Bioglass 45S5 in dentistry: Current evidence, clinical applications and future perspectives (Review)

FRANCESCA GORASSINI[1,2], COSIMO GALLETTI[3], CESARE D'AMICO[4], FULVIA GALLETTI[5], JAVIER FLORES-FRAILE[2] and LUCA FIORILLO[3,6]

[1]Multidisciplinary Department of Medical-Surgical and Odontostomatological Specialties, University of Campania 'Luigi Vanvitelli', I-80121 Naples, Italy; [2]Department of Surgery, Faculty of Medicine and Dentistry, University of Salamanca, 37008 Salamanca, Spain; [3]Department of Medicine and Surgery, University of Enna 'Kore', I-94100 Enna, Italy; [4]Department of General Surgery and Surgical-Medical Specialties, School of Dentistry, University of Catania, I-95124 Catania, Italy; [5]Department of Biomedical and Dental Sciences and Morphological and Functional Imaging, University of Messina, I-98100 Messina, Italy; [6]Department of Dental Research Cell, Dr. D. Y. Patil Dental College & Hospital, Dr. D. Y. Patil Vidyapeeth (Deemed to be University), Pimpri, Pune 411018, India

Received March 10, 2026; Accepted April 9, 2026

DOI: 10.3892/wasj.2026.476

Abstract. Bioglass 45S5 (45 wt% SiO_2, 24.5 wt% Na_2O, 24.5 wt% CaO, 6 wt% P_2O_5), developed in the early 1970s, was the first synthetic material shown to chemically bond with living bone. The present narrative review surveys the currently available evidence on its use across the major dental specialties. A literature search was conducted on the PubMed, Scopus and Web of Science databases covering publications from 1971 to March, 2026. Bioglass 45S5 forms a carbonated hydroxyapatite layer at the tissue interface through rapid ion-exchange reactions, thereby promoting cell adhesion, mineralization and tissue bonding. In periodontal surgery, it supports alveolar bone fill and attachment gain; in endodontics, it shows promise for pulp capping and root-end sealing; 45S5-containing toothpastes occlude dentinal tubules and reduce hypersensitivity; and as a coating on titanium implants it enhances early osseointegration. However, low fracture toughness, rapid degradation in some formulations, and clinical literature dominated by small, short-term trials remain key limitations. Advances in sol-gel synthesis, ion doping, nanoscale engineering and additive manufacturing continue to broaden the therapeutic scope of the material; however, further well-designed randomized clinical trials are warranted to consolidate the evidence base.

Correspondence to: Professor Luca Fiorillo, Department of Medicine and Surgery, University of Enna 'Kore', Via Cittadella Universitaria, I-94100 Enna, Italy
E-mail: luca.fiorillo@unikore.it

Abbreviations: BG, bioactive glass; BMP-2, bone morphogenetic protein-2; CAL, clinical attachment level; CHA, carbonated hydroxyapatite; DH, dentin hypersensitivity; DPSC, dental pulp stem cell; MBG, mesoporous bioactive glass; PD, probing depth; PDL, periodontal ligament; PRF, platelet-rich fibrin

Key words: Bioglass 45S5, bioactive glass, dentistry, periodontal regeneration, dentin hypersensitivity, endodontics, osseointegration, remineralization, biomaterials

Contents

1. Introduction

Bioactive glasses (BGs) rank among the most consequential innovations in biomaterials science produced in the twentieth century. In 1969, Hench *et al* (1,2), at the University of Florida, Gainesville, FL, USA developed the first synthetic material able to form a direct, chemically bonded interface with living bone. This was subsequently commercialized as Bioglass 45S5 and later marketed under the trade names Biogran® and PerioGlas® (1,2). The designation '45S5' denotes its chemical composition: 45 wt% silicon dioxide (SiO_2), with a network connectivity value of 2 (3).

In contrast to earlier bioinert implant materials, alumina ceramics, cobalt-chrome alloys and ultra-high-molecular-weight polyethylene, Bioglass 45S5 does not simply tolerate the biological milieu; it participates in it. Upon coming into contact with physiological fluids, a cascade of ion-exchange reactions occurs at the glass surface, culminating in nucleation and growth of a biologically equivalent

carbonated hydroxyapatite (CHA) layer. This layer recruits proteins and cells that ultimately direct bone formation and repair (4,5).

Dentistry was one of the earliest disciplines to explore the therapeutic potential of 45S5. From experimental alveolar bone regeneration studies in the 1980s to contemporary work in endodontics, preventive dentistry and implantology, the material has shown an extraordinary breadth of clinical utility. Its capacity to bond simultaneously with both hard and soft connective tissues, a property not shared by other bioceramics, is particularly advantageous in the complex microenvironment of the oral cavity (3,5,6).

Despite this long history and a substantial body of literature, to the best of our knowledge, no comprehensive narrative review has recently brought together the current state of evidence across all dental application domains. Given the rapid expansion of 45S5-based formulations and the growing number of clinical studies, an updated synthesis is both timely and clinically relevant.

The present review aimed to: i) Describe the physicochemical properties and biological mechanisms of Bioglass 45S5; ii) critically appraise the evidence for its use across major dental specialties; iii) identify current limitations; and iv) outline emerging directions for future research and clinical translation.

The literature search was conducted across the PubMed, Scopus and Web of Science databases for publications dated between 1971 and March, 2026. The search strategy combined terms related to the material (e.g.'Bioglass', '45S5', 'bioactive glass') with terms for each dental application domain (e.g. 'periodontal', 'endodontic', 'dentin hypersensitivity', 'implant', 'remineralisation'). Articles published in the English language reporting original research (*in vitro*, *in vivo* and clinical studies), systematic reviews and authoritative narrative reviews were considered for inclusion. Case reports without control groups, conference abstracts lacking full-text data, non-peer-reviewed sources and studies addressing BG compositions other than 45S5 without direct comparison were excluded. The reference lists of retrieved articles were screened to identify additional relevant publications. As the present study was a narrative, rather than a systematic, review, formal risk-of-bias assessment and meta-analysis were not undertaken; however, the quality and consistency of the available evidence are discussed within each application section. A summary of the selected clinical studies on Bioglass 45S5 in periodontal regeneration is presented in Table I.

