Biomaterials for orbital implants and ocular prostheses: overview and future prospects

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Abstract

The removal of an eye is one of the most difficult and dramatic decisions that a surgeon must consider in case of severe trauma or life-threatening diseases to the patient. The philosophy behind the design of orbital implants has significantly evolved over the last 60 years, and the use of ever more appropriate biomaterials has successfully reduced the complication rate and improved the patient's clinical outcomes and satisfaction. This review provides a comprehensive picture of the main advances that have been made in the development of innovative biomaterials for orbital implants and ocular prostheses. Specifically, the advantages, limitations and performance of the

existing devices are examined and critically compared, and the potential of new, smart and suitable biomaterials are described and discussed in detail to outline a forecast for future research directions.

Keywords: Orbital implant; Ocular prosthesis; Enucleation; Porous biomaterials; Antibacterial properties.

1. Introduction

Dating back thousands of years, there is evidence that the Sumerians and Egyptians were able to surgically remove the ocular globe as well as to make artificial eyes; however, it was not until the late 1500s that enucleation procedures were reported in detail in the medical literature [1]. The advances in this field progressed relatively slowly and only in 1885 the use of a well-defined orbital implant, a glass sphere, to restore the socket volume was documented [2]. Improvements in surgical techniques, anesthesia, implant materials and design over the last decades have significantly got better clinical outcomes and patient's satisfaction. Furthermore, the ability to more effectively deal with the long-term complications of the anophthalmic socket such as enophthalmos, exposure and lower lid laxity (ectropion) have greatly improved. Today, most patients can confidently return to their daily activities with good cosmetic results following the removal of an eye.

This article chronicles the evolution of orbital implants and ocular prostheses, gives a comprehensive overview of the current state of the art and provides a picture for prospective research. Other devices used in oculo-orbital surgery, such as the biomaterials for orbital floor repair, have been recently reviewed elsewhere [3-5] and are not included in the present work. Medical details are often given, so that the reader can well understand the key problems related to the use and applications of the described devices, the suitability and limitations of existing solutions and the potential of some novel approaches suggested at the end of the article. Just to give the reader a "road map" showing the organization of the article, it can be divided into three parts,

devoted to presenting an essential medical background, a comprehensive materials/implants review and some indications for prospective research and future challenges, respectively. The first part, section 2, gives the reader a concise overview of the surgical approaches that can be adopted to remove a diseased eye, as well as the basic information related to orbital implants and ocular prostheses. In this context Table 1 provides a short glossary of the medical terms that are not explained directly in the text which may be unclear or unknown to non-specialist readers. In the second part, the different types of biomaterials and devices used as orbital implants (section 3) and ocular prostheses (section 4) are extensively reviewed. At the end of the section 3, an organized and critical comparison among the several existing types of orbital implants is provided. The third part, Section 5, presents the future challenges in the field and particularly highlights the potential of new experimental biomaterials with advanced properties (e.g. angiogenetic ability, controlled resorption, antiseptic functionality).

2. Need for eye removal: aetiology and surgery

The removal of an eye or the orbital contents is one of the most serious and difficult decisions that a patient and a surgeon must consider. The patient facing the loss of an eye has often underwent multiple ophthalmic/orbital surgeries, experienced severe ocular trauma or been diagnosed with a potentially life-threatening disease, such as eye tissue tumours. Therefore, psychological support before and after surgery is fundamental in these patents, who are often feeling depressed and overwhelmed [6].

At present, removal of a diseased eye can be carried out by following different surgical approaches, according to the particular pathology and medical history of each patient. Evisceration involves the removal of the intraocular contents of the eye while the sclera, Tenon's capsule, conjunctiva, extraocular muscles and the optic nerve are left intact [7]. Enucleation is another option involving the removal of the globe from the orbital socket together with the scleral envelope and a portion of

