REVIEW PAPER

Applications of Bioceramics in the Management of Orbital Floor Fractures and Anophthalmic Cavity: A Review

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Abstract: *Biocompatible ceramics, commonly known as "bioceramics", are an extremely versatile class of materials with a wide range of applications in modern medicine. Given the inorganic nature and physico-mechanical properties of most bioceramics, which are relatively close to the mineral phase of bone, orthopedics and dentistry are the preferred areas of usage for such biomaterials. Another clinical field where bioceramics play an important role is oculo-orbital surgery, a highly cross- and interdisciplinary medical specialty addressing to the management of injured eye orbit, with particular focus on the repair of orbital bone fractures and/or the placement of orbital implants following removal of a diseased eye. In the latter case, orbital implants are not intended for bone repair but, being placed inside the ocular cavity, have to be biointegrated in soft ocular tissues. This article reviews the state of the art of currently-used bioceramics in orbital surgery, highlighting the current limitations and the promises for the future in this field.*

Keywords: *Hydroxyapatite, Bioactive glass, Composites, Orbital floor, Orbital implants.*

1. INTRODUCTION

Biomaterials are natural or synthetic materials used to replace parts of a living system or to evaluate, treat, augment or replace tissues, organs or functions of the body [1-3].

Biomaterials are available in various physical forms such as particles, blocks (dense or porous), injectable compositions, powders, granules, self-setting cements and composites, coatings and fibers. Biomaterials may have diverse origin (natural, biological or synthetic) and can be applied to fabricate implants, prosthetic devices and three-dimensional (3D) scaffolds of specific shapes and dimensions [4-6].

Implantable materials should ideally be non-toxic, stable, biocompatible, capable of supporting cell colonization but avoiding bacteria adhesion and, according to the chemical composition, can be classified into: biometals, biopolymers, bioceramics and biocomposites.

According to the type of interaction with the tissues, materials can also be categorized as bioinert or bioactive. Bioinert is a material with minimal or absent adhesion between the implant and the host tissue, inducing the formation of a thin fibrous pseudo-capsule around the implant. Typical examples include non-resorbable polymers like polyethylene (PE).

Bioactive implants have a controlled action and reaction with the surrounding tissues in a dynamic process, with the possibility of the host cells to recover the surface or colonize pores within the implant if these are present, dissolving slowly and promoting the formation of a surface layer of biological apatite interfacing directly with the tissue at the atomic level, which results in a tight chemical bond to the host tissues (primarily bone). The bioactivity of the material is determined by molecular, chemical and physical factors, such as inherent composition, electrical forces, surface roughness, topography and porosity.

Bioactive materials can be absorbable or non-absorbable. Non-absorbable are those that remain *in situ* over the whole life of a person without undergoing any significant degradation over time. Bioresorbable materials can have size reduction with time due to the chemical reactions that occur upon contact with body fluids and living cells.

Some bioresorbable implants can dissolve over time allowing a newly formed tissue derived from host tissues to replace the original structure. Recently, bioresorbable materials are pointed as a perfect solution to solve problems of the interface between the host tissues and the implant as the foreign material can be ultimately replaced by regenerating tissues [7]. The absorption of the implant is related to some biophysical aspects. A non-porous and dense material, such as highly crystalline hydroxyapatite (HA), can be retained in an organism for at least 5–7 years without any noticeable changes, while the same material in a highly porous or nanometrical formulation can be resorbed approximately within one year [8].

Bioceramics are inorganic materials of natural, biological or artificial origin with structural functions as joint or tissue replacement and are used in a number of different medical applications such as bone fillers, surface coatings to improve the biocompatibility of permanent implants, porous scaffolds or even drug delivery systems [1, 6].

Since the 1980s, bioceramics have been variously combined to produce composites. They can be manufactured with different surface properties, texture and compositions, usually associating bioinert and bioactive materials to improve mechanical and biological properties [9]. In general, modern bioceramics comprise various polycrystalline ceramics, glasses, glass-ceramics as well as ceramic-filled bioactive composites and might be prepared from alumina, zirconia, carbon, silica-based and calcium-containing compounds, as well as some other chemicals. All of them might be manufactured in both porous and dense form, in bulks as well as in form of powders, granules and/or coatings [6, 10].

Bioactive glasses are ideal biomaterials due to their exceptional versatility in terms of composition and related functional properties [11-13]. Recently, bioactive glasses have been investigated as platforms for embedding and then releasing therapeutic metallic ions that can be added during the glass synthesis via either the melt-quenching route or the sol-gel method. For example, copper-doped silicate glass-ceramic implants can improve angiogenesis and elicit antibacterial properties via the controlled release of Cu^{2+} ions, thus facilitating the bio-integration with host tissues [14, 15].

