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Abstract

This review focuses on the applications of bioactive glasses and glass-ceramics in the field of orbital implants for ocular surgery. This use is relatively novel and less popular compared to the applications in orthopedics and dentistry for the repair of bone and teeth. Recent studies have shown the suitability of bioactive glasses and glass-ceramics in contact with soft tissues for promoting additional effects associated to the release of therapeutic inorganic ions. Specifically, the angiogenic and antibacterial actions that may be elicited by selected glass compositions are highly appealing for the development of new-generation orbital implants, since improved vascularization and antiseptic properties are the key for a higher success rate of anophthalmic socket procedures. An overall picture of existing orbital implants based on bioactive glasses is here provided, and the further potential and open challenges for future research in this field are highlighted and discussed.

Keywords: Bioceramic; Bioactive glass; Porous implant; Orbital implant.

1. INTRODUCTION

The eye loss is disfiguring and the concern with redoing facial aesthetics is very old. Even though it is a difficult decision, there are some critical conditions, e.g. blind and painful eyes, eyes with intraocular tumors or after severe trauma, in which the removal of the entire eye or its content is still mandatory [1].

Archaeological findings have revealed that around 500 BC Egyptian and Roman people losing an eye wore painted prostheses (a clay shell worn over or under the lids) to recover the proper

appearance [2]. Till the Middle Age, different combinations of moldable materials (e.g. wool, clay) and noble metals (e.g. gold, silver) were used to fabricate different kinds of ocular prosthesis; the thin metallic foil covering the anophthalmic socket was often enameled or painted to reproduce the color of natural iris, thereby providing the patient's face with more acceptable aesthetics [3].

The surgical techniques used to remove the eye *in toto* or its content evolved at the same time than the evolution of the orbital implants. There are descriptions of old techniques (16^{th} century) using a strong wire transfixing the globe, which was then drawn until the eye was out of the orbit [4]. The procedures of human eye removal were not clearly standardized until the end of the 19^{th} century [5] and then evolved quickly. Nowadays there are two well-established main techniques: (i) evisceration which refers to the removal of the contents of the eye while the scleral shell and ocular muscle attachments are spared, and (ii) enucleation which is a more radical measure involving the removal of the whole globe from the orbital socket. The majority of cases are suitable for evisceration whereas enucleation is mandatory for intraocular tumors (e.g. retinoblastoma or melanoma), since without eye removal the malignant lesion could spread to the surrounding structures or metastasize.

After the enucleation or evisceration, implants must be placed in the orbit to restore the lost ocular volume [6]. If the patient undergoes evisceration, the implant is usually wrapped by the own scleral shell and the extraocular muscles are left in place. When the surgical procedure is an enucleation, the implant is wrapped within a foil of donor sclera or smooth polymeric mesh to which the patient's extraocular muscles are sutured. The Tenon's capsule and the conjunctiva must be closed over the sclera and in the anterior portion of the orbital cavity in order to prevent the exposure of the implant, avoid conjunctival abrasion, "isolate" the implant from the outer environment and protect it from foreign pathogens (Figure 1a).

Since the late 1500s, Venetian glassmakers in Italy began to produce the early so-called "glass eyes", i.e. hollow spheres of blown glass that were inserted inside the empty orbital cavity [7].

Although being fragile and needing to be worn cautiously by patients, these implants rapidly gained success and were also exported to other European countries.

At the end of the 19th century, Mules reported a detailed description of a hollow glass sphere and its placement inside the orbit to replace the loss of volume in an enucleated socket [5]. This type of implant was the standard option in anophthalmic socket surgery till the end of the Second World War. The most important factory of glass orbital implants in the first half of the 20th century was located in Germany and was destroyed in the 1940s [4]; since then, glass orbital implants had fallen in almost total disuse.

From 1950 to 1970 silicone or poly(methyl methacrylate) (PMMA) solid balls [4] became the most popular materials for replacing the volume of anophthalmic socket. Both these materials, as well as the previously-applied glass spheres, have a smooth surface that do not interact either with the host tissues or with the external ocular prosthesis – which is usually a painted PMMA shell mimicking the aesthetics of the contralateral eye –, and hence they were named non-integrated implants.

The anophthalmic socket reconstruction scenario dramatically changed in the 1980s with the advent of porous orbital implants [8,9,10]. Porous implants allowed improving the clinical success rate and the life of the implant due to postoperative fibrovascular colonization inside the implant. While non-porous polymeric materials are typically embedded in a collagenous pseudo-capsule once implanted *in vivo*, the connective tissue composed by vessels and inflammatory host cells contributing to the healing process invades the void network of the porous implant and anchors it to the orbital tissues. This is believed to minimize the risk of postoperative implant migration [11]. Furthermore, there is a convincing evidence that porous implants lead to better clinical outcomes compared to non-porous devices as the presence of a blood supply within the implant permits immune surveillance as well as the treatment of bacterial infection via systemic antibiotics [12]. Some reports have also

suggested that fibrovascularization could promote the spontaneous healing of small exposures of the implant [13]; however, this potential advantage is still under debate.

