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Review

Bioactive-glass in periodontal surgery and implant dentistry

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Bioactive-glass (B-G) is a material known for its favorable biological response when in contact with surrounding fibro-osseous tissues, due not only to an osteoconductive property, but also to an osteostimulatory capacity, and superior biocompatibility for use in human body. The objectives of this paper are to review recent studies on B-G in periodontal and implant therapy, describing its basic properties and mechanism of activity as well as discoursing about state of art and future perspective of utilization. From a demonstrated clinical benefit as bone graft for the elimination of osseous defects due to periodontal disease (intrabony/furcation defects) and surgeries (alveolar ridge preservation, maxillary sinus augmentation), to a potential use for manufacturing bioactive dental implants, possibly allowing wider case selection criteria together with improved integration rates even in the more challenging osteoporotic and medically compromised patients, this biomaterial represents an important field of study with high academic, clinical and industrial importance.

Keywords: Bioactive-glass, Periodontal and implant therapy, Bonelike coating

INTRODUCTION

Over the last decade or so, several kinds of biomaterials/biological agents have been employed in the treatment of deep intraosseous defects[1]. Among these grafting materials, a restricted group of surface reactive glass-ceramics (calcium sodium phosphosilicates), including the original bioactive-glass (B-G) developed by Hench and co-workers in the late 1960s[2], have attracted more and more attentions for their application in periodontal and implant therapy[3,4]. B-G has numerous features, most important of which are a proven history of biocompatibility and the capacity to act rapidly as biomimetic mineralizer, matching the human skeleton's own mineralizing traits[2]. A compendium of data by Wilson *et al.*[5] was the first to document the safety of use of B-G and long-term studies confirmed that it is well tolerated in children[6] and adults[7]. The chemical composition is significant. The constituents are minerals that occur naturally in the body {silica [SiO_2 (46.1 wt%)], sodium oxide [Na_2O (24.4 wt%)], calcium oxide [CaO (26.9 wt%)], and phosphorus pentoxide [P_2O_5 (2.6 wt%)]}, and the molecular proportions of the calcium and phosphorous oxides are similar to those in the bones[2]. It seems that there are two key composition features of B-G:

I. A high CaO/P_2O_5 ratio, which makes B-G distinctly reactive. This favourable ratio of calcium to phosphorus has been shown to enable the release of ionic species from the bulk material upon contact with physiological fluids, culminating with the formation of a surface layer of hydroxycarbonate apatite (HCA) in a short time[2]. Remarkably, critical concentrations of biologically active ions become available exactly at the rate and location where they are needed for cell proliferation and differentiation, which entails negligible or absent side effects[2,8]. Molecular biology studies showed that bioactive shift of osteoblast cell cycle is under genetic control[2]. B-G on dissolving activates genes that modulate osteogenesis, to stimulate bone's own regenerative capabilities, without occurrence of fibrous tissue encapsulation, often encountered with other synthetic materials, neither causing inflammation nor toxicity[2,8]. On the contrary, antimicrobial properties are exhibited due to the creation of a local alkaline environment and the resistance of the material to bacterial adhesion and biofilm formation[9]. It has been shown that B-G significantly reduce cell counts of bacteria involved in implant-related infections such as *Staphylococcus aureus* or *Staphylococcus epidermidis*, but also bacteria known for their role in caries (*Streptococcus mutans*)[9] or in periodontal disease (*Porphyromonas gingivalis*)[10].
II. A content of around 60 mol% of silica. There is evidence that silica content plays an important role in making the glass easy to melt, but also contributes to form HCA, which eventually leads to direct chemical attachment to both soft and hard tissues, causing a strong interface between these and glass particulates[2]. As a result, the interfacial bonding strength is equivalent to or greater than that of bone. Unlike the case with non bioactive alloplasts, failure under

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mechanical stress does not occur at the interface but rather occurs in the host bone or within the biomaterial[2].

A large and ever-increasing body of literature has become available to support the application of B-G in a variety of clinical applications, including alveolar ridge preservation, maxillary sinus augmentation, and treatment of various intrabony and furcation defects. An excellent review and meta-analysis was recently presented by Sohrabi *et al.*[3] on the efficacy and effectiveness of B-G compounds in regenerative periodontal therapy. With information sources collated from original scientific papers, the aim of the present study was to reappraise the most recent developments in this field, which included the novel use of B-G as surface coating for implants over alternate forms of synthetic materials to achieve improvements in resistance to corrosion, protection against metal ion release, biocompatibility, and, ultimately, a better environment as well as structure for rapid and strong biological attachment to bone. The available evidence from clinical trials, case reports and experiments in model systems (*in vivo* and *in vitro*) was investigated. Extensive literature searches of MEDLINE (PUBMED), WEB OF SCIENCE, SCOPUS, SCIELO and COCHRANE electronic databases were performed by using free text and MeSH terms, from 1971 (year of B-G being introduced[2]) up to, and including, 10th January 2015. Only English language articles were considered; the title and abstract of relevant publications were read, and after this first screening eligible studies were selected and their full-texts downloaded. Additional search of reference lists within identified articles and antecedent systematic reviews were included in an attempt to reveal additional studies. The key features of relevant investigations were evaluated and the conclusions summarized in a narrative review.

AN OVERVIEW OF THE FUNDAMENTAL SCIENCE

Materials properties of B-G, mechanism of activity and biological responses

A key to regenerative repair of bone is to: I) control the population of cells that are capable of entering into active phases of the cell cycle; II) complete the mitosis of cells with accurate replication of genes (cell proliferation); and III) achieve cellular differentiation into a phenotype capable of synthesizing a full complement of extracellular proteins that constitute a mature osteocyte[11-13]. B-G research deals in large part with developing a fundamental understanding of its dissolution and surface reactions, along with the tissue response to the dissolving material. 3D architecture of mineralized bone is created by osteoblasts that are exposed to critical concentrations of the soluble ionic constituents released from B-G. Approximately 17 to 20 ppm of soluble Si and 88 to 100 ppm of soluble Ca ions are required[2]. The mechanism of activity upon implantation of B-G has been discussed extensively in the literature[2,8] and will only be summarized in the current study. Figure 1 recapitulates the cascade of reactions occurring at the surface of B-G during the formation of a solid grip with bone. This process involves five initial stages that occur rapidly on the surface of B-G particles: initial ion exchange of alkali ions with hydrogen ions from the liquid medium, which increases the pH-value at the