The biochemical reaction with the *situs* of implantation may also induce local or systemic toxicity. Toxic concentrations of the ionic dissolution products from bioactive ceramics and glasses may trigger local inflammatory reaction and septic rejection, resulting in extrusion of the material. Systemic reaction to the implanted biomaterial may evolve with formation of antigens and cause immune reactions ranging from simple allergies to severe health consequences [5].

Bioceramics are traditionally applied to repair hard tissues, such as bone and teeth. Recently, some special bioactive glass compositions have also been found suitable for applications in contact with damaged soft tissues, such as wound healing [16, 17], peripheral nerve regeneration [18, 19] and cardiac tissue repair [20, 21]. In ophthalmology, bioceramics can be used to repair orbital fractures or to replace the lost eye volume in anophthalmic socket reconstruction. Inert and relatively less stiff biomaterials, such as synthetic polymers (e.g. poly(methyl methacrylate (PMMA)), are often preferred in contact with the delicate ocular tissues and structures. Apart from being used to make non-porous orbital implants, PMMA is widely applied for other ophthalmic purposes including rigid and semi-rigid contact lenses or intraocular lenses due to its excellent biocompatibility with ocular tissues and transparency to visible light [22].

This review provides a picture of the clinical applications of ceramics and related composites in ocular surgery, highlighting the tissue-material interactions as well as the open challenges in this field.

2. APPLICATIONS IN ORBITAL FRACTURE REPAIR

The orbit is a pyramid-shaped cavity, with anterior base and posterior-medial apex, composed of four walls: lateral wall, medial wall, floor and the orbital roof. The orbit has communications with neighboring regions through orifices located on the orbital walls. Due to the low mechanical resistance of the thin orbital walls, there is a high frequency of fractures located in the orbital floor, zygomatic-maxillary and zygomatic-frontal sutures [23], occurring isolated or as part of complex traumas of the face. Restoration of orbital walls can be necessary to the reposition of the orbital volume since it plays a vital role to solve enophthalmos, to restore

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movements of the globe, and to improve diplopia [23].

Fracture of the orbital bones can be repaired by using transplant materials (mainly autografts; see Table 1) or alloplastic implants (Table 2). Autologous biomaterials are cost-effective and elicit no immunogenic response in the host but are associated to increase of intraoperative time due to the need for additional surgery, can cause morbidity at the donor site and can be associated to variable rate of resorption [24].

As an alternative to bone transplantation, man-made biomaterials can be applied for orbital fracture repair; in this regard there are many options, being the choice determined by characteristics of the patient, the fracture itself and disposable materials. Place and size of the defect, presence of quantitatively adequate and stable bone, need for orbital rim reconstruction, mechanical and biological properties of the materials, availability and costs are all factors that play a crucial role in the surgeon's decision.

Inert or bioactive as well as non-porous and porous materials can be used. Porous implants have higher specific surface area compared to bulk ones, thus guarantying a good mechanical fixation via tissue in-growth and providing sites that allow chemical bonding between the bioceramic surface and bones decreasing the risk of migration and extrusion [5].

The contact of bioceramics with orbital bone can typically result in four characteristic reactions: osteo-integration (ability to establish a chemical bond with the host tissue without the formation of a strong fibrous capsule); osteo-conduction (ability to support the growth of orientated blood vessels and new Haversian systems in the interfacial region between the implant and the bone); osteo-induction (activation of pluripotent stem cells leading to their differentiation to an osteoblastic phenotype); or osteogenesis (synthesis of new bone by osteoblasts within the graft) [2]. Porous blocks of coralline or synthetic HA are typically osteo-conductive [25, 26] while monolithic non-porous plates of S53P4 bioactive glass ($53SiO_2$-$23Na_2O$-20%CaO-$4P_2O_5$ wt.%) were found to stimulate osteogenesis in human patients' orbital defects [27]. However, all these types of ceramic and glass implants are brittle and rigid, thus being difficult to be shaped intraoperatively by the surgeon.

Polymeric implants such as porous PE thin sheets (Medpor® line) can also be used for the surgical repair of orbital floor fractures, with the advantageous possibility to be easily cut the sheet in the exact needed size and also to mold it to fit the defect dimensions during surgery. Comparison between porous PE and HA showed that HA is more fragile, more expensive, and cannot be easily shaped intraoperatively [23, 24, 28].

Composite implants of calcium phosphate cement associated to porous PE or porous PE associated to titanium meshes was already proved to be useful biomaterials in the reconstruction of the orbital region. Specifically, the porous PE/titanium composite implants (Medpor® Titan) allow greater fibrovascular integration and decreased risk of postoperative complications compared to the porous PE or titanium used alone, combining the high stability and strength of the tradition titanium mesh with the pliability of the polymer [29].

HA/porous PE composites, marketed under the commercial name "HAPEX", are also currently used in the clinical practice for the repair of orbital floor fractures [9]. In addition, a bioactive composite comprising a porous PE matrix with 10% of glass particles (unspecified composition) was successfully tested and recently approved as a promising biomaterial to repair the zygomatic complex in humans [30].