Over the years there was some confusion about the meaning of the term “integrated” in the context of orbital implants because for some authors “integration” means the tissue reaction inside the implant – which typically occurs in porous implants –, while, according to others, integrated implants are the ones which can receive a peg system for direct coupling with the external prosthesis [9] (Figure 1b). A first, clear attempt to solve this issue was carried out in 2002 when the scientific panel of the American Academy of Ophthalmology (AAO) established that “integration” refers to the nature of fit between the external ocular prosthesis and the orbital implant. However, this controversy is still far from the end.

Porous orbital implants available on the market are made of natural or synthetic hydroxyapatite, polyethylene or alumina and exhibit a network of open and interconnected macropores in the range of 100 to 500 µm [10]. There is evidence that porous alumina implants lead to better clinical outcomes than both porous hydroxyapatite, mainly due to the lower surface roughness (less than 1 µm vs. few micrometers [14]) which minimizes the risk of implant exposure, and porous polyethylene that, however, exhibits quite smooth walls [15]. This observation can be explained in the light of the faster fibrovascularization rate of alumina implants, which is promoted by the more favorable chemical surface of the material. In fact, cell and tissue ingrowth within porous implants is accelerated by hydrophilic surfaces like those of alumina, and discouraged by hydrophobic polymers that tend to be encapsulated in a fibrous collagenous capsule [16].

In spite of all these attractive characteristics, commercial porous implants – and especially alumina implants – are not accessible to a large number of patients due to the high cost. Very interestingly, Sousa et al. reported that the traditional, non-integrated PMMA implant is still the most-

commonly used all over the world [17], and other studies indicate that cheap non-integrated silicone spheres are in widespread use in developing countries [18].

At present, the majority of orbital implants are spherical; however, other "styles" and formats were developed over the years. A special mention should be dedicated to the "quasi-integrated" implant, which was introduced in the 1970s and was characterized by a "lock-and-key" coupling system to better support the external ocular prosthesis and expand its range of movements [19]. Specifically, this PMMA implant exhibited a grossly semispherical geometry provided with four anterior mounds that matched four corresponding depressions on the posterior surface of the ocular prosthesis [20]. The mounds created two perpendicular channels so that the stumps of horizontal and vertical extraocular muscles could be sutured together before being covered by the conjunctiva. It is worth pointing out that there was no interruption of conjunctival lining, but the irregular anterior surface of the implant was used to improve translation of implant movement to external prosthesis movement. This type of implant underwent several evolutions over time and it was shown that the adoption of a conical geometry can have better contact with the extraocular muscles and maybe can be a good option to increase the external prosthesis movements along both vertical and horizontal axes [21].

Complications related to orbital implants may happen due to inherent characteristics of the implant material. For example, the exposure rate of porous implants can be favored by a rough and stiff surface [22,23]. Exposure in porous implants can be treated with conservative management using pharmacological treatment or salvage strategies (anterior apposition of scleral or polymeric patches), without the need for implant removal and replacement with a new one [24,25]. Furthermore, there are other factors not directly related to the implants which can lead to postoperative complications, such as bad surgical technique or patient's systemic diseases.

2. WHY USING BIOACTIVE GLASSES FOR MAKING ORBITAL IMPLANTS?

Despite the variety of options available on the market, nowadays an orbital implant to be considered as "ideal" does not exist. The non-negligible drawbacks of current solutions have been motivating further research in terms of both implant design and materials used.

There are multiple reasons behind the recent "resurrection" of glass as a material for orbital implants after a hiatus of about fifty years. This is a typical demonstration of how old, temporarily discarded materials can be somehow reinvented in the light of new scientific and technological advances. In the 1950s, the hollow spheres of blown glass were replaced by non-porous acrylic or silicone orbital implants that were relatively light, mechanically more compatible with orbital tissues due to lower stiffness, and not prone to sudden and traumatic brittle fracture as the thin-walled glass balls might be [26,27].

Furthermore, today's manufacturing techniques allows glass products to be easily produced in a porous form by means of foaming, porogen removal or replication strategies [28], which were not available at the time of first-generation blown glass orbital implants. Glass possesses an exceptional versatility from both compositional and technological viewpoints and can be processed at lower temperature and cost compared to other orbital implant materials, such as alumina.

In addition to the previous considerations, there is a more profound and substantial reason that differentiate these new glass-based orbital implants not only from the early glass spheres but also from all other porous and non-porous existing options: instead of using biocompatible but inert glass compositions, researchers began to investigate the suitability of orbital implant biomaterials able to actively interact with living cells and tissues, eliciting specific biological responses.