2. Physicochemical properties and composition

Chemical composition and network structure. Bioglass 45S5 belongs to the SiO_2-Na_2O-CaO-P_2O_5 quaternary system. Its precise weight-percentage composition is: 45% SiO_2, 24.5% Na_2O, 24.5% CaO and 6% P_2O_5 (7). The relatively low silica content, below the 60 mol% threshold Hench (2) identified as critical for bioactivity, yields a highly disrupted silicate network. Sodium and calcium ions serve as network modifiers, breaking Si-O-Si bridging bonds and creating non-bridging oxygen sites that allow rapid ionic exchange with biological fluids (8).

The network connectivity of 45S5 is ~2.11, placing it at the boundary of glass-forming stability and accounting for both its outstanding bioactivity and its susceptibility to dissolution, a double-edged feature with important clinical consequences (9).

Phosphorus in the composition exists predominantly as orthophosphate groups (PO_4^{3-}) rather than as a structural constituent of the silicate network. These groups are deemed to facilitate the formation of apatite-like phases early in the bioactive response, acting as nucleation sites for hydroxyapatite precipitation (10).

Physical properties. In its original melt-derived form, Bioglass 45S5 is optically transparent, with a glass transition temperature (Tg) near 520˚C and a crystallization temperature of ~610˚C. Its density is 2.7 g/cm^3; its elastic modulus is ~35 GPa, lower than cortical bone (~20 GPa), but well above cancellous bone (~0.5-2 GPa). Compressive strength ranges from 500 to 1,000 MPa, yet the fracture toughness (K^1c ~0.7-0.9 MPa·m½) falls well short of cortical bone (~2-6 MPa· m½), which restricts use in load-bearing sites (11,12).

Particle size profoundly influences the biological response. Fine particles (90-710 μm) are standard for periodontal applications, whereas submicron- and nanosized 45S5 particles produced by sol-gel synthesis exhibit ~30-fold greater specific surface area than melt-derived equivalents, thereby accelerating bioactivity and enabling new application formats such as coatings, scaffolds, and toothpaste additives (13).

Surface reactivity and bioactivity index. Hench [Hench (2) and Hench and Thompson (14)] introduced the 'bioactivity index' ($I^{\wedge}$) as a quantitative measure of *in vivo* bond formation. Bioglass 45S5 ranks among the highest $I^{\wedge}$ values of any bioactive material, forming bonds with bone within hours of implantation in animal models, a property attributed to the rapid formation of a silica-rich gel layer followed by CHA precipitation (14).

3. Mechanism of bioactivity

Ionic exchange reactions and HCA layer formation. The sequence of surface reactions leading to hydroxyapatite formation is well-characterized and proceeds through at least 11 stages, as first proposed by Hench [Hench (2), Hench and Polak (4) and Hench and Thompson (14)] and later refined (4,15). Stages 1-2 involve the rapid exchange of Na^+ and Ca^{2+} from the glass for H^+/H_3O^+ from the solution, creating a silica-rich surface and raising local pH, followed by loss of soluble silica through hydrolysis of Si-O-Si bonds, generating Si-OH (silanol) groups. Stages 3-5 involve the condensation and repolymerization of the silica-rich layer into a hydrated silica gel. During stages 6-8, Ca^{2+} and PO_4^{3-} ions migrate to the surface and form an amorphous calcium phosphate layer. Finally, stages 9-11 involve crystallization of this amorphous layer into biologically equivalent CHA, incorporating carbonate, fluoride and magnesium from the surrounding medium.

The resulting CHA layer is chemically and structurally analogous to bone mineral, enabling adsorption of growth factors and extracellular matrix proteins and providing a

Table I. Summary of selected clinical studies on Bioglass 45S5 in periodontal regeneration.

Authors, year of publication	No. of patients/ defects	Study design	Intervention	Primary outcome	Key findings	Follow-up	(Refs.)
Froum *et al*, 1998	37	Controlled CT	PerioGlas® vs. OFD	Bone fill; PD reduction	Greater bone fill (+1.7 mm) and PD reduction	6 months	(24)
Mengel *et al*, 2006	20	RCT	PerioGlas® vs. DFDBA	CAL gain; Radiographic bone fill	Equivalent outcomes to DFDBA	12 months	(25)
Sculean *et al*, 2008	118 defects	Systematic review	45S5 vs. OFD	CAL gain	WMD +1.2 mm (95% CI, 0.7-1.7) favoring 45S5	Various	(26)
Bodhare *et al*, 2019s	40	RCT	45S5 + PRF vs. 45S5 alone	CAL gain; bone fill	Greater CAL gain with combination (+1.2 mm)	9 months	(27)

CT, controlled trial; OFD, open flap debridement; RCT, randomized controlled trial; DFDBA, demineralized freeze-dried bone allograft; CAL, clinical attachment level; WMD, weighted mean difference; PRF, platelet-rich fibrin.