Table 1. Ceramics of biological origin employed for making orbital bone repair implants that are used in humans.

Material	Implant format	Notes
Autologous human bone	Shapable sheet	Resorption rate depending on bone type (cancellous, cortical) and source (harvesting site).
Bone homograft	Shapable sheet	Allogenic bone banks are available to surgeons.
Bovine bone	Shapable sheet	Resorption rate faster than human host bone.
Coralline HA	Porous plate	Commercial product: Biocoral®. Problems of brittleness upon implantation.
Algae-derived HA	Porous plate	Commercial product: AlgOss-C Graft/Algipore) implant

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Table 2. Synthetic ceramics employed for making orbital bone repair implants that are/were used in humans.

Class	Material or combinations	Implant format	Notes
Synthetic calcium phosphates	Synthetic HA	Porous plate	Problems of brittleness during implantation
Bioactive glasses	Melt-derived S53P4 glass	Solid plate	Slowly resorbable
Composites	HA/PE	Porous plates	Commercial product: HAPEX®
	Periosteum joined to a HA/PLLA/PCL sheet	Sheet	Absorbable implant
	HA/PLLA	Plate	
	HA cements	Mouldable paste	
	Fibrin-rich β-TCP/HA biphasic calcium phosphate	Mouldable paste	
	Alumina/PTFE (Proplast II)	Sheet	Currently abandoned

Development of multifunctional implants acting as drug delivery systems can offer great promise to improve bone regeneration and direct patient's own tissue remodeling [23]. The use of tissue engineered polymeric constructs, such as BMP-loaded hydrogels, in the treatment of orbital floor and general maxillofacial fractures can significantly promote bone regeneration, thereby accelerating orbital injury healing; furthermore, BMP-induced accelerated bone in-growth inside the implant can contribute to overcome the problems related to the polymeric matrix integrity and decrease of mechanical support over time [31] (Fig. 1). Despite of being very promising and attractive, the safety and efficacy of these recent developments have not been verified in humans yet.

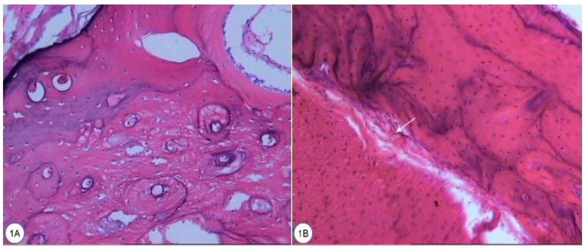

Fig. 1. Bone morphogenetic protein (BMP) implant after 6 months of implantation in an experimental rabbit orbital floor fracture model: (A) newly-formed bone with areas of matrix resorption; (B) compact portion of the BMP implant and mature bone coated by periosteum (arrow) attached to the neighboring structures. (Hematoxylin-Eosin, 40X).

Complications related to the implants that are currently applied in orbital fracture repair include migration, extrusion, infection, foreign body reaction, fibrous encapsulation, persistent enophthalmos, intra-orbital epithelial cyst formation with secondary globe elevation or proptosis, sinus-orbital fistula, intra-orbital sinus mucocele, carotid cavernous fistula and others [23, 24].

3. APPLICATIONS IN ANOPHTHALMIC SOCKET REPAIR

Anophthalmic socket is the absence of the eye in the orbital cavity as a result of congenital (Fig. 2) or acquired diseases, such as severe trauma, systemic or eye diseases resulting in blind and painful eye (chronic uveitis, absolute glaucoma, proliferative diabetic retinopathy) or extensive intraocular tumors (melanoma, retinoblastoma).

Fig. 2. Examples of congenital diseases needing anophthalmic socket management: (A) bilateral congenital anophthalmic socket in a child with socket volume reduced associated to brow, lashes and eyelids alterations; (B) child with microphthalmia at the right side.

After the removal of the eye (enucleation) or its content (evisceration) it is necessary to replace the lost volume of the orbit to avoid important transformations such as contracture of the

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extrinsic ocular muscles, reduction of the conjunctival fornices and repositioning of the orbital fat, often resulting in enophthalmos, lower eyelid deformities and blepharoptosis [32]. The lost volume can be replaced by using autologous, homologous, heterologous or synthetic materials as implantable biomaterials.

3.1. Implants to replace volume in the anophthalmic socket – an overview

The ideal orbital implant is the one which can provide adequate volume replacement, good motility of the external prosthesis and low rate of complications (exposure, extrusion, infection or migration); furthermore, it should be well tolerated in the host tissues and accessible to a (relatively) low cost [33]. In other words, the orbital implant should be permanent, replacing definitively the lost eye volume, be buried inside the orbit using simple surgical techniques, be biocompatible, not induce local or systemic inflammation or toxicity, and be available with low costs to the patient.