Bioactive glasses were first developed in 1969 by Hench and coworkers, who designed the famous 45S5 composition ($45SiO_2$-$24.5CaO$-$24.5Na_2O$-$6P_2O_5$ wt.%) [29]. This glass, commercialized

under the tradename of Bioglass®, was found able to bond to living bone and stimulate the genes of bone cells towards paths of regeneration and self-repair [30]; it is currently used for making many clinical products (e.g. cast monoliths, micrometric particles, porous granules, injectable putty) for bone defect filling in orthopedics and dentistry [31,32]. These bioactive glass products are capable to bond to host bone forming a tight interface and to promote the growth of new bone tissue while dissolving over time. The creation of a glass-bone bond is attributed to the formation of a nano-crystalline hydroxyapatite layer that interacts actively with the collagen fibrils of the living bone [33]. The formation of a bond *in vivo* between this surface layer and the host bone is a complex process involving protein adsorption, incorporation of collagen fibrils, adhesion of osteoprogenitor cells, cell differentiation, production and mineralization of bone extracellular matrix [34]. The surface nano-hydroxyapatite layer forms following solution-mediated dissolution of the bioactive glass according to a process similar to the corrosion of conventional glasses [35]. Accumulation of dissolution products causes both the chemical composition of the glass surface and the pH of the body fluids to change locally, thus providing surface sites and a pH favorable to hydroxyapatite nucleation. Once the surface hydroxyapatite layer has formed, proteins are adsorbed on it and cells can attach, differentiate and produce new bone matrix [36].

Formation of a surface hydroxyapatite layer is not a goal in the field of orbital implants, but other properties of suitable biocompatible glasses can be very appealing for such application. Over the years, a number of other silicate, borosilicate and phosphosilicate glass and glass-ceramic compositions have been developed for biomedical use [37] and, very interestingly, some of them were found suitable for use in contact with soft tissues [38]. In fact, ionic dissolution products released from bioactive glasses (Figure 2) can stimulate not only osteogenesis but also angiogenesis, which is the key to accelerate wound healing and tissue regeneration [39]. The formation of new blood vessels is of utmost

importance for ensuring the delivery of nutrients, growth factors and oxygen as well as for allowing stem cells to reach the injured site.

The original 45S5 Bioglass® was widely proved able to stimulate angiogenesis both *in vitro* and *in vivo* (rat model) via the release of silicate and calcium ions [40]. In fact, silicate ions can induce endothelial cell homing, polarization and migration, and sprouting of new blood vessels [41,42]; calcium ions increase the gene expression of platelet-derived growth factor (PDGF), endothelial growth factor (EGF), insulin-like growth factor-1 (IGF-I), basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), thereby promoting the proliferation of endothelial cells [43,44]. Apart from 45S5 composition, this property was also revealed in other bioactive glasses, such as 58S ($58.2SiO_2$-$32.6CaO$-$9.2P_2O_5$ wt.%) [45] and 13-93B3 ($56.6B_2O_3$-$5.5Na_2O$-$11.2K_2O$-$18.5CaO$-$4.6MgO$-$3.7P_2O_5$ wt.%) [46].

Proangiogenic effect is highly relevant and attractive for applications in the field of orbital implants: while porous polyethylene, hydroxyapatite, and alumina act as a passive framework for fibrovascular ingrowth, the rate of which seems to be mainly dictated by surface wettability, bioactive glass implants can release ionic dissolution products that greatly stimulates angiogenesis, thus accelerating the fibrovascular reaction inside the implant.

Looking at the existing literature, bioactive glasses have been mainly (i) used to fabricate porous or monolithic glass-ceramic products, or (ii) embedded as bioactive inclusions within a porous polymeric matrix to create a composite, or else (iii) applied as a coating on a non-resorbable porous framework [47-51]. These strategies were also pursued in the field of orbital implants, as described in the next sections. Specifically, the approaches (ii) and (iii) are motivated by the need for retaining a permanent skeleton that supports the peri-ocular tissues over the patient's lifetime as the bioactive glass slowly dissolves.

3. IN VIVO STUDIES AND CLINICAL APPLICATIONS

3.1 Early trials

After being fascinated by the interaction between bioactive glasses and living tissues, a group of Chinese researchers first reported the use of these materials as orbital implants in the late 1990s [52]. Glass-ceramic porous spheres of unspecified composition were implanted in the orbital cavity of enucleated rabbits and no material rejection was observed over a 6-month follow-up. Mid-term ultrasound analysis at 3 months revealed implant vascularization, which reached 90% of the porous volume of the implant after 6 months. Fibrovascular reaction occurred in these glass-ceramic implants at a quicker rate compared to porous polyethylene, according to the results reported elsewhere in rabbits [53].

The same glass-ceramic spheres were then implanted in 102 enucleated human patients who apparently reported no material-related complications after a follow-up period ranging from 6 to 24 months [54]. Four patients experienced postoperative complications attributable to the operative techniques as their conjunctiva was damaged during the removal of the stitches, and one implant needed to be substituted with a new one. All patients felt satisfied with their cosmetic appearance and ocular motility acquired, without the need for an additional procedure of implant pegging.

It is interesting to underline that these early studies were performed while the researchers were apparently unaware of the proangiogenic potential of bioactive glasses, the first evidence of which was published only some years later by Day et al. (*in vitro* assessment using fibroblasts) [55,56].

A sporadic but interesting application of bioactive glasses was reported by Heringer and Ng [57] who filled old pegged tracts of hydroxyapatite porous orbital implants in order to allow re-pegging. Specifically, the pegs and sleeves that were previously placed in the orbital implants of three

patients were removed due to incorrect positioning (mis-centering and radial deviation), which caused discomfort during the coupling with the ocular prosthesis. The tunnel was filled with glass particulate and, after 2 months, the implant was successfully drilled again to host a new titanium peg. No complications were reported in all patients over a 3-year follow-up and a satisfactory connection of the implant to the ocular prosthesis was achieved.

