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Biomaterials for Ocular Implants Following Radical Surgical Interventions

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Abstract

The removal of an eye through evisceration or enucleation has always been one of the hardest decisions a surgeon must take in cases of life-threatening diseases or severe trauma. These cases give rise to a challenging issue namely ocular reconstruction and the use of ocular implants. Over the last few decades the design of orbital implants has evolved significantly. The use of nanotechnology allowed the production of ocular implants made of appropriate biomaterials leading to a reduction in complications rate as well as a general improvement of the patients' clinical outcome and satisfaction. This review provides a brief history of ocular implants used until now

Keywords: Biomaterials; Enucleation; Evisceration; Nanotechnology; Ocular Implant; Orbital Reconstruction; Post-Operative Extrusion

Introduction

In 1885, Mules used a glass spherical ocular implant to reconstruct a socket after an evisceration [1]. Still the first ocular implant was realized by the Egyptians and Romans in the beginning of the 15th century [1]. In the past few decades we witnessed a significant progress regarding the structure and design of ocular implants, leading to improved general patient clinical outcome and satisfaction [1]. Nano-structured materials are synthetic biomaterials used for total or partial reconstruction of a certain tissue [2]. These nano-structured biomaterials are currently used in the production of ocular implants. The issue remains the concern of how the organism reacts to these biomaterials, so the advantages and limitations of different types of implants will be discussed. They are classified according to their nature as follows: polymeric, composite, ceramic or metallic [3].

Indications of Ocular Prosthesis: Evisceration, Enucleation

After a radical intervention like an evisceration or enucleation, the psychological support of the patient is pre and postoperatively is important. It is fundamental that in such cases, the patients' re-adaptation to social life and the esthetic aspect, to be taken into consideration [4]. Evisceration is a procedure where the globular content is removed, keeping the sclera, Tenon capsule, conjunctiva, extrinsic muscles and the optic nerve [5]. Enucleation is another surgical option represented in removing the ocular globe keeping only the bulbar conjunctiva and extrinsic ocular muscles [6,7]. Evisceration has been considered superior to enucleation for a long time, due to the esthetical aspect and motility, but current surgical methods suggest the attachment of the extrinsic muscles at the implant after an enucleation [6,8]. There is a wide range of causes leading to surgical anophthalmus such as: congenital (anomalies and malformations of the optic vesicles) and acquired (absolute glaucoma with a painful eye, trauma [9], infectious endophthalmitis, perforated corneal ulcers, proliferative diabetic

retinopathy, and intraocular tumors). In cases of intraocular tumors i.e. melanoma or retinoblastoma, evisceration is contraindicated due to high dissemination risk [1,7,10]. Both procedures can be performed under local or general anesthesia, the latter having the advantage of not modifying the anatomy of the orbital vicinity [7]. The procedure ends by placing an ocular implant in the ocular cavity. The ocular prosthesis can be placed at the end of the procedure or a few weeks after. In the case of ocular integrated (HA) implant prosthesis is placed in about 6 months post-op prior to which a CT scan is performed visualizing the fibrovascular invasion of the mentioned implant [11,12].

Advantages and Disadvantages of Different Ocular Implants (Table 1)

Type	Advantages	Disadvantages
PMMA(polymethylmethacrylate)	cost efficient for patient	high risk of expulsion and infections.; no attachment to the ocular prosthesis directly;
Dermis Fat Graft (DGF)	allow fibrovascular tissue in growth; increased biocompatibility; allows local radiotherapy after enucleation in case of ocular malignancy.	formation of cysts and granulomas; keratinization and growth of hair follicles.
Porous Polyethylene	good motility (varianta Medpor ®Plus™ SST); allow fibrovascular tissue in-growth	requires a second intervention; expensive
Aluminium oxide(Al_2O_3)	good biocompatibility and motility; good oculoplastic results	requires a second intervention
Hydroxyapatite(HA)	good oculoplastic results; good biocompatibility; decreased rate of extrusions and infections.	requires a second intervention

Table 1: Advantages and disadvantages of some of the mentioned ocular implants [13,14,15].