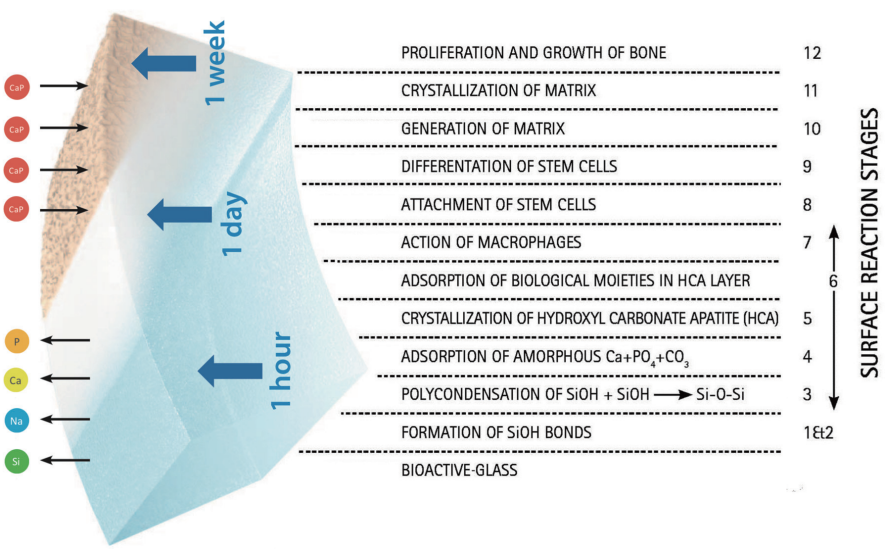

Fig. 1 Sequence of interfacial reactions involved in forming a bond between B-G and bone. The first 5 stages take place at the periphery of B-G and include release of alkali ions (bacterial growth is inhibited as a result of pH increase) along with the formation of crystallized HCA. Hence, the implanted material fastens down with the tissue from step 6 to 11 in consequence of osteostimulation and bone growth.

biomaterial-bone interface to values >7.4 (stage 1); glass network dissolution (stage 2); silica-gel polymerisation (stage 3); and finally formation of an over-saturated solution that exceeds the solubility product constants for a number of mineral forms, inducing crystal growth of HCA (stages 4 and 5). Such a phase is chemically and structurally similar to the mineral phase of human bone, allowing accelerated interface strength acquisition. The exact character of the bonds with the host tissue is not known, though it has been suggested that collagen of type I, mucopolysaccharides, and glycoproteins from surrounding bone are incorporated into the newly formed HCA layer[2]. Of note, the first three stages occur in parallel and culminate in the release of silicic acid, which condenses to form a negatively charged gel at the surface of the particles. This gel serves to hold the glass particles in a cohesive mass and resembles HCA matrix so much to induce osteoblast differentiation[2]. Genetic control over the osteoblast cell cycle is also exerted by the dissolution products from B-G, which actively increase the secretion of osteoid matrix directly on the granules' surface[14]. The families of genes that are unregulated and/or activated are related to the relevant segments of the cell cycle, cell proliferation and cell differentiation. Controlled rates of glass dissolution provide the critical concentration of biologically active ions to the cells *via* the interfacial solution. It has been shown that new tissue is remodelled at a rate equal to that at which the glass dissolves: the longer is the dissolution, the better will be the deposition of bone tissue and growth[15]. References[11-13] summarize the sequence of biological events that comprise a cell cycle for a single osteoblast progenitor (adult stem) and its differentiation into mature osteocytes. These represent the cellular population responsible for extracellular matrix production and mineralization, the final step in bone development. Therefore, it is important to observe that the end result of the cell cycle activated by the ionic products of B-G dissolution is the upregulation of numerous genes that express growth factors and cytokines and extracellular matrix components. Details of the feedback controls and cell cycle checkpoints are reviewed in refs[2,8,11-13]. The gene activation, bone regenerative capability, and high level of bioactivity are unique only to B-G when compared to synthetic hydroxyapatite (SHA) and any other allograft, which more than justifies its use. The biological effect level of any material is measured by Bioactivity Index (I_B), namely the time taken for more than half of the interface to bond. Any material with the value of I_B greater than 8, like B-G, will bond to both soft and hard tissues. Materials such as synthetic SHA with I_B value <8 but >0 will bind only to hard tissue[16]. Interestingly, B-G can be moulded into any desired shape and is available in multiple forms: pellets, mesh, cones, particulate, and powder. B-G particles range in size from 90 to 710 μm. Resorption of particles of 150 μm or less occurs as silicic acid is released. Larger particles are incorporated in the growing bone matrix and are eventually broken down by osteoclasts[17].

CLINICAL APPLICATIONS

Alveolar ridge preservation and/or pre-prosthetic reconstruction procedures

Alveolar and basal bones of maxilla and mandible, along with upper and lower teeth, are extremely complex organs, showing a combination of hard tissues (trabecular and cortical bone, or enamel, dentine and cementum) as well as soft tissues (bone marrow, or dental pulp and periodontium) in unique hierarchical structures. Bone reconstructive surgical interventions are commonly employed when the physiological remodeling/recovering mechanisms fail to heal osseous defects caused by trauma, congenital disorder or disease. These treatments have encompassed the utilization of a series of bone grafts and other osteopromotive materials. Surveys such as that conducted by Janicki and Schmidmaier[18] showed that an ideal bone replacement material should have the following properties:

I. It should be available at any time and in any amount.
II. It should be easy to handle.
III. There should be no donor site morbidity.
IV. It should not cause a foreign-body reaction or be toxic.
V. Any transmission of infectious diseases must be excluded.
VI. The material should not have any effect at follow-up examinations.
VII. The bone substitute should be economical, namely, it should entail no additional cost or prolong the operation time.

Autogenous bone grafts, a rich source of osteoblasts and marrow cells, are considered as the golden standard in terms of osteogenic properties[19], but even this option presents some disadvantages, such as limited availability for large bone defects together with additional surgery, which prolongs operation time, convalescence and donor site morbidity[20]. Also, their resorption may be unpredictable[21] and the bone tissue from the same individual may be contaminated by microorganisms when harvested in the oral cavity[22]. When not enough autogenous bone is available, this is combined with particles or granules (granules are large particles) of a bone graft extender material[23]. Surgeons also tend to mix particles with blood from the patient to create a putty-like material, which is pressed easily into the osseous defect. The blood improves handling of the material and the hope is that the natural growth factors and cells that it contains will help bone repair. The procedure is often attempted with calcium phosphate particles. Unfortunately these ceramic materials act as fillers, and any new bone formation takes place only along their surface[24]. Dense and porous SHA and tricalcium-phosphate particulates have been used as such reconstructive materials. But even their use is limited to providing a scaffold for enhanced bone repair and growth[25]. Another particulate material frequently used to restore osseous defects is Bio-Oss, reportedly a resorbable anorganic bovine SHA. However, recent

research has shown the material to be unpredictable in its amount of bone formation and not to be totally resorbable[1].