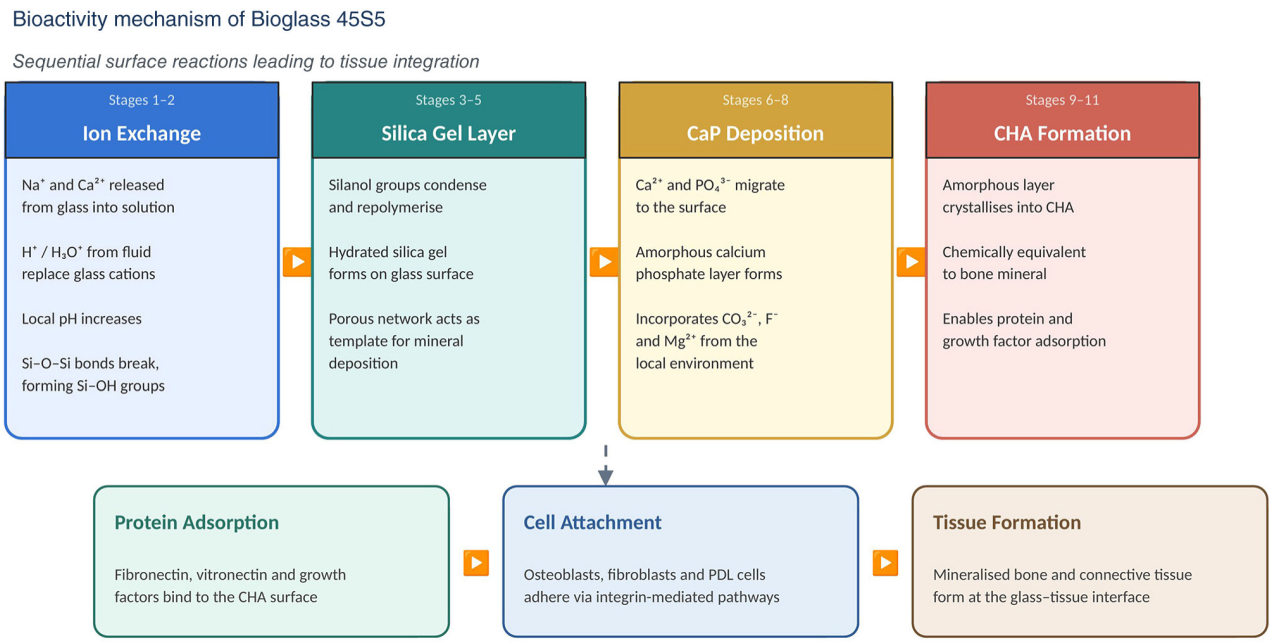

Figure 1. Schematic diagram of the multi-stage bioactivity mechanism of Bioglass 45S5. The illustration depicts the sequential surface reactions from the initial ion exchange (stages 1-2), through silica gel formation (stages 3-5), amorphous calcium phosphate deposition (stages 6-8), and final crystallization into carbonated hydroxyapatite (CHA) (stages 9-11). The CHA layer enables protein adsorption, cell attachment, and mineralized tissue formation at the glass-tissue interface. The figure was created by the authors based on data derived from the study by Hench (2).

scaffold for osteoblast attachment and differentiation (16) (Fig. 1).

Molecular and cellular mechanisms. At the cellular level, silicon ions released during glass dissolution upregulate osteocalcin, bone sialoprotein and collagen type I expression in osteoblasts, providing a molecular basis for the osteoinductive potential of 45S5 (17). Calcium and phosphate ions sustain supersaturation at the implant-tissue interface, potentiating mineralization. Notably, the local alkaline shift triggered by Na^+ and Ca^{2+} release creates conditions that favor osteogenic differentiation while inhibiting osteoclastic activity (18).

In soft-tissue contexts relevant to dentistry, including gingival fibroblasts and periodontal ligament (PDL) cells, 45S5 dissolution products stimulate proliferation and collagen synthesis. The study by Wilson and Low (6) demonstrated that 45S5 binds to both hard and soft connective tissues within days of implantation, an ability attributed to formation of a collagen-CHA composite at the implant-soft tissue interface.

Antibacterial properties. An aspect of 45S5 bioactivity that has not received the sufficient attention is its intrinsic antibacterial effect, arising from the rapid elevation of local pH on dissolution. Studies have documented significant reductions in the viability of *Streptococcus mutans*, *Porphyromonas gingivalis* and *Fusobacterium nucleatum* on 45S5 surfaces at pH values reaching 9-11 (19,20). This property holds particular relevance for dental applications involving infected sites or materials that must resist microbial colonization, such as endodontic sealers, periodontal grafts and implant coatings.

4. Dental applications

Periodontal regeneration

Preclinical evidence. The earliest dental application of Bioglass 45S5 in periodontal regeneration was reported by Wilson and Low (6), who used a Patus monkey model of periodontal defects to evaluate 45S5 particulate of various sizes. The results demonstrated new bone formation throughout the defect, with bone growth initiated at the surface of the bioactive glass particles forming a trabecular network that reproduced the architecture of the original alveolar bone (6). Subsequently, Low *et al* (21)) evaluated bioactive ceramic in the treatment of periodontal osseous defects in a clinical setting, reporting improvements in probing depth, attachment gain and radiographic bone fill. Subsequent research using standardized three-wall intrabony defects in dogs and non-human primates confirmed the osteoconductive capacity of 45S5 particulates, demonstrating radiographic bone fill comparable to autogenous grafts at 3-6 months (22).

PDL cells are a heterogeneous population of fibroblast-like cells located in the PDL, a specialized connective tissue that anchors the tooth root to the alveolar bone. These cells possess multi-lineage differentiation potential, they can adopt osteoblastic, cementoblastic and fibroblastic phenotypes, which renders them central to periodontal regeneration research. *In vitro* studies using human PDL cells have demonstrated that 45S5 ionic dissolution products promote cell proliferation, alkaline phosphatase activity and mineralized nodule formation. For example, Varanasi *et al* (23) reported that PDL cells cultured in 45S5-conditioned media exhibited the upregulation of cementoblastic markers, including cementum attachment protein and osteopontin, suggesting a role in cementogenesis (Table II).

Clinical evidence. PerioGlas® (NovaBone Products), a commercially available 45S5 particulate developed for periodontal indications, has been evaluated in numerous clinical trials. Froum *et al* (24) conducted a controlled trial evaluating 59 defects in 16 healthy adults, reporting significantly greater probing depth (PD) reduction (4.26 vs. 3.44 mm) and clinical attachment level (CAL) gain (2.96 vs. 1.54 mm) in 45S5-treated sites compared to open-flap debridement alone at 12 months.

The 5-year clinical and radiological study by Mengel *et al* (25) comparing a bioabsorbable membrane with BG in 12 patients with generalized aggressive periodontitis, demonstrated that both treatments yielded significant improvements in CAL and PD, with a radiographically greater defect fill in the BG group. The systematic review of preclinical evidence by Sculean *et al* (26), which examined the biological rationale for combining barrier membranes with grafting materials, confirmed histological evidence of periodontal regeneration in animal models treated with bioactive materials.