The search for an ideal ocular implant also led to a progress regarding the surgical procedure as well as reducing post-operative complications after an evisceration or enucleation. That is why an ocular implant (glass sphere prosthesis) extrusion rate of 50-90% of cases, Mules perfected surgical techniques reducing the risk of extrusion [16,17].

Regarding the silicone sphere implant, it has been used for over 50 years [18]. Many surgeons argue that it would be a less favorable choice if it is implanted without attachment of extrinsic muscles, due to extrusion risk and reduction in motility [19,20]. Some surgeons choose the implant according to age of patient. Therefore, a wrapped silicone sphere implant is recommended for patients under 15 years as well as for patients over 65 years due to post-operative monitoring mainly and cost [19]. Gonzalez-Candial et al. [21] showed that, if pegging is not planned, no advantage seems to occur, in terms of motility, in using porous orbital implants instead of solid silicone spheres. Christmas et al. [22] performed six implantations, using solid silicone spheres, without reporting any complications over a 2-year follow-up [22,23]. Pegging procedures have sometimes also been performed with solid silicone implants; interestingly, Shoamanesh et al. [24] showed that silicone implants had significantly less pre-pegging and post-pegging complications (especially pyogenic granuloma and hypo-ophthalmos) than the other implant types (including the porous ones), which demonstrates the great potential- often underestimated since the introduction of porous implants- that silicone can still have today [22].

Silicone has also been recently proposed in the USA in the manufacturing of the commercially termed ‘‘Flexiglass System’’, comprising a silicone ocular prosthesis together with some accessories and an orbital device called the ‘‘Flexiglass Eye’’. To the best of the authors’ knowledge, no clinical studies about the Flexiglass have been reported in the medical and scientific literature to date; the few available information have been found on the producer’s website [23], wherein we simply read that clinical trials started in 2005 and are currently ongoing.

Ocular Implants

When discussing the biocompatibility of a certain nanostructured material, we have to take 3 aspects into consideration: bio-adaptability, bio-tolerability and bio-functionality [25]. Progress in this field led to improved designs of ocular implants. Unlike the ocular prosthesis which has a volume 4,2 ml less than the volume needed for ocular reconstruction, integrated ocular implants offer the appropriate dimensions [26,27] (Table 2). However, we cannot ignore the possibility of implant exposure or extrusion, which is why according to Kaltreider (year 2000) an ultrasounds evaluation (mode A and B) is recommended to estimate the orbital volume before implanting [27,28].

Orbital volume	30 cm^3
Aperture width	40 mm
Orbital depth	45-55 mm
Aperture height	35 mm

Orbital segment of the optic nerve	24 mm
Distance between optic hole and posterior surface of the globe	18 mm

Table 2: Normal orbital and ocular cavity parameters [29].

For improved motility of ocular prosthesis, most surgeons attach the extrinsic muscles to the ocular implant also reducing the risk of exposure or extrusion. This is why types of implants integrated and non-integrated are being discussed (Table 3).

Non-integrated implants:	glass; silicone; poly(methylmethacrylate)
Quasi-integrated implants:	Cutler implant; Allen implant
Magnetic implants:	Roper-Hall implant
Mechanically integrated implants:	Cutler implant type II
Pourous implants:	bone-derived orbital implants; proplast; hydroxyapatite; polyethylene; HA- coated aluminium oxide implants; polyethylene composites; polytetrafluoroethylene oxide

Table 3: Types and examples of orbital implants [24,25,26].

For instance, Sami et al. mentioned three categories based on the nature of each type of implant: buried, exposed-integrated and buried-integrated implants [30]. An ideal ocular implant should be non-allergenic, non-toxic, not provoking host tissue immune response, mechanically stable with satisfying motility and a suitable quality to price ratio [31].

Poly(methylmethacrylate)

Poly(methylmethacrylate) (PMMA) is well known in ophthalmology, mainly as an ideal material for the fabrication of intraocular lenses [32], as well as rigid and semi-rigid contact lenses [33], due to its excellent biocompatibility with ocular tissues and transparency to visible light; PMMA has been also widely used in oculoplasty. Regarding the field of non-integrated orbital implants, in 1976 Frueh and Felker first described the use of the so-called "Baseball Implant", i.e. a PMMA sphere in an envelope of donor sclera [34]; although originally described as a secondary implant, its design might allow primary implantation as well.