Historically since the beginning of the 20th century, the need to replace the lost volume to the anophthalmic socket was emphasized. Hollow glass spheres with a smooth surface were the first non-integrated and very weightless implants used for this purpose. The glass sphere was the principal material applied until the 1940s. After that, several other materials were suggested. However, PMMA and silicone, being both inert, highly biocompatible, non-porous and non-integrated implants, still are the most widespread all over the world [34, 35].

Around the 1950s, porous (or integrated) materials were suggested to be applied in many medical fields and they were introduced in the anophthalmic socket reconstruction in the 1980s. The first integrated implant used to replace the lost volume in the anophthalmic socket was the natural porous HA derived from corals (Bio-Eye®). The interconnected porous structure of the natural HA implant allows host fibrovascular in-growth with the possibility of coupling the implant to the external prosthesis using pegging, thus improving the mobility of the artificial eye [36]. Theoretically, the porous implant can also reduce migration and decrease the infection rate of the implant due to the presence of a blood supply within the pores.

After the advent of coralline HA with its associated good outcomes in terms of success rate [37], the scenario of the anophthalmic socket reconstruction changed and new types of porous implants were suggested such as the synthetic HA [38], the porous PE [39], and the alumina spherical or conical implants [40, 41].

Other less common porous materials were also suggested over the years to replace the volume in the anophthalmic socket reconstruction, including xenografts (bovine bone HA), bioactive glasses, polytetrafluoroethylene and various kinds of composites (Teflon/ alumina, HA/ silicone, HA/ alumina, PE/ bioactive glass) [42].

In general, porous bioceramic implants are highly attractive for the anophthalmic socket management being highly biocompatible and allowing fibro-vascular reaction within their pore network, which lead to high success rate and few complications [43, 44]. Table 3 and 4 collect the different types of natural and man-made ceramics (single-phase or composite materials) that have been used over the years to produce orbital implants.

Apart from coralline and synthetic HA, bioactive glasses and alumina are the most popular materials used for this application. 45S5 Bioglass® ($45SiO_2$- $24.5CaO$- $24.5Na_2O$- $6P_2O_5$ wt%) was first suggested for medical treatments in the 1970s [45] as the unique biomaterial able to both form a tight bond to living bone with a stable interface and stimulate bone tissue regeneration. 45S5 Bioglass® particles were used as bioactive inclusions embedded in porous PE orbital implants (Medpor®- Plus), which are currently available on the market for anophthalmic socket treatment [46-48].

Alumina was proposed in the 1990s in a porous form for the fabrication of fine-grained orbital implants, registered as ‘‘Bioceramic implants’’. Bioceramic (alumina) implants allow better proliferation of fibroblasts inside the pores as compared to Bio-Eye® (natural HA), synthetic HA and PE [49] and their clinical use is associated with less postoperative complications mainly when the orbital sphere is wrapped by sclera [50].

An overview of clinically-used (current and abandoned) ceramic-based orbital implants of natural and synthetic origin is reported in Tables 3 and 4, respectively.

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Table 3. Ceramics of biological origin employed for making orbital implants that are/were used in humans

Material	Implant format	Notes
Ivory	Non-porous sphere	Used till the 1940s and then abandoned
HA derived from heat-treated bovine bone	Porous sphere	Used till the 1940s and considered an excellent alternative to blown glass orbital implants
Bovine bone-derived HA	Porous sphere	Commercial product: Molteno M-Sphere
Coralline HA	Porous sphere and ovoid implants	Commercial product: Bio-Eye®

Table 4. Table 4. Synthetic ceramics employed for making orbital implants that are/were used in humans.

Class	Material or combinations	Implant format	Notes
Synthetic calcium phosphates	Synthetic HA	Porous sphere, ovoid porous implants	Most common commercial products: FCI_3. Few less expensive implants are available worldwide, especially in emerging countries (with problems associated with low purity of HA)
Almost-inert ceramics	Alumina	Porous sphere	Commercial product: Bioceramic implant
Glasses and glass-ceramics	Common silicate glass (non-crystalline ceramic)	Blown sphere	First implant used by Mules in evisceration procedures (1885). The “Mules implant” and its evolutions were the most commonly-used orbital implants till the 1940s
	Biosilicate®	Non-porous conical implants	Promising results in early trials in Brazil
Composites	Carbon/PTFE composite (Proplast I)	Hemispherical implants	Despite the fibrovascular ingrowth and generally good outcomes, it was abandoned in the 1980s due to the high risk of late infections
	Alumina/PTFE composite (Proplast II)	Porous implant having a siliconized non-porous posterior surface to allow smoother movements	It was abandoned due to poor motility and absence of fibrovascular ingrowth
	HA/silicone	Implant comprising a hemispherical anterior part made of synthetic porous HA and a posterior part made of silicone rubber	Commonly known as “Guthoff implant”. It exhibits good postoperative outcomes but has high cost and requires complex surgical procedures of implantation
	45S5 Bioglass®/PE	Porous sphere	Commercial product: Medpor®-Plus. Early evidence of improvement in implant fibrovascularization compared to conventional porous PE; large clinical studies are needed to elucidate this advantage more clearly