As described in the previous section, B-Gs are effective in eliciting specific cellular responses. Other distinctive qualities are the ability to remain where placed even with adjacent suctioning, and hemostasis during incorporation into the host bone[26]. On this account, they are widely used in hard-tissue engineering, as sole material or inorganic phase in composite and hybrid compositions[27]. Besides an use in three-dimensional (3-D) temporary scaffolds, the possibility of employing these biomaterials to fill and repair dentoalveolar defects in a rapid and controllable way has been thoroughly investigated by oral and maxillofacial surgeons as well as dentists[17]. Since its introduction, the original B-G has been released as PerioGlas® (now sold by NovaBone Products LLC, Alachua, FL, USA) for periodontal regeneration, and NovaBone® (NovaBone Products LLC) or Biogran® (BIOMET 3i, Palm Beach Gardens, FL, USA) used in oral and maxillofacial surgery. Other commercial products based on melt-derived calcium sodium phosphosilicates, BonAlive® (BonAlive Biomaterials, Turku, Finland) and StronBoneTM (RepRegen Ltd, UK), are also available for bone reconstructive surgery[17]. One of the first commercial applications of B-Gs in dentistry was to prevent the resorption of alveolar bone after tooth removal and to maintain or enhance bony ridge form for subsequent restorative treatments with implant-supported prostheses (Fig. 2)[28]. Root cones of B-G, placed in fresh residual extraction cavities as well as into artificial sockets produced by bone splitting of previous extraction sites, were able to recreate original alveolar ridge dimensions prior to dental implant surgery[29]. In the re-entry procedure 12 months after insertion, bone formation was clearly visible providing evidence of the superiority of this material compared to other bone

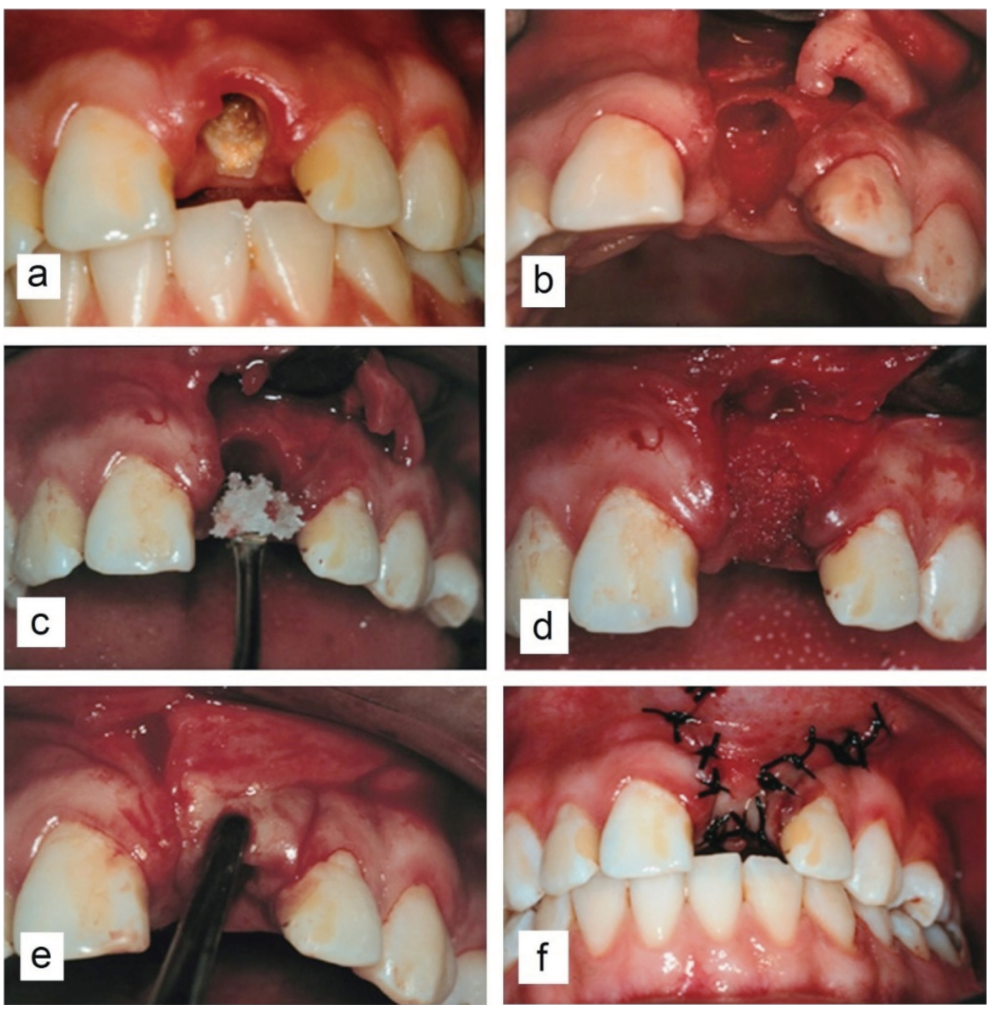

Fig. 2 Clinical application of B-G to reconstruct the framework of the alveolar process[28].
a: Tooth to be extracted. b: Empty alveolar socket. c: B-G inserted into the alveolar socket. d: Alveolar socket filled with B-G. e, f: The edges of the soft tissue loosened to completely close the bone defect (left) and sutured (right).