Combination approaches using 45S5 with resorbable membranes (guided tissue regeneration) or platelet-rich fibrin (PRF) have shown additive benefits in more complex multi-wall defects. Bodhare *et al* (27) reported significantly greater CAL gain (4.1 vs. 2.9 mm) when 45S5 was combined with PRF compared to 45S5 alone, pointing towards synergistic promotion of tissue regeneration.

The overall quality of the periodontal evidence base for Bioglass 45S5 is, at best, moderate. The majority of the available clinical trials are characterized by small sample sizes (often <20 patients), short follow-up intervals (typically ≤12 months), heterogeneous outcome measures, and moderate risk of bias linked to incomplete blinding or inadequate randomization procedures. These methodological shortcomings hinder firm conclusions regarding long-term treatment stability and superiority over established grafting materials. Large-scale, multicenter randomized clinical trials with standardized primary outcomes, including radiographic defect fill, CAL gain and patient-reported outcomes measured over at least 24 months of follow-up, are therefore required to strengthen the evidence base for 45S5 in periodontal therapy.

Alveolar ridge preservation and bone augmentation. Post-extraction alveolar bone resorption produces significant volumetric deficiencies that complicate implant placement. Bioglass 45S5 has been investigated as a socket grafting material to preserve ridge dimensions. Preclinical and early clinical data indicate that 45S5 particulates placed into extraction sockets can maintain alveolar width and bone volume relative to ungrafted controls, though high-quality randomized clinical trial data evaluating PerioGlas® specifically for ridge preservation remain limited.

The use of 45S5 combined with collagen membranes for guided bone regeneration in horizontal and vertical bone augmentation has shown promising results in case series. Its gradual resorption, typically complete within 6-18 months depending on particle size, provides a temporary scaffold that is replaced by newly formed bone, histologically comparable to native bone in biopsies obtained at implant placement (28).

Endodontics

Pulp capping and pulpotomy. The biological compatibility of Bioglass 45S5 with dental pulp tissue has been evaluated in both direct and indirect pulp-capping settings. Animal studies have demonstrated that 45S5 placed in direct contact with exposed pulp tissue induces reparative dentinogenesis, with a dentinal bridge forming within 4-8 weeks, mediated by upregulation of transforming growth factor-β1 and bone morphogenetic protein-2 (BMP-2) in odontoblasts (29).

Relative to calcium hydroxide [$Ca(OH)_2$], long considered the gold standard for indirect pulp capping, 45S5 exhibits equivalent or superior dentinal bridge quality in animal models, with a more homogeneous, less porous bridge structure (30). The antibacterial effect of 45S5, attributable to its alkaline dissolution, may offer additional protection against residual bacteria at the capping interface. That said, evidence from human clinical trials remains limited, and further well-controlled studies are warranted before 45S5 can

Table II. Summary of the dental applications of Bioglass 45S5: Evidence base, key findings and main limitations.

Application domain	Evidence type	Key findings	Main limitations
Periodontal regeneration	Preclinical (canine, primate); RCTs	Improved PD reduction and CAL gain vs. OFD alone; additive benefit with PRF/GTR	Small sample sizes; short follow-up; heterogeneous outcomes
Alveolar ridge preservation	Case series; limited RCT data	Maintenance of ridge width; histological bone comparable to native bone	Lack of high-quality RCT data
Endodontics (pulp capping)	Animal studies; limited human data	Reparative dentinal bridge formation; comparable to $Ca(OH)_2$	Insufficient clinical trial evidence
Root-end filling	*In vitro*/*ex vivo*	CHA seal at dentinal interface; good biocompatibility	Limited *in vivo* data
Dentin hypersensitivity	RCTs (NovaMin®/ Sensodyne RP)	Significant DH score reduction vs. placebo at 4-12 weeks	Inconclusive comparisons with other active agents
Caries prevention/ reminer alization	*In vitro* pH-cycling models	Reduced enamel mineral loss; up to 73% mineral recovery	Limited clinical validation
Implant coatings	Preclinical (rabbit, dog); case reports	Greater BIC (70-85% vs. 50-65% for SLA) at 4 weeks	Coating delamination concerns; limited clinical data
Orthodontics (WSL prevention)	*In vitro*	Ion release sufficient for local supersaturation	No clinical data yet

RCT, randomized controlled trial; PD, probing depth; CAL, clinical attachment level; OFD, open flap debridement; PRF, platelet-rich fibrin; GTR, guided tissue regeneration; CHA, carbonated hydroxyapatite; BIC, bone-to-implant contact; SLA, sand-blasted acid-etched; WSL, white spot lesion.

realistically challenge mineral trioxide aggregate or biodentine as a clinical standard of care.

Root-end filling and apico-exeresis. Several *in vitro* and *ex vivo* investigations have explored 45S5-based materials as root-end filling agents, taking advantage of their ability to form a CHA seal at the dentinal interface. Early findings suggest that 45S5 mixed with an appropriate vehicle may achieve marginal adaptation at the dentinal walls comparable to established root-end filling materials. The biocompatibility of the material with periapical tissues and its ability to promote cementogenesis render it theoretically attractive, although *in vivo* data from periapical surgery remain limited (4,5,15,31).

Root canal sealers. Novel 45S5-based endodontic sealers, typically incorporating 45S5 powder within a resin or calcium silicate matrix, have been evaluated for sealing ability, biocompatibility and apatite-forming potential. Trope *et al* (31) and subsequent investigators reported that 45S5-enriched sealers exhibit significantly lower cytotoxicity than epoxy resin-based sealers (AH Plus) in fibroblast cultures, and superior biocompatibility in subcutaneous implantation animal models. Their capacity to form CHA at the sealer-dentine interface may contribute to long-term marginal sealing and periapical healing (16-20).