3.2. Host tissue reaction – vascularization and inflammatory reaction in integrated implants

The integrated implants are the ones which can develop a reaction with the host tissues or the capability to be vascularized and bonded to the host. A three-dimensional network of pores exists, for example, in the natural HA and allows the in-growth of host fibrovascular tissue inside the implant, making the soft orbital tissues firmly anchored to the implant. However, the pores can be poorly interconnected as in the synthetic HA or in the porous PE, which strongly affects

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the vascularization rate–higher the pore interconnectivity, faster the fibrovascular tissue in-growth. The chemical composition of HA and PE provide several differences in the capability of integration of these porous materials, although both can be considered as integrated implants. HA contains micrometric grains inciting granulomatous inflammatory reaction composed by macrophagic and giant cells that surround the smaller crystals of calcium phosphate with persistent chronic orbital inflammation, possibility of phagocytosis and implant volume reduction as well as bony metaplasia and formation of a dense pseudo-capsule [51] (Fig. 3).

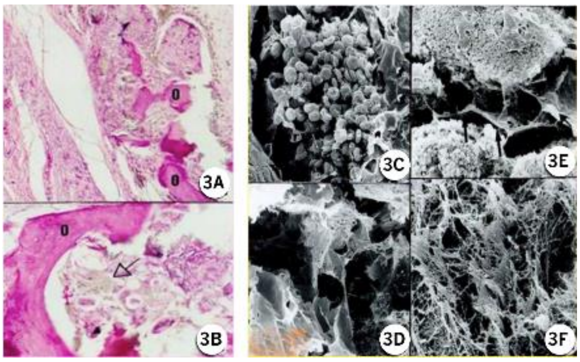

Fig. 3. Synthetic hydroxyapatite in a rabbit anophthalmic socket after 6 months of implantation. (3A, 3B) Histopathology showing intense inflammatory reaction with bone metaplasia (O) and inflammatory granulomatous reaction (arrow) (HE100X). Transmission electronic microscopy evidences the inflammatory reaction (3C) and bone metaplasia (3D, 3E, 3F). Images reproduced from [51].

The porous PE is an inert material and the in-growth of host tissue within the pores is based on a non-specific inflammatory reaction with scarce cells and fibrovascular tissue, inducing a thin pseudo-capsule formation [51] (Fig. 4).
The contact of a bioceramic implant with the soft tissues of the anophthalmic socket can promote the dissolution of part of the biomaterial; in the context of bone regeneration, this bioactive reaction is the key to allow osteogenesis and chondrogenesis to occur at the implant/host tissue interface [2].
Biodegradation of calcium phosphate materials mediated by cells starts shortly after bioceramic implantation, according to a process that is inversely proportional to the Ca-to-P ratio, phase purity and crystal size, as well as being directly related to the porosity and surface area since the surface roughness can strongly influence the activation of mononuclear precursors to mature osteoclasts [5].

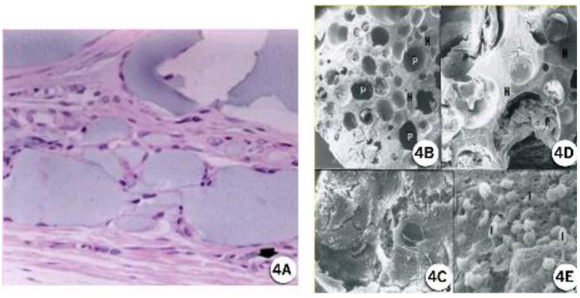

Fig. 4. Porous polyethylene in a rabbit anophthalmic socket 6 months after implantation. (4A) Histopathology showing fibrosis and scarce inflammatory reaction filling the pores (HEX100); Transmission electronic microscopy showing implant pores (P), scarce inflammatory reaction (I) covering parts of the polyethylene and host (H) fibrosis (4B, 4C, 4D, 4E). Images reproduced from [51].

Chronic inflammation can occur many years after orbital implant placement and often can be successfully treated only by implant removal [52].
The inflammatory reaction is much less significant in porous alumina or bioactive glass (Fig. 5) implants which allow good fibrovascular in-growth through the pore network, inducing similar response as porous PE implant, remaining in the patient's anophthalmic socket indefinitely without undergoing any degradation.
Theoretically, the neovessels provide a blood supply within the implant, thereby reducing the risk of bacterial colonization, permitting the treatment of low-grade ocular infections and promoting the spontaneous healing of small conjunctival exposures [53].

Fig. 5. Biosilicate® implant after 6 months in a rabbit anophthalmic socket showing a pseudocapsule around the implant and small granules of glass surrounded by scarce host tissue reaction and fibrosis (HEX100).