3.2 45S5 Bioglass®/polyethylene composite orbital implants

Bioactive glasses have been widely used for producing polymer-based biomedical composites over the past two decades [58]. Probably inspired by these previous studies, the researchers of Porex Surgical Inc. (Newman, GA, USA) explored the possibility of adding bioactive glass particles to porous polyethylene orbital implant (Medpor®). The line of Medpor® implants was launched in the 1980s and this porous polymer was produced by molding medical-grade high-density polyethylene particles into a spherical or conical shape with 30-70 vol.% of porosity [59]; they gained soon an increased popularity due to the lower cost compared to porous hydroxyapatite and alumina [60]. Mixing melt-derived 45S5 Bioglass® particles (Novabone®, NovaBone Products LLC, Alachua, FL, USA) throughout the Medpor® structure was thought as a promising mean to improve the fibrovascularization rate: hence, the resulting glass/polyethylene (30:70 volume ratio) composite product, tradenamed as Medpor® Plus™ Sphere, was cleared for clinical use via the 510(k) process by the Food and Drug Administration (FDA) in 2002 and, since then, has been marketed worldwide.

A relatively limited number of studies is available on this type of orbital implant. Choi et al. [61] first investigated the effect of bioactive glass on the fibrovascularization of Medpor® Plus™ Spheres in rabbits. Forty-eight animals were evenly divided in four groups according to the different surgical techniques and implanted materials used: groups 3 and 4 received the Medpor® Plus™ Sphere

after enucleation or evisceration, respectively, while groups 1 and 2 received a glass-free Medpor® implant after the two surgical procedures (reference groups). Interestingly, histological examinations at 2 postoperative months revealed that there were no statistically significant differences among the four groups in terms of fibrovascular ingrowth. Hence, this early study suggested that, apparently, the presence of bioactive glass inclusions did not carry any added value for improving implant bio-integration and *in vivo* outcomes.

Opposite results were obtained by Naik et al. in a small clinical trial [62]. Ten human patients underwent enucleation followed by implantation of glass/polyethylene composite spheres (5 cases) or Medpor® ball (5 cases). Magnetic resonance imaging (MRI) analysis revealed a statistically significant increase of fibrovascularization rate, expressed as the percentage of tissue-filled pore volume at each time point, in the patients receiving the glass-containing implants compared to the Medpor® group (69 vs. 58% at 1.5 months; 85 vs. 76% at 4.5 months).

A more extensive clinical study was reported by Ma et al. [63] who reviewed the clinical outcomes of 170 human patients after placement of Medpor® Plus™ Spheres following enucleation. Most patients (161 cases) experienced no complications (good motility of implant and ocular prosthesis, no cases of conjunctival thinning or inflammation), while excessive discharge and implant postoperative exposure occurred in 2 and 7 cases, respectively; of those, 8 patients needed additional surgery. These results suggest that glass/polyethylene composite porous spheres may be a useful alternative to other options, but an actual clinical advantage remains unclear as a comparison with glass-free Medpor® or a reference implant was lacking in this study.

3.3 Biosilicate®-derived implants

Around 2010, the Brazilian research group led by Profs. Zanotto and Peitl proposed the use of Biosilicate® (composition $23.75Na_2O$-$23.75CaO$-$48.5SiO_2$-$4P_2O_5$ wt.%) to make a new generation of glass-ceramic orbital implants to restore volume in the anophthalmic socket. The story of the concept and applications of Biosilicate® and its devitrified derivatives was recently reviewed by Crovace et al. [64]. Initially developed to be an alternative to 45S5 Bioglass® for use in bone and dental repair [65,66], Biosilicate®-derived glass-ceramics were found to be active also in contact with soft tissues, which is key for orbital implants.

In a first study published in 2012, Brandão et al. [67] assessed the biocompatibility of cones composed by Biosilicate® or 45S5 Bioglass® (Figure 3a) in the eviscerated right eye of male albino Norfolk rabbits. Cones were produced by casting the melt into graphite molds; no crystallization was induced in 45S5 Bioglass® cones, whereas Biosilicate® cones underwent two different thermal treatments to deliberately develop one or two crystalline phases. Specifically, Biosilicate® 1P cones were treated so as to contain only one crystalline phase ($1Na_2O{\cdot}2CaO{\cdot}3SiO_2$), with P_2O_5 remaining in solid solution, whereas the thermal treatment cycle chosen for Biosilicate® 2P allowed the phosphate ions to form an additional crystalline phase with calcium, thus creating apatite crystals. All cones were individually sterilized in ethylene oxide prior to use *in vivo*. The animals were divided into three groups that differed by type of conical biomaterial implanted, and were sacrificed at 7, 90 and 180 days after placement of the cones in the eviscerated scleral cavity. Over the whole follow-up period, none of the animals experienced orbital infection or implant migration/extrusion, and the morphological analyses revealed the formation of a fibrovascularized pseudo-capsule around all the implants. The 45S5 Bioglass® and Biosilicate® 1P implants induced lower inflammation and less pseudo-capsule formation compared to Biosilicate® 2P. The inflammatory reaction reached the maximum at 7 days after evisceration and cone placement, and then gradually diminished in all groups, especially in the 45S5 Bioglass® group. Similar results were obtained by the same research group in a second study carried

out in 45 eviscerated rabbits [68]. On the basis of these animal studies, they concluded that Biosilicate® 1P could be a promising alternative to 45S5 Bioglass® for the management of the anophthalmic socket, as it elicited neither systemic nor local toxicity in the orbit of eviscerated rabbits.