Dentin hypersensitivity (DH). DH affects 10-30% of adults and is characterized by a short, sharp pain response to thermal, evaporative, osmotic or tactile stimuli. According to the hydrodynamic theory, stimuli induce fluid movement within exposed dentinal tubules, activating pulpal nociceptors. Tubule occlusion therefore constitutes a primary therapeutic strategy (32-35).

Bioglass 45S5 entered desensitizing toothpastes following the seminal research by Greenspan *et al* (32) in the 1990s, who demonstrated that 45S5 particles mechanically and chemically occlude dentinal tubules through rapid deposition of a CHA plug. This mechanism differs from that of potassium nitrate (nerve depolarization) or strontium chloride (tubule occlusion via strontium apatite), and has been shown to be more durable in simulated oral abrasion challenges.

Clinical trials evaluating Sensodyne® Repair & Protect (GlaxoSmithKline), which contains NovaMin®, a commercialized 45S5 formulation, have demonstrated significant reductions in DH scores (Schiff sensitivity scale and visual analogue scale) compared to placebo toothpastes at 4, 8 and 12 weeks (33). An overview of the evidence by Gendreau *et al* (34) published in the Journal of Clinical Dentistry concluded that NovaMin-containing toothpaste was effective in reducing DH, although comparisons with other active agents (stannous fluoride, potassium oxalate) remained inconclusive owing to heterogeneity.

The addition of fluoride to 45S5 formulations, producing fluorapatite rather than hydroxyapatite in the tubular plug, has been shown to enhance acid resistance and provide additional caries-protective benefits, opening avenues for combined desensitizing and anti-caries products (35).

Prevention of caries and remineralization. The capacity of 45S5 to release calcium, phosphate and silicate ions in supersaturating concentrations provides a physico-chemical basis

for anti-caries activity. *In vitro* pH-cycling models simulating cariogenic challenge have demonstrated that 45S5-containing dentifrices significantly reduce enamel mineral loss and promote subsurface lesion remineralization compared to conventional sodium fluoride toothpastes (36).

Confocal Raman spectroscopy and transverse microradiography analyses performed in the study by Mneimne *et al* (35) demonstrated that 45S5 combined with fluoride produces fluorohydroxyapatite deposits within artificial carious lesions, with mineral recovery reaching 73% of the original mineral content after 20 pH cycles. These findings have stimulated interest in 45S5 as an active ingredient in professionally applied demineralizing varnishes and as a component of glass ionomer cements, where its incorporation accelerates early fluoride release and improves bioactivity.

Recent studies have explored nano-45S5 incorporated into resin composites to create intrinsically demineralizing restorative materials capable of counteracting secondary caries, a leading cause of restoration failure. Odermatt *et al* (37) demonstrated that nano-45S5-containing composites maintain CHA-forming ability in pH-cycling models without the significant compromise of mechanical properties.

Dental implantology and osseointegration

Surface coatings on titanium implants. Although Bioglass 45S5 is unsuitable as a bulk implant material in dentistry due to its insufficient fracture toughness, it has found widespread use as a surface coating on titanium or titanium alloy implants. Techniques including enameling, sol-gel deposition, electrophoretic deposition and magnetron sputtering have been used to deposit thin (2-50 μm) 45S5 films on implant surfaces (38).

These coatings accelerate early bone apposition at the implant surface. In rabbit and dog models, 45S5-coated implants have exhibited significantly greater bone-to-implant contact values, typically 70-85% vs. 50-65% for sand-blasted, acid-etched controls, at 4 weeks of healing (39). The mechanism involves the preferential adsorption of fibronectin and vitronectin onto the CHA-forming surface, facilitating integrin-mediated osteoblast attachment and early matrix mineralization.

Clinical evidence. The clinical literature on 45S5-coated dental implants remains limited relative to the abundant preclinical data. Early clinical reports have suggested favorable survival rates for BG-coated cylindrical implants, with peri-implant bone loss comparable to that reported for conventional titanium implants of the era. However, concerns over coating delamination under functional loading and difficulties in controlling film thickness uniformly across complex implant geometries have curtailed the commercial adoption of 45S5 coatings in mainstream implantology.

Orthodontics and preventive applications. Beyond its regenerative and restorative roles, 45S5 has been investigated in orthodontic contexts, particularly for the prevention of white spot lesions, a common iatrogenic complication of fixed appliance therapy. Experimental bonding agents and bracket adhesives incorporating 45S5 particles or NovaMin® exhibit ion-releasing profiles sufficient to maintain local supersaturation and inhibit subsurface enamel demineralization in pH-cycling models.

In vitro evidence also supports the use of 45S5 in dental sealant formulations for occlusal caries prevention in children, although clinical data are not yet available. The biocompatibility, low cytotoxicity and self-setting ion-releasing properties of the material render it a compelling candidate for preventive dental materials research.

5. Advanced formulations and modifications

Sol-gel synthesis and mesoporous bioglass. Melt-derived Bioglass 45S5 is constrained in terms of porosity, specific surface area and formulation flexibility. Sol-gel synthesis, introduced by Li *et al* (40) in 1991, circumvents these limitations by enabling production of glass particles with controlled mesoporosity (2-50 nm pore diameter) and surface areas exceeding 200 m^2/g, >30-fold higher than those of melt-derived 45S5. Mesoporous BG (MBG) of 45S5 composition exhibits accelerated ion-release kinetics, depositing CHA within hours rather than days in simulated body fluid, and has been explored as a drug delivery carrier for antibiotics, growth factors, and anti-inflammatory agents, thereby enabling combination therapy in infected bone defects (41). The recent comparative study by Pacheco-Vergara *et al* (42) demonstrated that 3D-printed MBG, BG 45S5 and β-tricalcium phosphate scaffolds all support osteogenic differentiation *in vitro*, with MBG exhibiting the most rapid mineral deposition kinetics.