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3.3. Role of porosity

Implant pores can be interconnected or not and the size of pores can influence the velocity of colonization by host cells. Pore diameters of 150 μm to 400 μm favor tissue ingrowth. Vascularization, cell migration and nutrient diffusion are required to sustain cell viability and tissue function. Fluids can be transported if pores within the implant are well interconnected. The pore interconnection facilitates nutrient exchange, cell migration and formation of a blood vessel network to allow tissue oxygenation [54]. However, macro-porosity can induce fragility to the biomaterial, which is an issue if there are high stresses applied over the implant intra- or post-operatively [44].

The rough surface of porous ceramic orbital implants can damage the conjunctiva in the anterior portion of the socket inducing dehiscence and implant exposure. In order to decrease the potential damage to the conjunctival tissue, the surgeon can use special surgical technique or use implants composed of two parts, i.e. an anterior smooth polymeric part and a posterior porous ceramic part – which can be fibrovascularized; a typical example is the silicone/ HA Guthoff implant, which however is still relatively uncommon due to the need for a highly skilled ophthalmic surgeon and the high cost as compared to other options [55].

3.4. Format and size of the implants

The implants used to replace the lost eye volume in the anophthalmic socket can vary in format and size. The spherical implants are the most widely used ones in both porous and non-porous forms. Typically, HA and alumina orbital implants are commercially available as porous spheres. There are also other implant formats at the surgeon's disposal, such as ovoid, conic, pear-shaped, "ball-and-ring," and quasi-integrated implants [42]. Porous PE conical implants are available on the market, being very easy to insert into the anophthalmic cavity; however, to date there are no clinical reports about this type of conic implants. A couple of experimental studies performed in rabbits indicated that Biosilicate® (glass composition: 23.75Na_2O- 23.75CaO-48.5SiO_2- 4P_2O_5 wt.%) conic implants had good integration in the orbital tissues with no dehiscence or extrusion [56, 57]; these promising results were later confirmed in early clinical trials in a small cohort of human patients [58].

The size of the implant should be related to the orbital dimensions: smaller implants are used in childhood and usually they need to be replaced when the patients reach the adult orbital size. Diameter can vary from 14 to 24 mm and the most widely-used sphere diameter for adults is of 20 mm. Because of the possible necessity of implant removal and exchange, porous implants are not advocated for the pediatric population, making the non-porous implants the preferred choice in children by the majority of surgeons [59].

The replacement of the exact volume of the socket is difficult. Mainly because of this and aiming to offer the best option to the patients, customized implants with high levels of geometric accuracy could be fabricated by computer-aided design and manufacturing in a variety of sizes according to the necessities.

At present, a number of ceramic and polymeric 3D objects for biomedical applications (e.g. porous scaffolds) are constructed layer-by-layer before surgery through using rapid prototyping techniques such as fused deposition modeling, selective laser sintering, 3D printing or stereo-lithography [60], thus reducing time for implantation procedure and subsequently lowering the risk of complications to the patient. In fact, apart from the great control on the size, shape and internal geometry, another advantage of a prefabricated custom-made implant is that it can be used more effectively and applied directly to the damaged site rather than being molded during surgery from a paste or granular material [61].

3.5. Motility

The main reason behind having porous implants was related to the improvement of motility due to the possibility to have a pegging system linking the orbital implant and the external prosthesis after implant fibro-vascularization [36]. Implant pegging requires careful imaging exams to evaluate the degree of vascularization achieved by the implant to proceed with implant perforation for placing a peg (Fig. 6).

The need for a second surgical procedure to adapt the pegging system carries further costs and the possibility of complications; therefore, the "pegging option" is often refused by patients. In order to overcome these drawbacks, some surgeons have experimented the peg insertion at

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the time of the orbital implant placement, but this practice still remains controversial. Surgical technique variations were suggested to improve motility and to protect the anterior surface of the implant from dehiscence, such as suturing the extraocular muscles crosswise in front of the implant [22]; however, these strategies have led to no or minimal effective improvement of motility. Interestingly, no objective difference has been documented in terms of motility associated with porous or non-porous spherical implants when pegging is not performed.

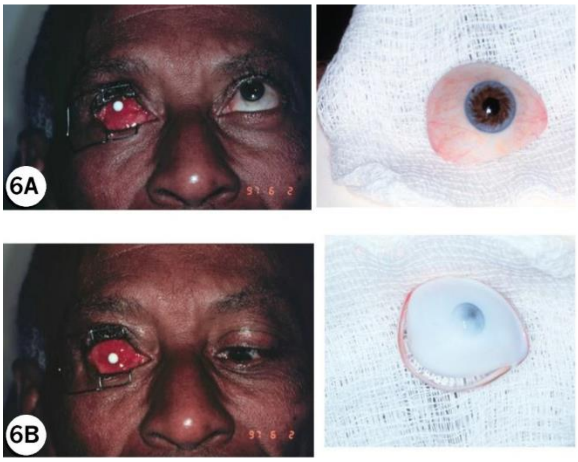

Fig. 6. A patient with anophthalmic socket at the right side and a natural hydroxyapatite implant looking up (6A) and down (6B). The white dot in the center of the socket corresponds to the place to receive a peg. At the right side, the external ocular prosthesis has a depression in the internal portion where the peg can be adapted.

