacko et al.²⁶ and showed that the overall PD reduction and CAL gain were insignificant between the groups. This may be related to the skewed distribution of patients in the study since 67% of patients in the test group were smokers against 29% in the control group. However, Park et al.³⁵ reported significant PD reduction and CAL gain in the BAG group in sites with preoperative PD greater than 7mm. The difference between groups was not statistically significant when the preoperative PD was less than 7 mm. These findings are supported by other studies that indicate bone grafts act as a space-making material and prevent the apical migration of junctional epithelium.^{40, 42}

Autogenous bone graft is regarded as the golden standard for bone regeneration because of the absence of immunological reactions. Furthermore, it is the only available graft that combines osteoconductive, osteoinductive, and osteogenic properties.^{43, 44} However, autogenous bone graft has some limitations, such as restricted donor sites, limited availability, and unpredictable graft resorption.⁴⁵ Yet, ACBG is usually harvested from the surgical sites adjacent to the defect by scraping the cortical bone, thus limiting the need for a second surgical site. It is regarded as an osteoconductive material with few osteogenic cells.⁴⁶ In Sumer et al.²⁸ study, ACBG was compared to BAG. The similar treatment outcome obtained by using BAG or the ACBG may be related to the influence of morphology or location of the bone defects. Also, the effect of the lack of osteogenic and osteoinduction properties of the ACBG graft on these observations cannot be excluded.

Bone grafts with osteoinductive properties provide growth factors that enhance bone regeneration, such as bone morphogenic proteins (BMP) that trigger the migration, attachment, and osteogenesis of the mesenchymal cell.⁴⁷ DFDBA is a graft material with osteoinductive properties and has been used in periodontal defect regeneration and successfully regenerates bone, cementum, and periodontal

ligaments.⁴⁸ In Katuri et al.²⁷ study, the regeneration capacity of DFDBA was compared with BAG. The results demonstrated a comparable favorable outcome in treating intraosseous defects in 3- and 6-month observation time points. The similar radiographic outcome of both treatment groups at 3 and 6 months may be attributed to the fact that BAG is radio-opaque while DFDBA is radio-lucent material due to the removal of calcium in the preparation process. However, at 12 months, DFDBA showed more significant PD reduction, CAL gain and RBF over BAG augmented sites. The resorption properties of BAG materials may explain this. These observations align with findings reported in similar studies.^{49, 50}

Studies have also shown that EMD affects the osteogenic gene expression and cell adhesion,⁵¹ as well as the synthesis of growth factors such as TGF- β and interleukin-6 in the fibroblasts and periodontal ligament cells.^{52, 53} EMD is extracted from developing porcine teeth and comprises over 90% of a protein complex comprised of amelogenin. Owing to its properties, EMD has been widely used for periodontal regenerative therapy and effectively promotes regeneration of the alveolar bone, cementum, and periodontal ligaments in bone defects.^{54, 55} In Leknes et al.³² study, EMD was compared to BAG in intrabony defect regeneration over 12 months. In their study, both materials significantly improved all clinical parameters compared to the baseline. However, in the interproximal sites, BAG showed a slight improvement over its EMD counterparts. Contrarily, similar studies have reported contradicting results and shown more improvement in the clinical parameters in sites treated with EMD.^{56, 57} These contradicting results may be related to the inclusion criteria since only non-smokers were included in the later studies. In contrast, smokers and non-smokers were included in the Leknes et al.³² study.

The use of bioresorbable GTR membranes is a valid treatment option to restore the periodontal structure. The GTR membrane provides space for the primary blood clot, protects healing, and stabilizes wounds. It also prevents gingival epithelium and connective tissue from growing into the regeneration site, especially in non-contained infrabony defects.^{58, 59} In the Mangel et al.³⁴ study, the use of bioresorbable membranes was compared to BAG. Both treatment modalities were effective and showed significant treatment outcomes compared to baseline values. The intergroup comparison showed no significant difference in the clinical or radiographical outcomes. The treatment success of using a bioresorbable membrane reported by Mangel et al. was also demonstrated in similar studies.^{60, 61} However, a study by Caffesse et al.⁶² showed conflicting results and limited success in the CAL gain.