the optic nerve, while, as with evisceration, the conjunctiva, Tenon's capsule and extraocular muscles are spared [8,9]. It has long been believed that evisceration is superior to enucleation as to motility and cosmesis; however, modern enucleation procedures, which involves a careful attachment of extraocular muscles to the implant, actually rival those of evisceration in the preservation of motility of the artificial eye and cosmetic outcome. In the final stage of surgery, an orbital implant is placed within the scleral envelope after evisceration or within the Tenon's capsule after enucleation; an ocular prosthesis will be then worn by the patient to restore an appropriate aesthetic appearance (Fig. 1). Unfortunately, recovery of the visual function of the eye by implantation of what we might ideally term "seeing artificial device" still remains a dream; nonetheless, the present surgical strategies are fully able to restore an acceptable cosmetic appearance and life-like motility to the prosthetic eye.

Removal of an eye can be necessary in case of intraocular malignancy (e.g. retinoblastoma, which can develop especially in children), blind painful eye, prevention of sympathetic ophthalmia in a blind (or even seeing) eye, severe trauma, cosmesis and infections not responsive to pharmaceutical therapy. In some cases either approach can be adopted: from a general viewpoint, evisceration is less invasive and less surgically complex than enucleation and can be performed even under local anesthesia, but some reports demonstrated that the complication rate for evisceration, specifically implant extrusion, may be significantly higher [10]. Evisceration is indicated in the treatment of active, uncontrolled endophthalmitis and in all cases when there may be a danger of intraocular infection spreading back along a cut optic nerve sheath; however, enucleation may be indicated if the infection has spread to the sclera. Evisceration is also recommended in patients who cannot tolerate general anesthesia or have bleeding disorders since it is a faster, easier procedure and damages fewer blood vessels than enucleation. Evisceration is absolutely contraindicated in the presence of intraocular malignancy as it does not allow for eradication of tumour cells that have spread to the sclera. Enucleation is generally indicated for tumours that are confined to the ocular globe; exenteration procedure, which involves the removal of the entire orbit and surrounding

structures and tissues, should be performed if the malignancy has spread to the extraocular tissues and structures (e.g. adjacent sinuses, cranium bone, face muscles and skin, conjunctiva and eyelids) [11]. Exenterations vary in the amount of tissue removed and, apart from being indicated for the eradication of extended tumours, can be applied in the case of otherwise unmanageable rhino-orbital infections and, less commonly, severe orbital pain and deformity [12]. After the socket has healed, silicone or acrylic custom-made prosthetic devices can be constructed and attached to the orbit or skin with various types of adhesives to provide an excellent cosmetic result [13]. The use of osteointegration techniques, which involve the permanent placement of bone-anchored titanium implants, can also be used to successfully support maxillofacial prosthetic devices [14].

3. Orbital implants

Over the centuries, a wide variety of materials has been experimented to manufacture more or less rudimental orbital fillers with the aim of replacing the anophthalmic socket volume and restoring an acceptable aesthetic appearance to the patient's face. Use of metals (e.g. gold, silver, platinum, stainless steel), substances of vegetal (e.g. wool) or animal (e.g. cork, ivory) origin and even rock-derived materials (asbestos) has been documented [15]. Since the late 19^{th} century, surgical procedures and materials to be implanted progressively moved to more defined standards, in order to avoid or at least to limit the negative outcomes of a "trial and error" approach. Therefore, the term "orbital implant" has been employed to denote a properly-designed, reproducible, often man-made device which not only is able to replace orbital volume but also, hopefully, to ensure adequate motility to an aesthetic ocular prosthesis (artificial eye); in this review, particular emphasis will be dedicated to recently-developed solutions (approximately in the last two decades) and related studies. The earliest orbital implants were simple spheres buried within the Tenon's capsule [2]; the extraocular muscles were disinserted from the globe and left to contract within the socket. Due to the limited movement of the overlying ocular prosthesis, surgeons began to perform the muscles

attachment to the implant to better anchor it, thereby reducing extrusion rates, and to allow conjugate movement with the contralateral normal eye.