Ion-doped 45S5 variants. The therapeutic profile of 45S5 can be modulated by the partial substitution of network-forming or modifying ions with biologically active elements. Strontium-substituted 45S5 (Sr-45S5), in which strontium replaces calcium, enhances osteoblastic differentiation and inhibits osteoclastogenesis via the calcium-sensing receptor pathway, offering potential benefits for osteopenic bone regeneration (43). Geng *et al* (44) demonstrated that the careful optimization of the strontium content on titanium surfaces balances apatite-forming ability with osteogenic activity, achieving ideal osseointegration conditions *in vivo* (44). Silver-doped 45S5 exhibits broad-spectrum antibacterial activity against Gram-positive and Gram-negative pathogens, including methicillin-resistant *Staphylococcus aureus*, without significant cytotoxicity at therapeutic concentrations (45).

Zinc-containing 45S5 formulations have been investigated for their dual osteogenic and anti-infective properties, while fluoride-doped variants (fluorobioglass) produce fluorapatite, more resistant to acid dissolution than hydroxyapatite, at the bioactive interface, potentially offering enhanced caries protection (46,47). Magnesium substitution has been shown to delay *in vitro* dissolution rates, allowing the finer control of the biodegradation profile for load-bearing scaffold applications.

Composite and polymer-matrix formulations. To overcome the brittleness of monolithic 45S5, composite materials incorporating 45S5 particles within biodegradable polymer matrices, including polylactic acid, polyglycolic acid, polycaprolactone and natural polymers, such as chitosan, collagen and silk fibroin, have been extensively studied (48). These composites exhibit compressive strengths of 100-250 MPa with fracture toughnesses approaching 2-3 MPa·m½ while retaining the ion-releasing bioactivity of the glass phase.

3D printing techniques, including fused deposition modelling and stereolithography, have been applied to produce patient-specific 45S5/polymer scaffolds for complex alveolar bone defect reconstruction (49). Notably, McWilliam *et al* recently described a novel biofabrication method combining nanosecond laser micromachining with electrospun nanofiber meshes, enabling the creation of intricately designed scaffolds at anatomically relevant dimensions that could be adapted to craniofacial and dentoalveolar applications (50).

6. Current limitations and challenges

Despite its well-established bioactivity, several limitations constrain the widespread clinical adoption of Bioglass 45S5 in dentistry. The fracture toughness of melt-derived 45S5 (~0.7 MPa·m½) is substantially inferior to cortical bone, precluding use in load-bearing sites without composite reinforcement. Even in non-load-bearing periodontal applications, particle migration and inadequate cohesion can complicate surgical handling.

The dissolution rate of 45S5 is relatively rapid and pH-dependent, potentially releasing ions at concentrations that are cytotoxic at high doses. Ensuring controlled and predictable resorption rates in the oral microenvironment, characterized by fluctuating pH, bacterial load, and mechanical forces, remains technically challenging.

The periodontal literature, though encouraging, is characterized by small sample sizes, short follow-up periods (typically ≤12 months), heterogeneous outcome measures and moderate risk of bias. Robust long-term randomized clinical trial data with patient-centered outcomes are lacking for most dental application domains.

The variability in particle size distribution, purity, and surface characteristics among commercially available 45S5 products complicates direct comparisons between studies and raises concerns about reproducibility of clinical outcomes. Standardized characterization protocols, analogous to ISO 13485 for medical devices, are warranted.

7. Future perspectives

The future of Bioglass 45S5 in dentistry is likely to be shaped by several converging developments. Additive manufacturing (3D printing) of personalized 45S5-polymer scaffolds tailored to individual anatomical defects is advancing rapidly from proof-of-concept to clinical feasibility, with early case series reporting successful integration in mandibular defect reconstruction (49,50). In parallel, the integration of 3D bioprinting with organoid culture technology holds potential for constructing more physiologically faithful tissue models that better replicate the complex cell-matrix interactions of oral tissues; recent advances in this domain may inform future scaffold design strategies for dental regeneration (51). The integration of growth factors, including recombinant human BMP-2, platelet-derived growth factor-BB and enamel matrix derivative, into 45S5 mesoporous carriers may enable combinatorial regenerative strategies with synergistic effects that surpass those of individual agents (52).

Nano-scale 45S5 formulations are opening new frontiers in preventive and restorative dentistry. Nano-45S5-containing composites, adhesives and glass ionomers that actively remineralize the tooth-restoration interface may fundamentally alter secondary caries management and improve restoration longevity. Similarly, smart delivery systems exploiting the pH-responsive dissolution of 45S5, releasing therapeutic ions selectively in response to acidic cariogenic challenge, represent a promising direction for autonomous preventive materials (53).

In regenerative endodontics, 45S5-based scaffolds supporting dental pulp stem cell (DPSC) homing, proliferation and differentiation may enable biological pulp regeneration in immature teeth with necrotic pulps, providing an alternative to apexification procedures. Since the isolation and characterization of postnatal human DPSCs (54), preliminary studies have shown that these cells cultured on BG scaffolds undergo odontogenic differentiation and form mineralized matrices both *in vitro* and *in vivo*.

Finally, the integration of antibacterial ion-doped 45S5 formulations into implant surfaces and regenerative membranes may address the unmet clinical need for infection-resistant biomaterials in peri-implantitis and post-surgical infection management, representing one of the most impactful near-term translational opportunities.

8. Conclusions

Bioglass 45S5, since its inception over five decades ago, has established itself as one of the most versatile and biologically active materials available to the dental clinician. Its unique capacity to form a direct chemical bond with both osseous and soft connective tissues, mediated by rapid surface ion exchange and CHA formation, underpins its utility across an exceptionally broad spectrum of dental applications, from periodontal regeneration and bone augmentation to endodontics, DH management, caries prevention and implantology.

The existing evidence, while encouraging, reflects a literature characterized by heterogeneity and a predominance of short-term, small-scale studies. Translating the robust preclinical data into large, well-designed randomized clinical trials with standardized outcomes and extended follow-up periods should be a research priority. Equally important is the development of internationally recognized characterization standards for 45S5-based products to ensure comparability across studies and product categories.