3.6. Wrapping of orbital implants

The integrated and the non-integrated implants can be wrapped in different kinds of soft and smooth materials. Wrapping the implant makes it possible to attach the implant to the extraocular muscles, thus theoretically improving the motility towards a “life-like” situation. A range of wrapping materials have been proposed over the years for use in the anophthalmic socket reconstruction, including biological substances such as autologous or homologous sclera, fascia lata and dura-mater or synthetic materials such as Tutoplast-dura, Vicryl mesh, polyester–urethane and PTFE [62].

Another important reason to wrap the implant, especially if it is made of stiff, and hard ceramic material (e.g. HA), is to decrease the risk of exposure, since the smooth wrapping material acts as a barrier between the overlying delicate and thin conjunctival tissue and the porous and rough orbital implant. The wrap can be used only on the anterior surface of the implant, leaving the posterior portion in contact with the host tissues to improve bio-integration.

3.7. Complications

After some period of the introduction of the integrated implants to repair anophthalmic cavities, several case reports emerged mainly focusing complications such as conjunctival or scleral dehiscence, chronic inflammatory reaction, problems with coupling peg system, implant exposure and colonization of the implant by bacteria, extrusion or necessity of implant removal [63, 64].

Many of these complications were the same found in non-integrated implants and, actually, are possible regardless of the type of implant (integrated or not) being secondary to various causes.

Implant extrusion is more likely observed in non-integrated implants, whereas conjunctival thinning or dehiscence and implant exposure are the most likely associated complication of porous implants due to their porous and rough surface [64, 65].

The dynamic movement of the extrinsic extraocular muscles and orbital implant can facilitate the contact of the implant with the rigid external prosthesis, thus leading to conjunctival and/or scleral dehiscence and exposure of the implant, which becomes a portal of entry for foreign pathogens that may cause implant infection.

The exposure of the implant can induce recurrent pyogenic granuloma, chronic inflammation and conjunctival secretion [63].

Problems after pegging can happen in 50.7% of patients with HA implant [63]. Taking into consideration that implant exposure treatment is not simple and even with flaps or grafts many cases eventually result in implant removal, the pegging system is much less used nowadays.

4. SUMMARY AND FUTURE TRENDS

The role of bioactive ceramics and glasses in medicine is usually associated with the repair of damaged bone in orthopedics and dentistry. When used for the treatment of orbital floor/wall

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fractures, the function of these biomaterials is to accomplish such a purpose and can be considered a particular case of bone healing application. Unlike metals and polymers, HA and other calcium phosphates as well as bioactive glasses can bond to host bone and promote the regeneration of new healthy bone; however, they are rigid and difficult to exactly fit the bone defect dimensions unless applied in the form of moldable cements. From an operative viewpoint, polymeric sheets and even metallic meshes can be much more easily cut and shaped during surgery as compared to brittle monolithic or porous bioceramics. Pliable porous composites, which have been already fabricated by robocasting (e.g. glass/poly-caprolactone) scaffolds with hierarchical porosity from 2 nm to 200 µm [66], could be very suitable to overcome the above-mentioned limitation but no specific studies on their use in orbital surgery has been reported yet. Indeed, significant advantages could be carried by the application of additive manufacturing technologies in the field of orbital bone repair to produce custom-made substitutes with complex geometry, such as the curved shape of orbital walls. These versatile manufacturing approaches have been widely proposed in the field of bone regeneration for fabricating bioceramic and composite porous scaffolds [67], but has been seldom applied in the context of orbital floor reconstruction. Tesavibul et al. [68] suggested that stereolithography can allow processing of 45S5 Bioglass® in the form of porous "sheet" ("nets") that can easily conform to the curved profile of orbital rim. Castilho et al. [69] used 3D printing to fabricate biphasic HA/TCP scaffolds with minimal pore size of 300 µm addressed to the repair of orbital bone defects with complex shape.

If the application of bioceramics for orbital fracture repair falls in the wide class of bone repair, on the other hand the situation is much more complex in the case of orbital implants that are in contact with soft orbital tissues. At present, there is no generally-accepted consensus about the best orbital implant to replace the volume in the anophthalmic socket. A PMMA sphere is the first choice for adults among the Brazilian surgeons [70]. In the UK, 55% of surgeons prefer to use spherical porous orbital implants and 42% prefer PMMA quasi-integrated implants [71].