The attachment of the extraocular muscles to the implant, the implant incorporation within the surrounding orbital tissues and the implant-prosthesis interlocking have all become a source of some confusion in terminology over the years. For instance, some authors referred to "implant integration" as the simple attachment of the extraocular muscles to the implant, whereas other researchers defined integration as the mechanical contact between implant and ocular prosthesis. In order to solve this controversy, Sami et al. [15] recently suggested a 3-type categorization (buried, exposed-integrated and buried-integrated implants) based on the assumption that integration specifically refers to the nature of fit between the ocular prosthesis and the implant, whereas attachment of the extraocular muscles to the implant does not imply integration. In the present work, the authors propose a 7-type general classification of orbital implants (Table 2), in the attempt at taking in account all currently available implants, including the porous ones with their own peculiarities. According to this classification, some overlapping among the classes is unavoidable depending on the context of use; for instance, a solid silicone sphere may be a simple non-integrated device but, if wrapped within a foil of biological tissue, it will become a non-integrated and biogenic implant. As the research continuously proceeds and new materials are developed, in the next future even a 8^{th} class (bioactive implants) might be added to Table 2, as shortly discussed at the end of the article in the section 5.2.1.

The orbital implants developed over the years – available on the marketplace or currently abandoned – are collected in Table 3 with essential information for the reader's benefit. Just to provide a short overview of the complex issues related to the design and selection of suitable orbital implants, we have to mention that an ideal implant should display a number of characteristics, including biocompatibility, adequate volume replacement, adequate support for the ocular prosthesis, accessible cost for the patient, easiness of implantation, good motility transmitted to the ocular prosthesis and low rate of complications (e.g. post-operative infections). The use of non-

toxic materials should be a mandatory pre-condition to produce biocompatible implants. In order to fit the anatomic needs of each specific patient, including children, implants of different size are today available on the marketplace; the prices are quite variable (from few tens to several hundreds Euros in Europe) and mainly depend on employed material and implant style. Surgical implantation can be facilitated by wrapping the implant within a foil of a smooth material; this procedure is particularly recommended for porous implants characterized by a slightly irregular porous surface. Over the years, different strategies have been developed to suture the extraocular muscles to the implant in order to improve motility; for instance, the muscle can be directly and independently attached to the implant or sutured together in front of it (imbrication). Different approaches were also experimented to improve the motility of the ocular prosthesis, including pegging procedures and use of magnets to guide the prosthesis movement in accordance to that of the orbital implant. Infections following implant exposure are more amenable to treatment in porous implants, as vascular in-growth helps to anchor the implant and permits immune surveillance. Therefore, the use of a porous implant is a good option in adults but is generally discouraged in children, since implant substitution with another one of larger size may be necessary to stimulate adequate orbital growth. All these issues will be critically discussed in the following sections to give the reader a comprehensive picture about features, advantages and limitations of each implant type as well as some criteria for implant choice.

3.1. Non-integrated implants

3.1.1. Glass

In 1885, Mules placed the first orbital implant after evisceration [2] and one year later Frost described orbital implant placement after enucleation surgery [16,17]. The Mules implant was essentially a hollow blown glass sphere and commonly used till the World War II (WWII). Volume

replacement by the Mules implant within Tenon's capsule was a significant advance, reducing socket retraction, intra-orbital fat redistribution and superior sulcus deformity. Implants of different sizes were experimented for better fitting to patient's anatomy; it was also noted that the use of smaller and lighter devices led to decreased stress on the lower lid and associated ectropion formation. At the beginning, the Mules implant had high extrusion rates (50-90%), but the progressive improvement of surgical techniques led to the reduction in this complication, although still high compared to modern standards: Verrey reported an extrusion rate of 21% in 343 cases receiving the Mules implant up to 1898, and in 1944 Burch reported failures in less than 10% of 52 operations [18,19]. The major drawbacks of Mules implant were the brittleness, as the implant could break due to trauma, and the risk of implosion due to sudden temperature changes.

At present, use of glass spheres as orbital implants has been almost totally abandoned considering the availability of other implants generally ensuring better outcomes. Occasionally, glass has been still used in recent years: in the late 1980s Helms et al. [20] implanted a glass sphere (1 patient) that underwent posterior intracranial migration, and in the 1990s Christmas et al. [21] used a glass implant in a single patient without reporting any complication after a 2-year follow-up.