Advances in sol-gel synthesis, ion doping, nanoscale engineering and additive manufacturing are steadily expanding the functional repertoire of 45S5, positioning it not merely as a legacy biomaterial, but as a dynamic platform for next-generation dental therapeutics. The convergence of material science innovation, molecular biology and clinical dental research holds the promise of realizing the full regenerative potential of Bioglass 45S5 for the benefit of dental patients worldwide.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

LF and FGo were involved in the conceptualization of the study, in the writing of the original draft of the manuscript, in project administration, and study supervision. FGa was involved in the writing, reviewing and editing of the manuscript and in data curation (extracting, organizing, cleaning, and synthesizing data from selected studies). JFF, CG and CDA were involved in visualization, and in the writing, reviewing and editing of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Hench LL, Splinter RJ, Allen WC and Greenlee TK: Bonding mechanisms at the interface of ceramic prosthetic materials. J Biomed Mater Res 5: 117-141, 1971.
2. Hench LL: Bioceramics: From concept to clinic. J Am Ceram Soc 74: 1487-1510, 1991.
3. Hench LL: The story of Bioglass. J Mater Sci Mater Med 17: 967-978, 2006.
4. Hench LL and Polak JM: Third-generation biomedical materials. Science 295: 1014-1017, 2002.
5. Jones JR: Review of bioactive glass: From Hench to hybrids. Acta Biomater 9: 4457-4486, 2013.
6. Wilson J and Low SB: Bioactive ceramics for periodontal treatment: Comparative studies in the Patus monkey. J Appl Biomater 3: 123-129, 1992.
7. Rahaman MN, Day DE, Bal BS, Fu Q, Jung SB, Bonewald LF and Tomsia AP: Bioactive glass in tissue engineering. Acta Biomater 7: 2355-2373, 2011.
8. Vallet-Regí M, Ragel CV and Salinas AJ: Glasses with medical applications. Eur J Inorg Chem 2003: 1029-1042, 2023. doi:10.1002/ejic.200390134.
9. Hill R: An alternative view of the degradation of bioglass. J Mater Sci Lett 15: 1122-1125, 1996.
10. Pedone A, Charpentier T, Malavasi G and Menziani MC: New insights into the atomic structure of 45S5 Bioglass by means of solid-state NMR spectroscopy and accurate first-principles simulations. Chem Mater 22: 5644-5652, 2010. doi:10.1021/cm102089c.
11. Clupper DC and Hench LL: Crystallization kinetics of tape cast bioactive glass 45S5. J Non-Cryst Solids 318: 43-48, 2003.
12. Kokubo T, Kim HM and Kawashita M: Novel bioactive materials with different mechanical properties. Biomaterials 24: 2161-2175, 2003.
13. Sepulveda P, Jones JR and Hench LL: Characterization of melt-derived 45S5 and sol-gel-derived 58S bioactive glasses. J Biomed Mater Res 58: 734-740, 2001.
14. Hench LL and Thompson I: Twenty-first century challenges for biomaterials. J R Soc Interface 7 (Suppl 4): S379-S391, 2010.
15. Kokubo T and Takadama H: How useful is SBF in predicting in vivo bone bioactivity? Biomaterials 27: 2907-2915, 2006.
16. Xynos ID, Edgar AJ, Buttery LD, Hench LL and Polak JM: Gene-expression profiling of human osteoblasts following treatment with the ionic products of Bioglass 45S5 dissolution. J Biomed Mater Res 55: 151-157, 2001.
17. Xynos ID, Hukkanen MV, Batten JJ, Buttery LD, Hench LL and Polak JM: Bioglass 45S5 stimulates osteoblast turnover and enhances bone formation in vitro: Implications and applications for bone tissue engineering. Calcif Tissue Int 67: 321-329, 2000.
18. Boccaccini AR, Erol M, Stark WJ, Mohn D, Hong Z and Mano JF: Polymer/bioactive glass nanocomposites for biomedical applications: A review. Compos Sci Technol 70: 1764-1776, 2010.
19. Waltimo T, Brunner TJ, Vollenweider M, Stark WJ and Zehnder M: Antimicrobial effect of nanometric bioactive glass 45S5. J Dent Res 86: 754-757, 2007.
20. Zehnder M, Waltimo T, Sener B and Söderling E: Dentin enhances the effectiveness of bioactive glass S53P4 against a strain of Enterococcus faecalis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 101: 530-535, 2006.
21. Low SB, King CJ and Krieger J: An evaluation of bioactive ceramic in the treatment of periodontal osseous defects. Int J Periodontics Restorative Dent 17: 358-367, 1997.
22. Park JS, Suh JJ, Choi SH, Moon IS, Cho KS, Kim CK and Chai JK: Effects of pretreatment clinical parameters on bioactive glass implantation in intrabony periodontal defects. J Periodontol 72: 730-740, 2001.
23. Varanasi VG, Owyoung JB, Saiz E, Marshall SJ, Marshall GW and Loomer PM: 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 98A: 177-184, 2011.
24. Froum SJ, Weinberg MA and Tarnow D: Comparison of bioactive glass synthetic bone graft particles and open debridement in the treatment of human periodontal defects. A clinical study. J Periodontol 69: 698-709, 1998.
25. Mengel R, Schreiber D and Flores-de-Jacoby L: Bioabsorbable membrane and bioactive glass in the treatment of intrabony defects in patients with generalized aggressive periodontitis: Results of a 5-year clinical and radiological study. J Periodontol 77: 1781-1787, 2006.
26. Sculean A, Nikolidakis D and Schwarz F: Regeneration of periodontal tissues: Combinations of barrier membranes and grafting materials-biological foundation and preclinical evidence: A systematic review. J Clin Periodontol 35 (8 Suppl): 106-116, 2008.
27. Bodhare GH, Kolte AP, Kolte RA and Shirke PY: Clinical and radiographic evaluation and comparison of bioactive bone alloplast morsels when used alone and in combination with platelet-rich fibrin in the treatment of periodontal intrabony defects: A randomized controlled trial. J Periodontol 90: 584-594, 2019.
28. Guarnieri R, Pecora G, Fini M, Aldini NN, Giardino R, Orsini G and Piattelli A: Medical grade calcium sulfate hemihydrate in healing of human extraction sockets: Clinical and histological observations at 3 months. J Periodontol 75: 902-908, 2004.
29. About I, Laurent-Maquin D, Lendahl U and Mitsiadis TA: Nestin expression in embryonic and adult human teeth under normal and pathological conditions. Am J Pathol 157: 287-295, 2000.
30. Hasheminia SM, Feizi G, Razavi SM, Feizianfard M, Gutknecht N and Mir M: A comparative study of three treatment methods of direct pulp capping in canine teeth of cats: A histologic evaluation. Lasers Med Sci 25: 9-15, 2010.
31. Trope M, Lost C, Schmitz HJ and Friedman S: Healing of apical periodontitis in dogs after apicoectomy and retrofilling with various filling materials. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 81: 221-228, 1996.
32. Greenspan DC: NovaMin and tooth sensitivity: an overview. J Clin Dent 21: 61-65, 2010.
33. Burwell AK, Litkowski LJ and Greenspan DC: Calcium sodium phosphosilicate (NovaMin): Remineralization potential. Adv Dent Res 21: 35-39, 2009.
34. Gendreau L, Barlow AP and Mason SC: Overview of the clinical evidence for the use of NovaMin in providing relief from the pain of dentin hypersensitivity. J Clin Dent 22: 90-95, 2011.
35. Mneimne M, Hill RG, Bushby AJ and Brauer DS: High phosphate content significantly increases apatite formation of fluoride-containing bioactive glasses. Acta Biomater 7: 1827-1834, 2011.
36. Earl JS, Leary RK, Muller KH, Langford RM and Greenspan DC: Physical and chemical characterization of dentin surface following treatment with NovaMin technology. J Clin Dent 22: 62-67, 2011.