Hence, an early clinical trial (intervention phase III prospective study) on this type of glass-ceramic was performed at two Brazilian University Hospitals (the Clinic Hospitals of the State University of São Paulo (UNESP) and University of São Paulo (USP)) from 2013 to 2016; the results of these studies in humans are shortly reported here for the first time. Forty-five patients were randomly recruited (with no differences of age, gender and eye laterality) and separated according to the type of material implanted, i.e. Biosilicate® 1P (received by two thirds of patients) or PMMA (received by one third of patients), used as a control. All implants were conic with identical design, available in two sizes (16 and 18 mm), and were manufactured individually by Prof. Oscar Peitl at the Laboratory of Vitreous Materials (LaMaV) of the Federal University of São Carlos, São Paulo, Brazil (Figure 3b). Unlike the simple cones previously placed in rabbits [67,68], these tapered implants exhibited a new design with two circumferential channels promoting the physical attachment to soft orbital tissues and also bio-integration. A proper milling/cutting/polishing equipment was designed and developed to guarantee the reproducibility of channel positioning and dimensions (depth and width) as well as surface finishing of all glass-ceramic implants. Clinical evaluations were performed preoperatively and at 7, 30, 60, 120 and 180 days after surgery. Systemic analyses, laboratory tests and computed tomography (CT) of the orbits were performed preoperatively and 180 days after surgery. Thirty-eight patients completed the whole follow-up of 180 post-surgical days: both Biosilicate® 1P and PMMA conical implants resulted in a good clinical outcome, with no significant infectious or inflammatory processes. Only one patient from PMMA group experienced early extrusion of the implant, and another one from the same group had conjunctival dehiscence, which was spontaneously solved; both problems were supposed to be related to the operative technique rather than the type of

material implanted. CT analyses showed no migration of the implants of both materials in all examined patients over the follow-up period (Figures 3c and d), and laboratory analyses revealed no damage or apparent alteration in vital organs associated to the ionic dissolution products released from Biosilicate® 1P.

It is interesting to underline that, although not exhibiting an interconnected network of macropores, facilitating fibrovascular ingrowth, Biosilicate® tapered implants showed great promise from a clinical viewpoint due to the excellent biocompatibility, bactericidal activity – which positively contributes to minimizing post-operatory infections – and overall positive biological response around the implant and in the orbital tissues. The relationship between this highly favorable behavior and the ionic dissolution products released by the material, as well as the impact of these ions on angiogenesis and typical pathogens involved in ocular infections, deserve to be further elucidated in future studies.

4. CHALLENGES AND PERSPECTIVES

4.1 Optimizing pore features/surface roughness and implant selection

The presence of an interconnected network of open macropores or channels in orbital implants inherently promotes fibrovascularization, which was reported to occur faster in ceramic implants compared to the relatively cheap polyethylene due to the more favorable surface chemistry for tissue ingrowth [11]. In the search for a less-expensive non-polymeric alternative to macroporous sintered alumina, sponge replication has been recently proved to be a highly promising method to fabricate glass-ceramic porous orbital implants due to easiness of execution, low cost and high versatility [69]. A nearly-inert glass composition ($57SiO_2$-$30CaO$-$6Na_2O$-$7Al_2O_3$ mol.%) was used to manufacture $CaSiO_3$-containing foams having a network of open pores (total porosity 55 vol.%, mean pore size 240

μm) potentially available for fibrovascular tissue ingrowth (Figures 4a and b). These implants were enough strong (compressive strength 20 MPa) to permit safe manipulation during surgery as well as postoperative integrity, which was also assured by excellent chemical stability in contact with biological fluids. This study pointed out that sponge-replicated glass-ceramic implants exhibited a similar pore-strut architecture compared to alumina implants (Figure 4c), but were markedly different from porous polyethylene implant (Figure 4d).

Other silicate glass-ceramic porous implants of similar composition ($57SiO_2$-$34CaO$-$6Na_2O$-$3Al_2O_3$ mol.% (SCNA)) were also fabricated by foam replication [70]. Very interestingly, the surface roughness (R_a) of these SCNA-based implants measured by contact profilometry was 2.5 times lower than that of porous alumina (300 vs. 750 nm), which to date is considered as the "gold standard" option by many ophthalmic surgeons. Atomic force microscopy (AFM) carried out on the same samples confirmed these early results and, furthermore, suggested that SCNA-derived glass-ceramic implants have comparable surface roughness to porous polyethylene, too [71]. A similar trend of the ranges of surface roughness was also found by examining foam-replicated glass-ceramic orbital implants based on a six-oxide glass composition ($45SiO_2$-$26CaO$-$15Na_2O$-$7MgO$-$4K_2O$-$3P_2O_5$ mol.% (CEL2)) [70]. From a clinical viewpoint, this is a potentially very important achievement since lower the surface roughness, lower the risk of conjunctival abrasion in vivo, and better the postoperative performance of a given implant.