Furthermore, PRF, which is easy to prepare and apply, has shown favorable clinical results in treating periodontal intrabony defects⁶³. It is an autogenous living biomaterial that consists of a leukocyte-platelet-rich fibrin matrix, which acts as a bioresorbable scaffold.⁶⁴ In the Yajamanya et al.²⁴ study, the use of BAG or PRF was evaluated against OFD alone. Both grafted groups had clinical and radiographic

improvements compared to baseline or OFD alone. Also, Biswas et al.²⁵ compared PRF to BAG putty in treating class II furcation defects. Their study reported that using BAG putty significantly improved the vertical PD, CAL gain, and RBF over PRF. This positive response is probably related to the handling properties and better retention of BAG putty in the defect site compared to PRF. These observations were in agreement with the findings reported in another study.⁶⁵ Nevertheless, one study also reported conflicting results showing slight advantages in furcation sites treated with PRP over sites treated with BAG.⁶⁵ Like Yajamanya et al.²⁴ study, Pandit et al.³¹ also used two experimental groups, inorganic $\text{Ca}(\text{PO}_4)_2$ and BAG, and compared them to OFD. However, the findings of the latter study showed significantly better treatment outcomes in the clinical parameters by using either grafting material compared to OFD alone. These findings support the concept that using a graft material additional to OFD results in a better treatment outcome.

HA is also inorganic bioceramic which is widely used in periodontal regeneration due to its similarity to the main mineral constituent of bones and teeth. HA is well tolerated by oral tissues, characterized by osteoconductive ability, and has been shown to promote osteoblast differentiation and bone formation.⁶⁷ It can also stimulate stem cells and osteoblasts to proliferate and differentiate the process of new bone regeneration.⁶⁸ Koduru et al.²³ study showed that both HA and BAG putty resulted in satisfactory treatment outcomes in treating intrabony defects, but no significant difference was noticed between groups at any time point. These observations were in accordance with other similar studies.^{50,}⁶⁵ In Mandlik et al.²⁹ study, BAG was compared to CaSO_4 , also known as plaster of Paris. After a 9-month observation period, similar effects were reported in PD reduction and CAL gain. However, concerning bone defect fill, BAG demonstrated significantly better outcomes than CaSO_4 . This difference may be related to the rapid resorption rate of CaSO_4 compared to BAG.⁶⁹

Based on the above, it must be pointed out that the outcome of periodontal intrabony defect therapy is influenced by factors other than the type of graft material used. The defect depth, morphology, and radiographic bone depth are crucial factors as more regeneration is expected in deep 3-wall defects compared to shallow or 1-wall defects.⁷⁰ Also, the supracrestal soft tissue thickness has been shown to affect the amount of intrabony defect fill, as demonstrated by the Parashis et al. study.⁷¹ In addition, risk factors such as smoking have a critical impact on the outcome of periodontal treatment, as a less favorable response to surgical and non-surgical treatment is expected.³⁸ There are considerable variations among the findings of different studies, which may be related to other factors apart from the graft material used. Therefore, based on existing literature, the outcome of regenerative periodontal therapy cannot be solely related to the type of graft material alone.

Conclusions

Despite the included clinical trials being mainly controlled, most studies were carried out using a limited number of patients and limited follow-up time. In general, it can be concluded that using BAG in intrabony augmentation improves the healing outcomes related to probing depth reduction, clinical attachment gain, and radiographic bone fill compared to open flap debridement. In addition, using BAG resulted in comparable results to using other bone graft materials and bone substitutes, especially in earlier observation periods, with some advantages in treating furcation defects.

Author contributions

Faleh Abushahba: Conceptualization, methodology, literature search, screening and selection, data extraction, writing original draft, editing the manuscript. **Ahmed Algahawi:** screening and selection, data extraction, validation, review, and editing. **Nagat Areid:** screening and selection, data extraction, validation, review, and editing. **Leena Hupa:** validation, critical review, and editing. **Timo Närhi:** Conceptualization, supervision, validation, critical review, and editing. All authors read and approved the final version of this manuscript.

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Disclosure statement

All authors declare that they have no conflict of interest.

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