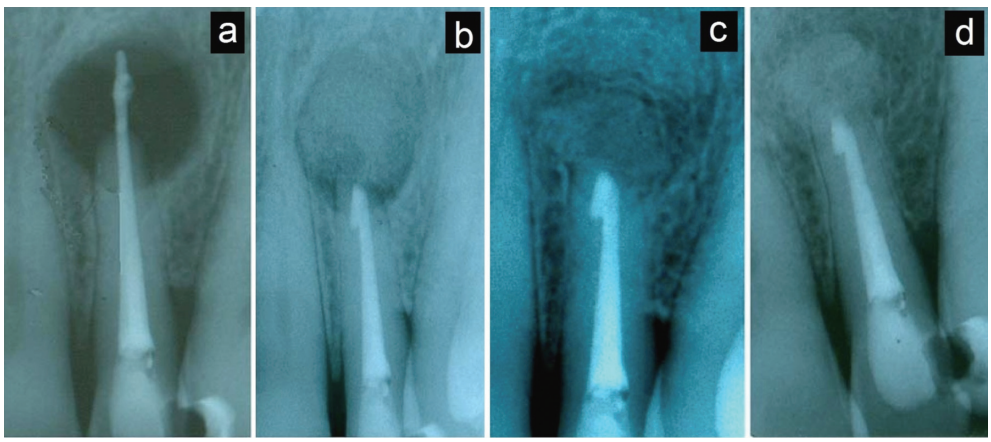

Fig. 3 Clinical application of B-G in the treatment of periapical bone destruction[32].
a: Radiological situation before endodontic microsurgery. b: Radiographic image of B-G embedded in the bone cavity immediately after the retrograde filling. c, d: Follow-up evaluation after 9 months (third radiograph) and 4 years (last radiograph).

graft substitutes. There has been a number of clinical studies that have demonstrated consistent results in a variety of alternative treatments including the surgical modification/reduction (elevation) of the maxillary sinus[30], the regeneration of interproximal bone defects in periodontal therapies[31], periapical application during endodontic microsurgery[32] (Fig. 3), management of cystic defects[33], as well as reconstructive procedures for treating peri-implantitis[34]. All these clinical applications have one thing in common —the proven efficacy and effectiveness to bond with hard tissue and enhance its growth due to the osteoconductive and osteostimulatory properties of the glass. Osteoconduction refers to the ability to support the migration of bone starting from the walls of the defect toward the central portion of the graft[2]. The process whereby the bioactive material is colonized by cells with osteogenic potential, called osseostimulation by Schepers and Ducheyne[35], complements osteoconduction and thus accelerates bone healing. The detailed mechanisms are not fully understood but are related to the well known corrosion reactions of B-G, leading to the formation of protective pouches within its internally eroded particles[35]. These can act as nuclei for subsequent cellular differentiation as well as bone tissue growth and enhance the repair of the defect. New bone formation has been demonstrated histologically in human oral bone defects treated with B-G[28]. There is also evidence that the replacement and infiltration of osseous tissue start at 4 months, and all B-G particles completely disappear at 16 months following the grafting procedure[36]. These particles appeared to have internal erosion where undifferentiated mesenchymal cells penetrated and were stimulated to differentiate into osteoblasts[35]. Consequently bone formation occurred in multiple growth sites, rapidly filling the bone defect. This new bone had the histologic and biomechanical properties of the surrounding bone as soon as 6–7 months after grafting[24]. Furthermore, histology revealed rare inflammatory cells and absence of giant cells even around the remaining particles, which confirmed the biocompatibility of B-G[28].

Maxillary sinus lift surgery

Application of endosteal dental implants to support artificial replacements for teeth has evolved into a viable alternative to conventional prosthetic procedures[4]. Generally, the presence of alveolar bone with sufficient volume and/or density is considered to be a prerequisite for implant placement, osseointegration, and load bearing. Following tooth loss, the maxillary alveolar ridge is affected by extensive buccolingual and/or apico-occlusal resorption and its trabecular bone substance undergoes intense remodelling processes, including enlargement of the maxillary sinus. As oral implantology developed, a surgical modification/reduction of this anatomical structure, called maxillary sinus lift, became a popular solution to increase vertical bone height, allow for reliable implant placement and obtain primary stability in the posterior atrophic maxilla[23]. It aims at regenerating bone in the lower border of the sinus cavity and is often achieved using graft materials that are placed inside a subantral space created between the residual alveolar ridge and the elevated membranous lining of the maxillary sinus[37]. Various bone substitutes have been used alone or as adjuncts to autogenous bone for sinus augmentation procedures[24]. It is claimed that the addition of osteoconductive materials can expand the volume of the graft, induce dense new bone formation, and prevent premature resorption at the augmented site[24].

Maxilla grafting with composite grafts of B-G granules and autogenous bone chips was shown to be as good as the treatment with autogenous bone alone, yielding the same quality and volume of mineralized tissue when a reasonable healing period (5–6 months) is allowed (Fig. 4)[23,30,36,37]. Bone formation in defects filled

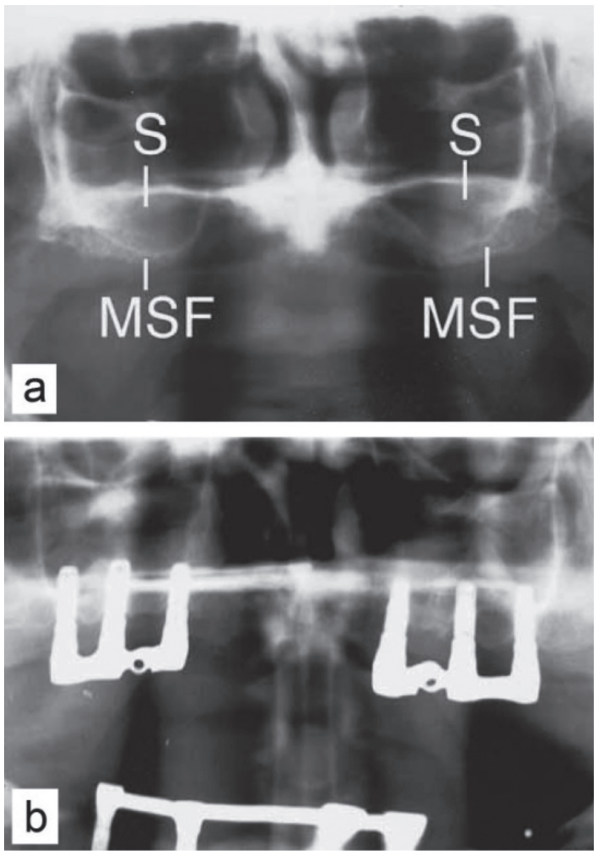

Fig. 4 Clinical application of B-G in maxillary sinus lift surgery[36].
a: Preoperative panoramic radiograph of an edentulous patient with bilateral severe maxillary atrophy. Note the thin, residual maxillary sinus floor, MSF, and the pneumatization of the maxillary sinus, S. b: Postoperative panoramic radiograph illustrating 6 implants placed after sinus floor elevation in order to support an overdenture.