Although favorable surface roughness and pore characteristics can indeed support the suitability of glass-ceramic materials (in this case, SCNA and CEL2) for making porous implants, a more robust approach is needed to reliably compare them to the other available solutions. When those studies were published [69-71], a widely accepted criterion to "globally" compare the structures and topographical characteristics of orbital implants did not exist. In order to bridge the gap, following a conceptualization previously adopted to compare tissue engineering scaffolds with spongy bone

[72,73], Baino et al. [74] tackled the challenge of developing an objective and quantitative approach for scoring porous orbital implant materials with different microstructural characteristics. In order to compare the micro-architecture of pairs of implants (e.g. porous glass-ceramic vs. alumina or polyethylene), a multiparametric orbital implant similarity score (OrbISS) was defined as the squared distance between the materials in the six-dimensional space of the six selected key features, i.e. total porosity, pore interconnectivity, specific surface area, pore connectivity density, degree of anisotropy, surface roughness – which were all previously assessed by micro-CT – and surface profilometry. According to its definition, the smaller this "global" index, the more similar the two samples of the pair. It was assessed that SCNA- and CEL2-derived glass-ceramic implants were similar to each other and to the alumina implant, while all ceramic implants were highly different from the porous polyethylene. These similarities and differences (e.g. in terms of pore size/shape and strut thickness) can be roughly seen by visual inspection of micro-CT reconstructions (Figure 5) and confirms previous SEM observations [69] (see Figure 4). This approach can be easily extended to quantify how new glass and glass-ceramic porous implants are morphologically "distant" from reference (commercial) implants.

This similarity index could also be exploited for predictive purposes, as the clinical performance of orbital implants strongly depends on the material-related parameters included in OrbISS. Its use could make the selection of orbital implants less arbitrary and less dependent on the skills and personal preference of ophthalmic surgeons. Future studies should be addressed to improve the prediction capability of OrbISS by incorporating additional parameters not limited to implant architecture, such as ion dissolution kinetics – if relevant – and therapeutic effects of ions, and appropriate weights for each parameter, thus taking into account the relative importance correlated to clinical performance. In principle, the concepts behind the original OrbISS, developed for foam-like

monophasic implants, can be extended to other pore/wall geometries and even multi-material formulations.

Additive manufacturing (AM) of bioactive materials and composites has recently gained increasing interest in the biomedical community and is currently regarded as the last frontier of medical implant fabrication as it allows an accurate design and control of their internal structure [75]. AM-based approaches have been widely employed to develop tissue-engineering bioactive glass scaffolds for the repair of bone and osteochondral defects [76]; however, their applicability in ophthalmology is still limited to few studies addressed to orbital floor repair (45S5 Bioglass® porous meshes produced by stereolithography [77] or laser-cladded non-porous plates [78]). At present, AM in the field of orbital implants has not been experimented yet, albeit carrying an enormous potential; this gap deserves to be bridged in the next few years.

4.2 Antibacterial properties

Orbital implant infections, which are usually contracted as a result of implant exposure and colonization by bacteria, can be effectively treated by systemic antibiotics – if the implant is vascularized – or local therapy. Implant removal is the most drastic remedy that is carried out if the infection does not resolve pharmacologically, thereby implying additional cost and stress to the patient. [79-81]. Ophthalmic surgeons use to dip porous orbital implants in an antibiotic solution prior to implantation in the orbital cavity [82]. Although this approach is useful intraoperatively, it is ineffective in the long term to combat late or exposure-related infections. Furthermore, the abuse of antibiotics over the last decades has led to the development of resistant bacterial strains [83], which are a global challenge for the 21st century and need to be treated by following different approaches.

At present, neither commercial orbital implants nor external ocular prostheses provided with inherent antiseptic properties are available on the market and, in general, there is a paucity of studies in this field. An acrylic ocular prosthesis embedding small amounts of silver nanoparticles throughout its volume (300-700 ppm) has been patented and proved to be effective against various bacterial strains *in vitro* (*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*) [84,85], but did not reach clinical applications yet. Another patented strategy involves the sputter-deposition of an antibacterial layer on the walls of orbital implants and on the rear surface of acrylic ocular prostheses (i.e., the area in contact with the conjunctiva) [86]. This coating is made of silver nanoclusters (10-50 nm) embedded in a pure-silica glass matrix and is highly stable from chemical and mechanical viewpoints under dry conditions up to 500 °C [87]. Upon soaking in biological fluids, the coating tends to progressively solubilize over time releasing silver ions that exert a potent antibacterial effect for above 1 month *in vitro* [88]. The antibacterial effect of silver ions (Ag^+) is associated with the strong binding of silver with disulfide (S–S) and sulfhydryl (–SH) groups located on the proteins of microbial cell walls. After the bonding with silver, the metabolic processes of bacteria (e.g. oxidative metabolism and uptake of nutrients) stop, thereby leading to cell death [89]. This is a key advantage over the systems that release silver nanoparticles instead of ions, as the formers are associated to both acute and long-term toxicity and pose critical safety issues [90]. The intensity and duration of the antibacterial effect elicited by the sputter-deposited layer can be tailored by modulating the silver concentration (through acting on the deposition parameters like power and pressure in the sputtering chamber), the metal nanocluster size (which increases if post-sputtering thermal treatments are applied within 500-600 °C), and the coating thickness (from tens of nanometers to few micrometers) [91].