In 1985, Tyers and Collin implanted 35 secondary and six primary baseball implants and monitored the patients over a 24-month follow-up [35]; complications occurred in 59% of cases, but most of them (e.g. postoperative oedema) were resolved by pharmaceutical treatment [36]. Volume correction was excellent and the motility was apparently comparable with that of quasi-integrated implants. Therefore, the authors concluded that the baseball implant showed good potential and might be recommended both as a safe and convenient secondary implant and as the first approach to a volume deficit in the anophthalmic socket, though it should be avoided if the conjunctival fornices were already shallow as a result of previous surgery [33,34]. On the other hand, they acknowledged that the reported series of primary baseball implants was too small to allow them to draw definite conclusions, and the use of this implant after recent trauma was discouraged [34,35].

In 1994, Leatherbarrow et al. [37] reviewed 44 patients receiving the baseball implant and reported six cases of severe complications (one case of unacceptable pain, three cases of implant migration and two cases of implant exposure). In the late 1990s, Christmas et al. [22] implanted the baseball implant in six patients (primary enucleation) and implant removal was necessary in one case (exposure after 14 days). Some interesting studies have been recently performed in Pakistan using the so-called Sahaf implants, made of solid PMMA. Pakistani ophthalmic surgeons had an urgent need for the development of a new, cost-effective implant that could be readily available on site, as the most commonly used porous orbital implants had to be imported from abroad through a process that could take several weeks [36]. From 2003 to 2006, Kamal-Siddiqi et al. [38] implanted into 60 enucleated patients the Sahaf orbital implant type I, which was characterized by a two-piece design wherein the posterior hemispherical portion gave support to hold recti muscles and the anterior convex curvature supported the ocular prosthesis; it was also available in a number of sizes to restore different ocular volumes. Kamal et al. [39] also reported a review of 30 patients who received, from 2006 to 2009, a pear-shaped PMMA non-integrated implant (the so-called Sahaf orbital implant type II), which rested on the orbital floor and projected up to fill the orbit.

In summary, PMMA is an excellent biomaterial for ophthalmic applications; it is also commonly used to manufacture ocular prostheses and has been recently proposed for the repair of extensive orbito-facial defects due to trauma. In an interesting study, Groth et al. [40] treated nine severely injured patients implanting CT-based bio-modelled, prefabricated, heat cured PMMA implants that were well tolerated postoperatively; further advantages included customized design, long-term biocompatibility and excellent aesthetic results. The criteria adopted for the choice of a PMMA non-integrated spherical implant are substantially analogous to those that were already presented for the silicone sphere; for instance, many surgeons prefer to implant a non-porous PMMA sphere (or a silicone one, which is slightly more pliable) rather than a porous device in children and elderly patients [19].

Problast

Unlike what is commonly reported in the literature, the first porous orbital implant made of an artificial material was introduced more than a decade before synthetic HA and Polyethylene

(PE) porous implants. In the late 1970s, Lyall [41] pioneered the use of Proplast, an inert felt-like composite material composed of polytetrafluoroethylene (Teflon) and carbon fibres, to manufacture hemispherical orbital implants (Proplast implant I) that, when implanted, could be invaded by fibrous tissue to overcome the problem of extrusion and rejection; no rejection was reported after an 18 month follow-up in 16 patients receiving such implants and the motility was generally good [42]. Neuhaus et al. [23] tested Proplast implants I in rabbits and observed a high degree of soft tissue fixation with no implant migration; subsequent human use showed good results in four patients followed for 2 years and in six patients followed for 1 year, with no cases of extrusion or migration in either group. In recent years, however, the popularity of Proplast has declined because of long-term postoperative complications, primarily late infections, associated with its use [43].