Despite all the advantages, commercial porous orbital implants still suffer from a non-negligible failure rate and are highly expensive, thereby often pushing patients to choose other cheaper solutions, such as solid polymeric spheres even though not allowing fibrovascular in-growth and, thus, being potentially susceptible to a higher risk of infection due to the absence of a blood supply that ensures host immune response within the implant.

A couple of recent critical studies - a systematic review of randomized clinical trials [72] and another one analyzing several case series [73] - showed that, until now, there is no clear evidence supporting the superiority of integrated orbital implants as compared to non-integrated ones. Some authors reported that acrylic and silicone non-integrated spheres have the lowest rate of complications, especially when used as primary implants [74]. If we consider only the class of porous orbital implants, the advantages of porous PE are mainly the low cost in comparison to HA and alumina and the possibility of suturing the extrinsic muscles directly to the implant without the need for wrapping within a soft material [22]. The use of wrapping materials can be a valuable mean to further increase the clinical success of porous PE implants, but wrapped implants have the same effectiveness of the non-porous polymeric ones [35]. Hence, after balancing pros and cons, Schellini et al. [73] concluded that the use of many currently-available porous orbital implants (mainly HA) is not justified taking into account that they are much more expensive than the non-porous ones. Further randomized clinical trial studies need to be well conducted to find the best solution for this problem.

The higher cost of porous implants could be motivated by a significant clinical advantage: in this regard, an interesting example is provided by the Medpor®-Plus implant, where the bioactive glass coating was advocated to greatly accelerate fibrovascularization. This hypothesis was supported by many studies focusing on the angiogenic properties of bioactive glasses as well as by a couple of specific clinical studies in anophthalmic sockets. Naik et al. [47] investigated the fibrovascular in-growth of Medpor®-Plus implants in comparison with conventional porous PE spheres (Medpor®) in enucleated human patients (five in each group) and reported a statistically significant increase in the vascularization rate for glass-coated implants.

Another research group examined the overall postoperative outcomes in 170 patients receiving a Medpor®-Plus implant after enucleation or secondary implantation and reported an overall success rate of 94.7%, but the comparison with reference implants was missing [48]. Hence, wider and more complete clinical trials are needed to draw definite conclusions.

In the search for less expensive solutions, new silicate glass compositions apart from 45S5 Bioglass® and Biosilicate® have been recently proposed for making porous orbital implants. Early results suggest the feasibility of glass-ceramic implants with adequate porosity to allow fibrovascular in-growth and significantly smoother surface compared to alumina implants [75, 76], which could be a key advantage to reduce the risk of conjunctival abrasion.

Glass doping with specific metallic cations, such as Cu^{2+}, eliciting pro-angiogenic and antibacterial effects has also been investigated to impart extra-functionalities to glass-derived orbital implants [77]. Preliminary results in animals (rabbit model) are promising [78] and encourage further research on these exciting topics.

The use of mesoporous ceramics, and especially mesoporous bioactive glasses, would carry other significant advantages in the context of orbital repair. Such materials are able to host drug molecules within their mesopores (size in the range of 2-50 nm), thus allowing a prolonged release and more effective therapy [79]. The amount of drug incorporated as well as the release kinetics can be designed and tailored as a function of the mesopore shape and size. Specifically, mesoporous ceramics were proved capable to load and then release anticancer drugs [80] that can also be useful for the treatment of orbital bone tumors and intra-orbital cancer, thus killing residual or newly-formed cancer cells around the implant site. New horizons could be potentially opened in the treatment of intra-orbital tumors such as retinoblastoma– which is the major cause of enucleation– as the anticancer drug released by mesoporous ceramics would allow performing a targeted therapy in the region around the severed optic nerve in order to prevent the spreading of cancer cells through it.

It is worth underlining that tumors affecting the orbital bone or ocular tissues are the main non-traumatic cause requiring the surgical resection of orbital bone or the removal of the ocular globe. In all these cases, a double clinical challenge should be faced: it is necessary not only to restore the surgically induced defect, but also to avoid cancer recurrence. In this regard, hyperthermia using implantable magnetic bioceramics shows great promise for the localized treatment of malignant tumors, especially in bone [81]. This special class of bioceramics, when exposed to an external magnetic field, can produce heat within the diseased tissue region, thus killing cancer cells that are sensitive to temperatures above 43 °C; on the contrary, healthy cells can survive in such conditions. Magnetic bioceramics, which are mainly based on magnetite, calcium phosphates, bioactive glasses, and glass-ceramics, can be produced in various forms including nanoparticles, mesoporous ceramics and porous scaffolds [82]. Hyperthermia can also be combined with other therapies, like chemotherapy (drug delivery) and phototherapy [83].

Future research deserves to be addressed also to injectable bioceramic pastes, which could be injected intraorbitally in the region around the severed optic nerve to kill the residual cancer cells that might migrate through it after enucleation.

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