A conceptually-similar approach, based on the deposition of an antibacterial glass-based surface layer, was reported by Ye et al. [92] who coated porous hydroxyapatite orbital implants with a Cu-doped mesoporous bioactive glass (MBG). MBGs are generally produced by incorporating

supramolecular chemistry (evaporation-induced self-assembly (EISA)) in the sol-gel method and are well recognized as versatile platforms for the controlled release of a number of drugs and therapeutic ions [93]. The aim of that study was to synergistically combine the antibacterial effects of released copper ions, which are able to kill bacteria via the generation of reactive oxygen species (ROS), lipid peroxidation, protein oxidation and DNA degradation [94], and ofloxacin, an antibiotic hosted inside the mesopores (diameter from 3 to 5 nm). MBG coatings doped with 2 or 5 mol.% of CuO were deposited by dipping of the hydroxyapatite implant in the sol and then consolidated via thermal treatment (Figure 6). *In vitro* tests showed that both Cu-doped implants inhibited the viability of *Staphylococcus aureu*s and *Escherichia coli*; the antibacterial halo increased from about 12 to 15 mm as the copper content increased, although the drug loading and release capacity was less efficient in the samples with higher copper concentration. This trend apparently suggests a predominant antiseptic effect associated to the release of copper ions.

It is worth highlighting that the coating-based approaches are successful in fulfilling two apparently irreconcilable requirements of these orbital implants, i.e. the need for a permanent material (the skeleton lying underneath the coating) combined with the release of antibacterial ions (silver, copper) that occurs as the glass layer dissolves over time.

Another aspect also deserves to be highlighted: some bioactive glass compositions were shown to elicit an inherent antiseptic activity, without the need for doping with specific metallic cations, due to the local increment of pH associated to the release of alkaline ions (primarily Na^+ and Ca^{2+}) in the biological fluids. Perhaps the most famous example is represented by the S53P4 glass ($53SiO_2$–$23Na_2O$–$20CaO$–$4P_2O_5$ wt.%), which is commercially sold as an antibacterial product (BoneAlive®, BoneAlive, Turku, Finland) for oral and dental applications. Stoor et al. investigated the effect of S53P4 on a wide range of oral pathogens in a series of studies carried out in humans [95-97]. S53P4 paste was reported to exhibit a potent and relatively fast antimicrobial effect (from 10 to 60 min

depending on the type of bacteria) in inhibiting the viability of microorganisms of both supra- and sub-gingival plaques [97]. S53P4 granules and discs were also used as interpositional implants in 11 human patients suffering from nasal septum perforations; successful closure was obtained in 10 cases and no implant extrusions or infections in the nasal cavity were reported over 37 months of follow-up [98]. Good clinical outcomes were also obtained in the treatment of atrophic rhinitis associated to *Klebsiella ozaenae* [97]. Future investigations should address the antiseptic properties of S53P4 composition against the pathogens commonly associated to ocular infections and failure of orbital implants in order to assess its suitability for this new application. Furthermore, similar studies should be also performed on 45S5 Bioglass® and Biosilicate®, which have already been successfully used for producing orbital implants; surprisingly, there is a lack of relevant reports in the literature on this specific point.

To combat infections through the action of antiseptic metal ions released from implant surfaces is a valuable and promising strategy in many biomedical fields [98]. However, several peculiar parameters related to the "working conditions" of orbital implants and external ocular prostheses should be taken into account for designing clinically-safe biomaterials: for example, the interaction of metal ions with ocular secretions, the fate of released ions, and the associated risk of local storage and tissue necrosis are all issues deserving careful consideration. An extreme case of corneal argyrosis was reported in a 67-year-old woman wearing silver nitrate-coated cosmetic soft contact lenses over 17 years for the treatment of diplopia [99]: this is a typical example of how an unknown and unpredicted ion-related side effect may be revealed only after many years of follow-up.

4.3 Improving fibrovascularization

Besides exerting an antibacterial effect, copper ions are known to regulate the expression of many factors involved in angiogenesis, such as VEGF, FGF1/2, fibronectin, angiogenin, collagenase,

prostaglandin E-1 and ceruloplasmin, which have key roles in initiation (vasodilation and vascular permeabilization), maturation (endothelial cell proliferation, migration and morphogenesis), and regulation of blood vessel formation [100,101]. From a biomolecular viewpoint, copper-induced angiogenesis is thought to be related with the MAPK signaling pathway, leading to endothelial cell sprouting [102]. This property can be helpful to accelerate wound healing, as shown in some animal studies (rat model) [103-105]. Based on this evidence, Baino first suggested in 2015 [106] that the Cu-doped MBG coating developed by Ye et al. [92] could be useful to promote fibrovascularization in porous orbital implants due to controlled delivery of copper ions. This hypothesis was actually verified *in vivo* in 2018 by Ye's group [107], who performed primary angiogenic tests in a panniculus carnosus muscle model in rabbits and reported that the Cu-doped glass coating significantly accelerated the vascularization of porous hydroxyapatite orbital implants compared to Cu-free materials.