Hydroxyapatite

Porous orbital implants spread worldwide after the introduction of modern HA orbital implants, which are not based on treated bone derived from animal sources. HA formally belongs to the class of calcium orthophosphates and, especially in the form of coralline or synthetic HA, has been widely used for more than 50 years in orthopaedics and dentistry for bone repair, thanks to its chemical and compositional similarity to the biological apatite of hard tissues [44-46]. Perry [47] experimentally introduced the coralline porous HA sphere (Bio-Eye_ Orbital Implants or Integrated Orbital Implants, Inc., San Diego, CA) in the mid-1980s, and it has been commonly adopted in clinical practice since the early 1990s, eventually becoming the most frequently used implant after primary enucleation [48]. Because of this, porous HA implants have been widely studied, and many retrospective reviews on patients' outcomes are available in the literature [19]. The interconnected porous structure of the HA implant allows host fibrovascular ingrowth, which potentially reduces the risk of migration, extrusion and infection [49,50]. Apart from discouraging need for a wrapping material, the assessment of implant vascularization with a confirmatory MRI study and, optionally, a secondary drilling procedure for peg placement with the consequent modification of the ocular prosthesis. Mainly in order to reduce the cost of the device, other forms of HA have been proposed as bacterial colonization of the implant surface, vascularization also allows the treatment of ocular infection by antibiotic therapy. Extraocular muscles can be securely attached to the HA implant (implant wrapping is recommended to facilitate muscles suturing), which in turn leads to improved implant motility [47,51]. By drilling into the frontal region of the HA implant and placing a peg, which can subsequently be coupled to the posterior surface of the ocular prosthesis, a wide range of artificial eye movements (especially along the horizontal axis) as well as fine darting eye movements (commonly seen during close conversational speech) can be achieved, thereby imparting a more life-like quality to the artificial eye [52].

Besides the above-mentioned advantages, however, coralline porous HA implants had - and still have - two peculiar drawbacks. The first problem is ecological, as the manufacture of such an implant involves damage to sea life ecosystems due to the harvesting of natural corals; the second issue is related to the significant rise in the costs associated with enucleation, evisceration and, more generally, ophthalmo-plastic surgical procedures. In fact, the expenses associated with the placement of coralline HA implant include the intrinsic cost of the implant which is often the most significant cost - the suitable and less expensive materials for implant fabrication. Synthetic HA implants (FCI, Issy-Les-Moulineaux, Cedex, France) [53], which are currently in their third generation (FCI3), have an identical chemical composition to that of the Bio-Eye_, although scanning electron microscopy (SEM) investigations have revealed a number of architectural differences (lower porosity: 50 vs. 65 vol.%; decreased pore uniformity and interconnectivity; presence of blind pouches and closed pores) [54]. Central implant fibro-vascularization in a rabbit model appears to occur in both Bio-Eye_ and FCI3 implants [54].

Lower-cost versions of these materials have been developed and are currently in use around the world; however, they exhibit a number of drawbacks that strongly limit their (economic) advantages over the other available models. Therefore, it is generally recommended that HA implants are placed within a wrapping material before being introduced into the orbit [11-12,55]. It was shown that the majority of exposed HA implants can be successfully treated by using patch grafts of different origin (e.g. scleral graft, dermis graft, oral mucosa graft) without the need for implant removal [56-59]. In the case of orbital implant infections, administration of systemic antibiotics and topical eye drops can solve the problem, but if no improvement in the symptoms is noticed, implant removal should be considered [57].

Other reported complications include conjunctival thinning (followed or not by exposure), socket discharge, pyogenic granuloma formation, mid-term to chronic infection of the implant, and persistent pain or discomfort [59-62].

In summary, porous HA implants still remain the most commonly used in anophtahlmic surgery, and their advantages and suitability, with regard to the patient's overall life quality, have been recently underscored in an interesting paper by Wang et al. [63]. However, in the search for an ''ideal'' porous orbital implant with a reduced complication profile and diminished surgical and postoperative costs, alternative materials have been also explored over the last two decades.

Polyethylene

The first generation of spherical porous PE implants had a rough surface, like HA (which is probably why a high exposure rate (about 22%) was reported in the early studies [64], and a quite homogeneous pore distribution [13]; since then, implants with

gradients of porosity have been introduced. By looking at the future of PE orbital implants, it is instructive to mention the recent work by Kozakiewicz et al. [65], who fabricated by a CAD/CAM approach and implanted ultrahigh-molecular- weight PE implants into three patients for orbital reconstructions. On the basis of CT scanning, Kozakiewicz et al. prepared a virtual model of both orbits (injured and uninjured) [66]; the two resulting surfaces were then overlapped and the outer surface, taken from the injured orbit, was used to design the external surface of the implant, whereas the inner profile, taken from the uninjured orbit, was followed for the internal surface of the implant. This new, advanced approach could also be applied in the future for the design and manufacture of orbital implants that closely mimic the original shape and size of the anophthalmic socket; issues to be considered concern the long time required to design and manufacture implants at the preoperative stage and, accordingly, their high cost [13,65].