with a given osteoconductive bone substitute, like B-G, originates from the margins of the defect and proceeds up to a certain distance, but not necessarily throughout the defect space[38]. Analogous conditions should be expected in maxillary sinuses, where osteogenesis originates from the sinus walls and extends progressively toward the center and the apical portions of the grafted space[38]. Prompt bone formation should be obtained close to the floor and lateral and medial walls of the sinus, while the most central and apical portions of the augmentation should exhibit less/minimum amounts of bone. Thus, complete bone healing would depend primarily on the dimensions and configuration of the defect, *i.e.*, smaller defects and/or with more bone walls would heal more readily than larger defects and/or with fewer bone walls. This means that harvesting of autogenous bone may be still necessary, but the amount of bone needed is considerably decreased and donor site morbidity is alleviated[23]. The use of autogenous bone is dictated by its osteogenic potential related to the number of surviving osteoblasts and osteoinductive effect brought about by the release of bone morphogenic proteins and other growth factors, which have the capacity to accelerate deposition of new bone along the graft material[37]. When using biomaterials for bony deficiencies, it is advisable to know their resorption behavior, and this should closely match the bone formation rate at the regeneration or implant sites[38]. Many bone substitutes such as dense sintered SHA or deproteinized bovine bone take a very long time before they become removed by the continued activity of multinuclear giant cells[36]. As a result, persisting particles of biomaterial remain at the bone-implant interface when fixtures are installed. Because B-G granules start to resorb postoperatively while new bone is formed within and around them, it is unlikely for glass remnants to interfere with bone dynamics at the implant-bone interface after fixtures have been installed, either simultaneously with the elevation procedure or as a second stage subsequent to healing of the grafted site[36]. Besides, it was demonstrated that B-G is able to produce more new bone than SHA[38], and this bone was very similar to the natural surrounding bone. Tadjoedin *et al.*[36] showed that the centers of the B-G granules become excavated, and are subsequently filled by large undifferentiated mesenchymal cells (Fig. 5). It was hypothesized that these cells quickly differentiate into osteoblasts and start to deposit newly formed bone tissue within the eroded dissolving particles[39]. This internally formed bone tissue is not necessarily connected to the surrounding bone tissue, and functions as a nucleation site for further bone repair. Dissolution events with replacement by bone and bone marrow *via* osteoconduction continue with time, until virtually all B-G granules have disappeared. New bone is thus formed in an area where apparently no preexisting bone was present. As reported by Schepers *et al.*[39] this phenomenon is related to the particle size and gives rise to the suggestion that every particle can function as a bone growth center, which will enhance the efficacy of the bone regeneration process. Lastly, this combination of findings provides some support for the conceptual premise that the antimicrobial activity of B-G against sinus pathogens[38] might contribute to the resolution of inflammatory responses and provide extraordinarily favorable conditions for an uneventful healing process[30,36].

Treatment of periodontal defects

Periodontitis, a major chronic inflammatory disorder affecting the periodontium, is characterized by formation of soft tissue pockets or deepened crevices between gingiva and tooth roots. If these sites of deterioration are left untreated, progressive resorption of the alveolar bone would occur, resulting in the formation of intraosseous or furcation defects that precede the loosening and subsequent loss of teeth[3]. Furthermore, it has been recognized that these defects may alter the course and pathogenesis of a variety of life-threatening systemic diseases, acting as the site of origin for the

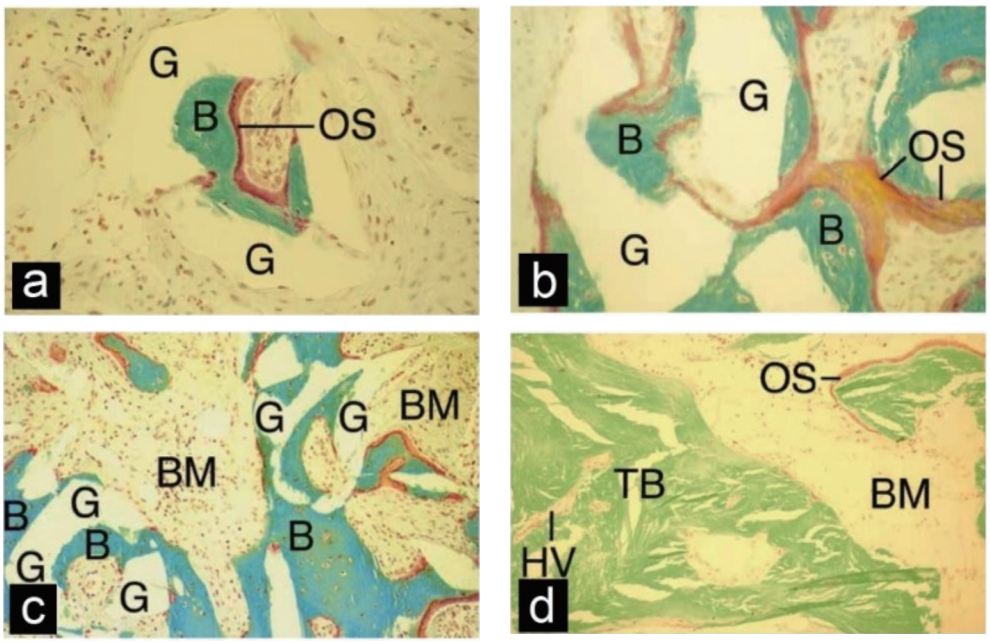

Fig. 5 Histological observations on biopsies harvested after bone grafting procedures with B-G[36]. a: Light micrograph of a 4 month biopsy showing new bone, B, formation at the center of an excavated, not stained B-G particle, G. Note the differentiation of mesenchymal cells into osteoblasts, lining a red osteoid front, OS, at the center of the B-G particle, G, and having no apparent connection with pre-existing bone. b: Light micrograph of a 5 month biopsy where bone formation has increased both in the centers and around the transformed BG-particles, G. Notice the osteoid layers, OS, at the periphery of newly formed bone and the woven aspect of the bone, B. c: Light micrograph of a 6 month biopsy showing substantial bone formation (green), B, with a trabecular bone pattern and normal appearing bone marrow spaces, BM. Remnants of the transformed BG-particles, G, are also visible. d: Light micrograph after 16 months where mature lamellar trabecular bone, TB, with Haversian systems, HV, osteoid layers, OS, and mature bone marrow, BM, are present.