Incorporation of copper in glass-ceramic orbital implants was also reported using a nearly-inert alumina-silicate glass as a base material [108]. In a first approach, melt-derived Cu-doped strong macro-porous scaffolds (compressive strength about 20 MPa) were produced by sponge replication, but the release of copper ions was inadequate to elicit a therapeutic effect. The second strategy, involving the deposition of a thin Cu-doped MBG layer on the walls of the previously-prepared porous glass-ceramic foam, allowed a more sustained release of copper to be achieved, thereby motivating further research on the biological suitability and therapeutic effects of these glass-based materials.

5. CONCLUSIONS

Although bioactive glasses cannot recover the sight of an enucleated or eviscerated patient, they can indeed contribute to replace volume in the anophthalmic socket, improving the appearance and self-esteem, and facilitating the reintegration of the individual into society. Bioactive glasses can also

improve the success of the surgical procedures and the performance of the orbital implants by imparting appealing added value and extra-functionalities. Through the local release of therapeutic ions (e.g. copper), bioactive glasses carry the potential to accelerate implant vascularization, which is the key to ensure an adequate bio-integration and motility of the orbital implant as well as a valuable mean to reduce the risk of postoperative infections. A direct antibacterial effect can be exerted by other ions embeddable in the glass implant, such as silver, and thus multifunctional implants provided with both antiseptic and pro-angiogenic properties could be obtained. Other advantages of using bioactive glasses include the low cost compared to sintered ceramic implants, which require higher processing temperatures, and tunable surface roughness that can be properly decreased to minimize the risk of conjunctival abrasion *in vivo* and implant exposure. Glasses are also relatively easy to manufacture in various porous or non-porous forms, and can be incorporated as bioactive inclusions in a polymeric soft matrix (Medpor® Plus™ Sphere). The application of bioactive glass and glass-ceramic implants after enucleation or evisceration is yet in its beginning and is less popular compared to other "traditional" areas of application, like orthopedics and dentistry, but is expected to emerge in the next few years, thus further expanding the benefits of glass in medicine.

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Figure legends

Figure 1. Schematic illustration showing a spherical orbital implant placed in the anophthalmic cavity after enucleation. The orbital implant can be (a) "buried" under the patient's conjunctiva ("non-integrated" implant) without any mechanical connection to the ocular prosthesis or (b) connected to the ocular prosthesis by a peg ("integrated" implant). Pegged implants, although allowing a wider range of movements to the ocular prosthesis, are seldom adopted nowadays due to the need for a second surgery for peg placement. Image reproduced from [71].

Figure 2. Overview of the main biological responses that can be elicited by the ionic dissolution products released from bioactive glasses once implanted *in vivo* (bone regeneration, angiogenesis, antibacterial effect). Image reproduced from [98].

Figure 3. Biosilicate®-derived glass-ceramic orbital implants: (a) conical implant used in eviscerated rabbits; (b) tapered implants with circumferential channels used in human patients (two sizes available: left 18 mm, right 16 mm); (c) coronal and (d) sagittal tomographic imaging of a patient receiving a 16-mm long Biosilicate® tapered implant in the left orbit, with good positioning without migration and successful maintenance of the orbital volume after 180 days of follow-up. Images (a) and (b) courtesy of Oscar Peitl, (c) and (d) courtesy of Simone M. Brandão.

Figure 4. SEM micrographs showing the porous structure of (a) experimental glass-ceramic implant (composition: $57SiO_2$-$30CaO$-$6Na_2O$-$7Al_2O_3$ mol.%) with (b) detail of the surface showing $CaSiO_3$ crystals, (c) alumina implant, and (d) Medpor® sphere. The glass-ceramic and alumina implants exhibit

a typical foam-like architecture, whereas the porous polyethylene have irregular pores with non-uniform and irregular struts. Images reproduced from [69].

Figure 5. 3D micro-tomographic reconstructions of representative sub-volumes of different orbital implants: (a) SCNA-derived glass-ceramic (glass composition: $57SiO_2$-$34CaO$-$6Na_2O$-$3Al_2O_3$ mol.%), (b) CEL2-based glass-ceramic (glass composition: $45SiO_2$-$26CaO$-$15Na_2O$-$7MgO$-$4K_2O$-$3P_2O_5$ mol.%), (c) alumina, (d) Medpor® sphere. Images reproduced from [74].

Figure 6. MBG-coated porous hydroxyapatite orbital implants: (a) overview of the porous surface, (b) interface between hydroxyapatite and Cu-doped MBG coating, (c) typical mesoporous texture (assessed by high-resolution TEM) of the MBG layer. Images adapted from [92].