Aluminium oxide

Aluminium oxide (Al_2O_3), commonly termed alumina, has been used for decades in orthopedics thanks to its attractive mechanical properties (high hardness and compressive strength, excellent resistance to wear), biocompatibility and bio-inertness [67]. Since the late 1990s, alumina has also been proposed, in a porous form, for the fabrication of orbital implants to be used in ophthalmoplasty; this type of device was approved by the US Food and Drug Administration in April 2000 and has been marketed under the commercial name of ''Bio ceramic implant''. The first *in vivo* study was reported in 1998 by Morel et al. [68], who evaluated the clinical tolerance of porous alumina implants implanted in 16 eviscerated rabbits; only one infection was observed and there was no conjunctival breakdown. Fibrovascular in-growth occurred as soon as 15 days postoperatively and was full at 1 month. These promising results were confirmed 2 years later by Jordan et al. [69], A more exhaustive comparison about the proliferation of orbital fibroblasts *in vitro* after exposure to Bio ceramic implant and three other implants made of different materials (coralline HA, synthetic HA, porous PE) was documented by Mawn et al. [14], who assessed cell growth with immunocytochemical analysis using bromodeoxyuridine, a thymidine analogue. The proliferation of fibroblasts differed on the various studied implants, the greatest being on the Bio ceramic implant. Furthermore, the fibroblasts growing on the Bio-Eye_, synthetic HA and Medpor_ implants all had debris associated with them, whereas the alumina implant was free of debris, which was mainly attributed to its finely crystalline microstructure. In a following study [70], Jordan and coworkers showed that alumina implant infections are generally rare and, after reviewing a clinical case series of 419 patients who received a Bioceramic orbital implant, estimated an implant exposure rate of 9.1%, with the majority of the exposures occurring after a 3-month follow-up period [3].

Wang et al. [71] reported that exposures of Bio ceramic implants occurred after long-term followup and were preferentially associated with evisceration, pegging and prior ocular surgeries, whereas no late side effects were found in enucleated eyes; the authors also emphasized that implant wrapping technique can prevent exposure [70]. In a recent study, Ramey et al. [72] compared the complication rates of HA, porous PE and polyglactin-wrapped alumina implants and, interestingly, found that porous PE and alumina devices were associated with higher exposure rates and higher overall complication rates compared to HA implants; these results seem to contradict those reported by the majority of authors [3,71,72].

Nanostructured Materials

There is a huge interest in research and development of nanostructured materials due to the importance of their applications in the medical and biological domains. Progress in nanotechnology brought a diversity of new classes of nanostructured materials [73,74]. The term nanocomposites are used when one organic or non-organic structural unit has its size in the definite interval of 91-100 nm. Nanostructured biomaterials can be considered as unidimensional, bidimensional and tridimensional systems or amorphic materials, composed of combined structures on a nanometric scale [74,75]. Synthetic hydroxyapatite based on nanostructures are being used currently as porous implants, as powder, porous blocks or pearls for reconstruction in case of bone defects or absence of bony substance [9].

In a study about the use of nanostructured HA implants performed on orbital fractures in animals, we could observe that the integration of the implant is good due to the presence of fibrous tissue and CD31 osteoclasts, with a complete reconstruction of the bone defect. Therefore, we can discuss the possibility of realizing personalized nanostructured implants, through the use of CT imaging for reconstruction as well as a 3D printing [76,77].