dissemination of pathogenic microorganisms to distant body sites[40]. To date, different root debridement modalities in open flap surgery as well as periodontal regenerative therapy with membranes and bone grafting materials, including autografts, allografts, xenografts and synthetic substances, have been employed with distinct levels of clinical success[41]. Resorbable and non-resorbable membranes act as a physical barrier against the migration of epithelial cells, which have the fastest migration rate, from the superficial soft tissue flap into the underlying grafted site, favoring the attachment of other cell types with regenerative potential to repopulate the periodontal defect (guided tissue regeneration)[42]. Recently, growth factors have also been used in an attempt to gain this therapeutic endpoint[41]. The dilemma remains as to which approach can generate the best clinical outcome with high predictability. To be considered as a regenerative modality, a material or technique must histologically demonstrate that tooth-supporting tissues including alveolar bone, cementum and a functional periodontal ligament can be formed on a previously diseased root surface[43].

Although there has been little human histologic evidence to show renewal of integrated bone, cementum and connective tissue attachment coronal to the base of the previous osseous defect[44], there is a large amount of clinical and radiological data supporting the application of B-Gs in the treatment of teeth that have advanced periodontal destruction. Several clinical studies have shown better results employing B-G in comparison with conventional treatment methods[19,31,45-51]. Mengel *et al.*[52] evaluated the effectiveness of a resorbable membrane and a B-G in the treatment of deep intrabony defects in patients with generalized aggressive periodontitis (Fig. 6). Statistically significant clinical results (reduction of probing pocket depth and gain in relative attachment level) were recorded after 6 and 12 months post surgery. The 5-year results were still optimal and each defect was found to be radiographically filled[53]. The conclusion that B-G treated sites showed a greater trend to improvement compared to conventionally treated sites is consistent with the findings of the recent systematic review of literature by Sohrabi *et al.*[3]. Together these studies provide some insights into the most probable mode of healing after application of B-G. The evidence presented in this section suggests that B-G induced a "repair"

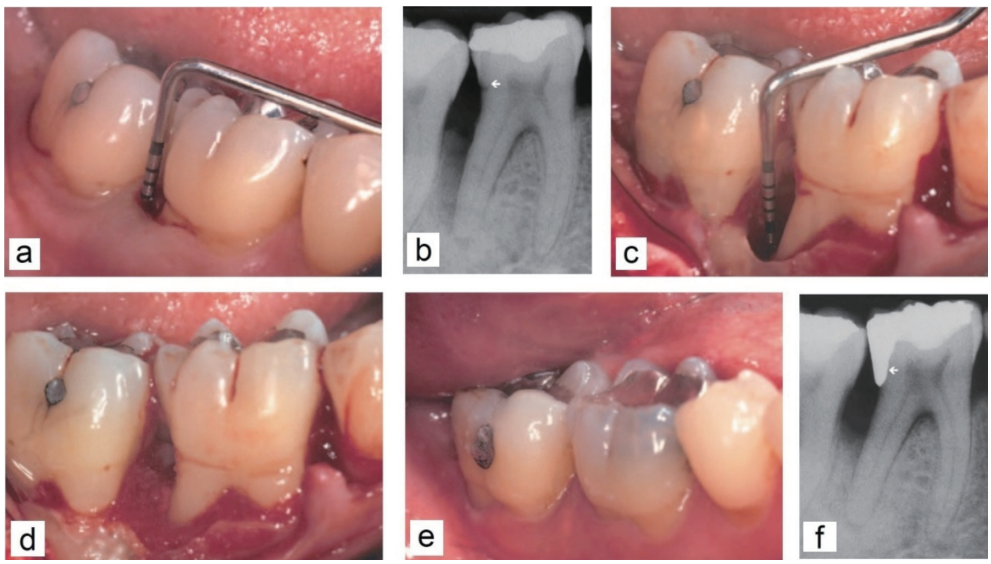

Fig. 6 Clinical application of B-G in a patient with generalized aggressive periodontitis[52].
a, b: Intrabony defect prior to surgery. The arrow sign on the radiograph indicates distal cervical caries and the location of the cemento-enamel junction as a landmark. c, d: Intraoperative situation after exposure of the defect. e, f: Clinical and radiological situation 12 months after surgery. Also, the distal cervical caries was treated with a new filling.

response (formation of long junctional epithelium with minimal new connective tissue attachment to the teeth, and ankylosis) rather than a true regenerative response[44]. Consequently, the gain in clinical attachment level could be due to chemical bonding between newly-formed HCA layer and host tissue as well as the soft tissue bonding property of B-G[45]. All evaluated B-G materials in the included studies appeared to be bio-compatible, and there were no reports of adverse effects, such as allergies or other immunologic reactions, abscess formation, or rejection of the grafting materials[3]. The main limitation inherent in the B-G products that are currently available is their granular nature and, as such, they cannot serve reliably as space-making materials in sites where there is no support for a membrane and the soft tissue cover may cause its collapse during healing. As a future outlook, the range of applications of B-G could be extended within the scope of periodontal regenerative therapy if this material could be redesigned to offer also space-making properties in combination with a novel generation of biologically active, spatially designed and functionally graded tissue guiding membranes[41].

Metal surface biofunctionalization: coating material for dental implants

Endosteal dental implants have been used in dentistry for many years to support dental prostheses and to improve appearance together with functional ability of the natural dentition. The critical requirements are mechanical resistance, to prevent inflammatory responses as well as osteolysis and to promote an active response in terms of bone apposition, maintenance and biological fixation. A high degree of patient compliance is also required and healing periods of at least 3 to 6 months are necessary for the mandible and the maxilla, respectively[4]. All currently used metals, such as commercially pure titanium and its ternary alloys, *i.e.*, Ti-6Al-4V, are bio-inert and do not bond chemically to host bone. As bio-inert materials often become encapsulated in fibrous tissue, it is important to develop new biomaterials that will ensure extended lifetime of implant performances in the corrosive, stressed and cyclically loaded service environment[45]. Current trends in dental implant therapy include modification of titanium surfaces for the purpose of improving osseointegration by different additive (surface coatings) and subtractive processes (grit-blasting, acid etching)[4]. It is commonly acknowledged that there is an increasing clinical demand for true bioactive dental implants, possibly allowing wider case selection criteria and improved implant integration rates even in the more challenging osteoporotic and medically compromised patients. Several different coating modalities are described in the literature, many of them with the purpose to be bioactive. Such surface coatings include different ceramic forms of calcium phosphate, particularly SHA[4]. However, SHA-coated dental implants have been associated with some clinical complications and concerns have been raised about the loss of coatings integrity over time, producing a space between core metal and bone, with resultant marginal bone loss[54], mechanical instability and high failure rates[55]. SHA coatings are reactive, with the potential to dissolve, release calcium phosphate particulates and lose structural integrity, particularly at the local acidic environment of abscessed osteotomy sites[56]. In-service

delamination and exfoliation of the interposed SHA surface layer has been reported by several authors[57,58], with the observation by some researchers that loose fragments were either surrounded by soft tissues, not by bone[54], or were excreted from the body as a function of time[4]. Other evidence suggested that the breakdown and dissolution of the coating grain boundaries could elicit a phagocytic response by macrophages[57] or a foreign-body reaction[56], resulting in greater resorption of bone.