37. Odermatt R, Par M, Mohn D, Wiedemeier DB, Attin T and Tauböck TT: Bioactivity and physico-chemical properties of dental composites functionalized with nano- vs. micro-sized bioactive glass. J Clin Med 9: 772, 2020. doi:10.3390/jcm9030772.
38. Gomez-Vega JM, Saiz E, Tomsia AP, Marshall GW and Marshall SJ: Bioactive glass coatings with hydroxyapatite and Bioglass particles on Ti-based implants. 1. Processing. Biomaterials 21: 105-111, 2000.
39. Vanzillotta PS, Sader MS, Bastos IN and Soares Gde A: Improvement of in vitro titanium bioactivity by three different surface treatments. Dent Mater 22: 275-282, 2006.
40. Li R, Clark AE and Hench LL: An investigation of bioactive glass powders by sol-gel processing. J Appl Biomater 2: 231-239, 1991.
41. Vallet-Regí M, Ruiz-González L, Izquierdo-Barba I and González-Calbet JM: Revisiting silica based ordered mesoporous materials: Medical applications. J Mater Chem 16: 26-31, 2006.
42. Pacheco-Vergara MJ, Ricci JL, Mijares D, Bromage TG, Rabieh S, Coelho PG and Witek L: 3D printed mesoporous bioactive glass, bioglass 45S5, and β-TCP scaffolds for regenerative medicine: A comparative in vitro study. Biomed Mater Eng 34: 439-458, 2023.
43. Gentleman E, Fredholm YC, Jell G, Lotfibakhshaiesh N, O'Donnell MD, Hill RG and Stevens MM: The effects of strontium-substituted bioactive glasses on osteoblasts and osteoclasts in vitro. Biomaterials 31: 3949-3956, 2010.
44. Geng Z, Sang S, Wang S, Meng F, Li Z, Zhu S, Cui Z, Jing Y, Wang C and Su J: Optimizing the strontium content to achieve an ideal osseointegration through balancing apatite-forming ability and osteogenic activity. Biomater Adv 133: 112647, 2022.
45. Mulligan AM, Wilson M and Knowles JC: Effect of increasing silver content in phosphate-based glasses on biofilms of Streptococcus sanguis. J Biomed Mater Res A 67: 401-412, 2003.
46. Boyd D, Carroll G, Towler MR, Freeman C, Farthing P and Brook IM: Preliminary investigation of novel bone graft substitutes based on strontium-calcium-zinc-silicate glasses. J Mater Sci Mater Med 20: 413-420, 2009.
47. Brauer DS, Mneimne M and Hill RG: Fluoride-containing bioactive glasses: Fluoride loss during melting and ion release in tris buffer solution. J Non-Cryst Solids 357: 3328-3333, 2011.
48. Boccaccini AR and Blaker JJ: Bioactive composite materials for tissue engineering scaffolds. Expert Rev Med Devices 2: 303-317, 2005.
49. Brunello G, Sivolella S, Meneghello R, Ferroni L, Gardin C, Piattelli A, Zavan B and Bressan E: Powder-based 3D printing for bone tissue engineering. Biotechnol Adv 34: 740-753, 2016.
50. McWilliam RH, Chang W, Liu Z, Wang J, Han F, Black RA, Wu J, Luo X, Li B and Shu W: Three-dimensional biofabrication of nanosecond laser micromachined nanofibre meshes for tissue engineered scaffolds. Biomater Transl 4: 104-114, 2023.
51. Ma W, Lu H, Xiao Y and Wu C: Advancing organoid development with 3D bioprinting. Organoid Res 1: 025040004, 2025.
52. Quinlan E, Thompson EM, Matsiko A, O'Brien FJ and López-Noriega A: Long-term controlled delivery of rhBMP-2 from collagen-hydroxyapatite scaffolds for superior bone tissue regeneration. J Control Release 207: 112-119, 2015.
53. Chatzistavrou X, Fenno JC, Faulk D, Badylak S, Kasuga T, Boccaccini AR and Papagerakis P: Fabrication and characterization of bioactive and antibacterial composites for dental applications. Acta Biomater 10: 3723-3732, 2014.
54. Gronthos S, Mankani M, Brahim J, Robey PG and Shi S: Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci USA 97: 13625-13630, 2000.