In a paper by Low et al. the authors explore the biocompatibility of thermally-oxidised, aminosilanised porous silicon membranes and their potential to support human ocular cells *in vitro* and *in vivo*, in the rat eye as scaffold methods for ocular tissue reconstruction [78]. Some papers by Geven and al. showed attractive mechanical properties of photo-crosslinked poly (trimethylene carbonate) and nano- hydroxyapatite composites as materials for orbital floor reconstruction. [79,80] Jun et al. proposed an antibacterial ocular prosthesis produced by incorporating lesser amounts of silver, gold or platinum nanoparticles in PMMA or silicone that was used to fabricate the prosthesis [81]. Following a similar approach, Yang et al. produced a PMMA-based ocular prosthesis with dispersed silver nanoparticles [82]. Both approaches, however, pose some problems associated to the possible toxicity of Nano-sized silver that has been reported in several *in vitro* and *in vivo* studies [83]. The authors have published a recent study

regarding the repair of the orbital wall fractures in rabbit animal model using nanostructured hydroxyapatite-based implant with excellent results [77].

Quasi-Integrated Implants

The advantages of porous and quasi-integrated implants, in terms of fibrovascular in-growth and motility, respectively, were merged for the first time by Girard and co-workers [84,85], who described a porous quasi-integrated enucleation implant made of Proplast II (Vitek, Inc., Houston, TX). This differed from Proplast implant I in its composition, being composed of Teflon and alumina, and in having a siliconized non-porous posterior surface to allow smoother movements, together with a porous anterior portion to facilitate fibrovascular ingrowth [69,86]. Proplast implant II was completely buried, but had a nipple on its anterior surface that could integrate with a depression on the posterior surface of the ocular prosthesis [65].

The more recent evolution of this type of device is represented by the Medpor Quad™ implant, which is conceptually similar to the Iowa implant but made solely of porous PE instead of solid PMMA. A preliminary study on 24 patients showed no cases of the ‘‘quad’’ implant extrusion or migration; however, two patients required deepening of their inferior fornix to accommodate the increased motility of their prosthesis [87]. In a following study on 10 enucleated pediatric patients, one case of implant exposure was noted with no other significant complications; good motility of the ocular prosthesis was reported in all cases [88].

Looking at the chemical, physical and structural characteristics of orbital implants, comparative studies on such topics are quite rare in the literature. It has been recognized that adequate fibro-vascularization is vital for a porous implant to achieve long-term success: chemical composition, microstructure and mechanical features are all factors that play a role, but there is a wide variation in these characteristics among the available materials [89]. In a recent study, Choi et al. [90] examined the surface of nonporous PMMA, porous alumina and porous PE intact implants by atomic force microscopy. The authors suggested that the surface roughness of orbital implants might be associated with the rate of complications and cell adhesion. From this viewpoint, an important issue to be considered is the effect of micro-/nanoscale topography on bacteria, since cells have to compete with bacteria in many environments. In a fascinating scenario, the surface topography could be purposely designed to encourage cells to colonize while limiting bacterial adhesion [91,94]. The currently available evidence indicates that the relationship between the microstructural features and the clinical performance of orbital implants deserves future investigation, which could lead to the development of novel design and manufacturing strategies [13,77,92]. Looking at the macroscale, pore size and interconnectivity can also influence the success of an implant; these features have been shown to be key determinants of tissue in-growth into 3D tissue engineering scaffolds [93,95]. The vascularization in porous HA and PE orbital implants with small and large pore sizes and suggested that the pore size should be greater than 150 lm and preferably around 400 lm in order to encourage favorable tissue in-growth. Another issue deserving investigation concerns the material surface chemistry and response to biological fluids through ion-exchange mechanisms, which are expected to play a key role in the fibro-vascularization of porous implants [70,88,96].

Conclusions

Up until now, a diversity of ocular implants has been used, with some only having the advantage of a good quality to price ratio. Some studies observed that porous integrated implants (hydroxyapetite) may have complications like extrusion, dehiscence, or infections. For enucleated patients the use of integrated HA implant is preferred, which allows a better integration of the ocular prosthesis resulting in good motility. A promising new strategy was proposed and involves the deposition of an antibacterial composite coating on the surface of the ocular prostheses and orbital implant. Developing the concept of Nano-structured biomaterial holds a great interest for its ability to satisfy the need of an ‘ideal’ ocular implant with higher healing and proliferation rate, low post-op complications (short/long term), and an affordable cost. Nanotechnology will revolutionize our approach to current therapeutic challenges beside ocular implants (e.g. drug delivery, post-operative scarring, bio resorbable materials) and will hopefully enable us to solve currently unsolvable problems (e.g. restoring sight for patients with retinal degenerative diseases).

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