It has been established that the rate of surface reaction of B-G to body tissues is very fast (within hours) in comparison to SHA[25] and that calcium sodium phosphosilicates can develop a chemical bond with living bone that is stronger than either the bone or ceramic alone[2]. Because of its high I_B, B-G is regarded as a viable alternative to cover metallic implants in order to combine the best properties of both materials[59]. On this account, the B-G coating may improve the rate of commitment of bone precursor cells to osteoblastic lineage differentiation and the resultant implants display a more rapid interfacial bone formation, with consequent stabilization at an early stage, load bearing capacity in poor quality bone along with whole treatment time reduction. In order to fulfil these goals, the glass composition, the coating technique and the coating parameters have to be designed and selected carefully. Several studies identified the importance of the thermal expansion coefficient (TEC) of B-G, making the coatings prone to crack if stresses arise due to the glass shrinking at a different rate from the metal substrate during processing[60]. The debonding effect of the residual stress is usually increased with coating thickness[61]. From a practical point of view, it is difficult to match the high TEC of the glass coating, with its predisposition to crystallize throughout heat treatment, to that of titanium[62]. However, in case of conventional coating methods such as the enamelling technique, matching the TEC of the glass coating to that of titanium is an essential step. Adjustments in the glass composition, by adding or substituting compounds, might tackle these problems. Therefore, efforts have been made to match the shrinkage of the ceramic to that of the metal by tailoring the higher TEC of B-G ($14–15\times10^{-6}$/ºC) to that of titanium substrate ($9.4–10.3\times10^{-6}$/ºC), in order to prevent the first from cracking and peeling off as the device cools after coating[62]. In fact, the glass should have a slightly lower thermal expansion than the metal. This may induce only small compressive stresses, avoiding the generation of tensile thermal stresses passing from the processing temperature to room temperature[63]. TEC of the glass can be reduced by increasing the silica content, but this reduces bioactivity as well[62]. A lower thermal expansion can also be reached by a partial substitution of CaO by magnesium oxide (MgO), and of Na_2O by potassium oxide (K_2O), matching the thermal expansion of the coating to that of Ti-based alloys[63]. This is based on the fact that the TEC of the substitutive oxides is lower than that of the former ones. With the second method, coatings with low silica contents that do not crack or delaminate can be successfully prepared. Another approach to combine the thermal expansion of the coating to that of metallic substrates is represented by the preparation of multi-layer coatings, in which a glass formulation with increased silica content is used as first layer in direct contact with the metallic substrate and is covered by an outer bioactive layer[60]. There is a narrow range of glass formulations in this compositional system that produce good coatings and that also form SHA, thus multiple layers of different compositions may be needed for optimal dissolution and bone integration. The deposition of such an intermediate layer is useful to obtain a good adhesion of the coating to the substrate, to minimize the reactivity between the substrate and the outer glass-ceramic coating, and thus to preserve the nature of its crystalline phases. An example is represented by the dip-coating of titanium implants with glass of the 1–98 composition {SiO_2 (53 wt%), Na_2O (6 wt%), CaO (22 wt%), MgO (5 wt%), K_2O (11 wt%), P_2O_5 (2 wt%), and boron trioxide [B_2O_3 (1 wt%)]}, which were tested in rabbit femurs[59]. The coated implants were integrated into host bone without a connective tissue capsule and were surrounded by significantly more bone than the non-coated implants. A lot of data have been collected about the interface reactivity between the glass coating and the substrate. Effectiveness of the interfacial adhesion depends on proper elemental interdiffusion, chemical bonding and physical interlocking between the dissimilar phases. Care should be taken to avoid excessive interface reaction, in order to prevent the formation of a thick reaction layer accompanied by bubbles in the glass. Hence the glass in contact with the alloy has to be saturated with the lowest valence oxide of the metal, without any interfacial layers[63]. In this way, a transition region can form between the metallic bonding of the substrate and the ionocovalent bonding of the glass, providing a continuity of electronic structure that results in a good bonding between the two materials. However, crystallization of the glasses during the coating procedure might result even from improper selection of the firing parameters. Therefore, factors such as holding time, maximum temperature and heating rate should be considered carefully. Neglecting one of these parameters might still cause crystallization of the glasses and failure of the glass powders to sinter and subsequent detachment of the coating from the substrate. The firing time should be as short as possible, in order to prevent the formation of undesired reaction layers at the interface. Long process times could cause extensive reaction between the glass and the substrate, with the formation of oxides or other products which can lead to poor adhesion of the coating[63]. The firing process must be performed at an appropriate temperature because this allows a good softening and sintering of the glass powders (*i.e.*, above the glass transition temperature, T_g) while completely avoiding any degradation of the metal. In the case of titanium substrates, the firing temperature should be below the α->β crystallographic transformation of Ti, which occurs between 885 and 950ºC for unalloyed Ti or between 955 and 1,010ºC for Ti-6AI-4V[63].

A number of methods are utilized to manufacture bioactive coatings on metal prostheses. In a recent short-term clinical study, newly developed B-G/coated dental titanium implants were fabricated using a conventional enamelling technique and evaluated following implantation in partially edentulous patients[64]. Vitreous enamelling is easy, inexpensive and quite similar to the process of glazing ceramic tiles. It can be used to coat complicated shapes and the thickness of the coating can be controlled[63]. For their clinical trial, Mistry *et al.*[64] applied a small amounts of borosilicate containing titania to the experimental implants and the glass composition {SiO_2(43–44 wt%), decahydrated borax [$Na_2B_4O_710H_2O$ (6–7 wt%)], dry soda ash [Na_2CO_3(11–12 wt%)], calcium carbonate [$CaCO_3$ (29–30 wt%), di-ammonium hydrogen orthophosphate [$(NH_4)_2HPO_4$(8–9 wt%)], and titanium oxide [TiO_2 (1–2 wt%)]} was optimized to show a lower tendency to crystallization during the thermal coating treatment. The resultant thickness was within the range of 70–100 μm. After 12 months no apparent retardation of normal bone healing process around the fixture occured, which is a primary requisite for biological fixation, and post-operative radiographic views showed intimate bone apposition (Fig. 7). Notably, neither a wear particle effect nor delamination, as was previously observed on SHA coatings[4,54], could be exerted in consequence of particles becoming detached from the titanium surface.

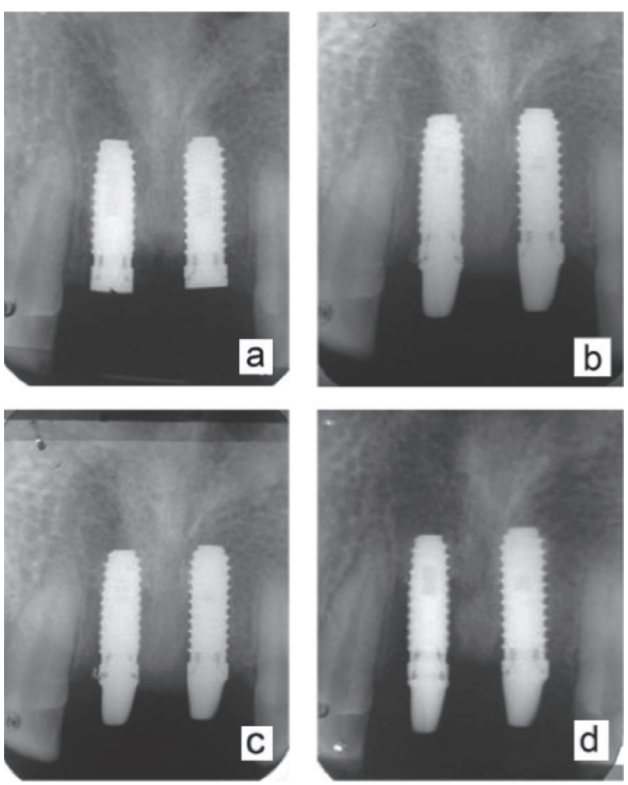

Fig. 7 Periapical X-ray of control (left) and B-G coated (right) implants at immediate postoperative period (a), 5 weeks (b), 6 months (c) and 12 months after permanent prosthetic attachment (d)[64].

Implants penetrating soft tissue into an environment rich in microorganisms may be at risk of harboring species that can develop infection. The soft tissues surrounding healthy osseo-integrated dental implants, known as peri-implant tissues, share anatomic and functional features with the periodontium around natural teeth. These structures are established after surgical insertion and as a result of tissue healing. Marchetti *et al.*[65] described this area of attachment as "a biological seal", since it isolates the oral cavity from bone and hence greatly affects the success of dental implants. Related to oral implants, peri-implantitis has been discussed extensively[34]. B-G has shown to be active against supra- and sub-gingival bacteria[9], further underlining its potential benefits as part of an implanted device by means of metal surface coating. Mistry *et al.*[64] declared one implant as failure but observed an almost intact coating as evidence of the capability of calcium sodium phosphosilicates to produce an alkaline medium around the fixture through dissolution of alkali ions, that might arrest premature coating degradation in infected osteotomy sites. Eventually, this might permit bone ongrowth into the implant surface while the glass coatings slowly degrade over time. Furthermore, no suppuration around the failed bioactive fixture was observed, which suggested that antimicrobial property of this type of coating might have an important role in preventing infection, or cure an already established one[9].

In the ideal implant, the coating compositions must be tailored to provide local attachment to different parts of the surrounding tissue. In yet another clinical study, a strategy to fabricate implants with different bioactive areas for soft tissue and bone attachments was proposed[66]. The bioactive coating was applied on titanium implant leaving 1–2 mm from crestal module, allowing the formation of peri-implant sulcus and junctional epithelium resembling those of surrounding natural teeth. This also permitted to localize the application of the bioactive coating without heat treatment of the whole implant, and helped to prevent early exposure of the coating at the oral environment during function, owing to the fact that a rough coating would invite excessive plaque accumulation.

Even if animals are not ideal models for humans because of the intrinsic metabolic, anatomic and cellular differences that can give inadequate or erroneous information[67], similar data had been allegedly reported in animal models by Moritz *et al.*[59] and by Wheeler *et al.*[68] who found that, in presence of B-G coating, implants were integrated into host bone without a connective tissue capsule and were surrounded by significantly more bone tissue than the control implants.

While newer early loading implant techniques that are reliant on primary mechanical fixation are becoming available, these findings all indicate that B-G/based coatings on titanium implants enhance the initial integration capacity with osseous tissue, facilitate bony healing and could pave the way for a new generation

of dental implants with permanent bone-bonding sites incorporated on their surfaces.

CONCLUSIONS

B-Gs are an important consideration when choosing the optimal biomaterial to be used as a bone substitute in periodontal and implant therapy, where both regenerative and antimicrobial properties are needed.

As highlighted in the present study, B-G is a versatile replacement material, since it is available in multiple forms and can be moulded into desired shapes as per the need of the user. Thus, its scope for use also increases manifold. Its unique bioactive properties allow for an osteoproductive environment in which the bone-biomaterial interface is uniquely stronger than it would be with other forms of alloplasts.

From a demonstrated clinical benefit as bone grafting material for the elimination of osseous defects due to periodontal diseases, pathologies, and surgeries, to a potential use for manufacturing commercial bioactive dental implants, B-G represents an important and exciting field of study. Advanced studies on the interactions between the host cell and the biomaterial, as well as cell gene expression, should be undertaken in order to understand surface topology, activity of cells and adhesion dynamics at the nanoscale. Current and possible future applications ensure that this biomaterial have a high academic, clinical and industrial importance.

DISCLOSURE

The authors deny any financial affiliations (*e.g.* employment, direct payment, stock holdings, retainers, consultantships, patent licensing arrangements or honoraria), or involvement with any commercial organization with direct financial interest in the subject or materials discussed in this manuscript. The authors alone are responsible for the content and writing of the paper.

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