3.1.2. Silicone

Silicone has been extensively proposed for more than 50 years as a suitable material for various surgical applications due to its attractive properties, including biological/chemical inertness, flexibility, ease of handling and low cost. For instance, episcleral implants made of solid or porous silicone are still today the unique devices clinically approved and commercially available worldwide for scleral buckling in retinal detachment surgery [22].

As to orbital implants, a non-porous silicone sphere, as-such (bare) or wrapped, centered within the muscle cone and attached to the four rectus muscles has been the most common alternative to Allen and Universal implants before porous implants have been introduced on the market at the end of

1980s. The use of a non-porous silicone sphere is still now a good option if pegging is discouraged or cannot be performed; however, although prosthetic movement occurs, it is not as much as is seen with mounded (i.e. quasi-integrated) devices or pegged porous implants. In the view of many surgeons, a standard silicone sphere simply placed into the orbit, without a wrap and without connection to the rectus muscles, is the least desirable choice as it offers little movement and the implant is prone to migrate with time [23].

Non-porous silicone spheres can be also preferred depending on the patient's age. In infants and preschool-aged children, a wrapped silicone sphere centered within the muscle cone and connected to the four rectus muscles and inferior oblique muscle is often recommended; implant exchange with a porous orbital implant that may potentially be pegged is considered at a later age (> 15 years). Some surgeons also prefer to implant a wrapped non-porous silicone sphere in aging patients (> 65 years); porous implants are not used routinely in this age group, as experience suggested that these patients are often bad candidates for pegging due to gradually failing health and difficulty in maintaining regular follow-up visits [23].

Excellent outcomes have been reported by suturing the recti independently to a 20-mm spherical silicone implant reinforced with autogenous fascia or preserved sclera: an extrusion rate of only 0.84% (1 of 119 patients over a 10-year follow-up period) and no cases of implant migration were reported [24]. This is an interesting achievements as, when muscles are imbricated over the surface of a spherical implant, implant migration normally occurs more frequently with non-porous implants [25,26].

Many surgeons experienced that this implant is an excellent choice also in cases of trauma, such as a severe gunshot wound to the orbit, where extraocular muscles are unidentifiable and will not be reattached to the implant. The implant, usually wrapped within a sclera foil or other suitable biomaterial, can be placed into the orbit and the Tenon's capsule and conjunctiva sewn over the top.

Gonzalez-Candial et al. 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 [27]. Christmas

et al. [21] performed six implantation, by using solid silicone spheres, without reporting any complications over a 2-year follow-up. Pegging procedures were sometimes performed also in presence of solid silicone implants; interestingly, Shoamanesh et al. [28] 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 after the introduction of porous implants – that silicone can still have today.

Apart from solid spherical implants, for sake of completeness it is also worth mentioning the silicone-based orbital implant proposed in the late 1960s by Soll, who devised an inflatable silicone implant filled with silicone gel [29,30]. By using a 30-gauge needle, saline or antibiotic solution could be injected centrally through a self-sealing area; this implant was designed to preferentially expand superiorly in order to address superior sulcus deficit. Due to pressure-related problems occurring both intraoperatively and after implantation, associated to the risk of silicone gel release, this approach was abandoned.

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 (more information will be presented in the section 4.2) and an orbital device called “Flexiglass eye”. To the best of the authors’ knowledge, no clinical studies about the “Flexiglass eye” have been reported in the medical and scientific literature up to now; the few available information have been found on the producer’s website [31], wherein we simply read that clinical trials started in 2005 and are currently on going. We textually report the sentences describing this product [31]: “With the use of a safe, topical ‘growing’ oil application, the Flexiglass™ eye can actually be made to expand to fill the pediatric patient’s eye socket. Therefore, one can quickly see that the advantages of having an eye growing with the pediatric patient are quite significant. When an ocular prosthesis inadequately compensates for the space of an eye socket, the socket will inevitably contract and deform resulting in an unsatisfactory cosmesis. This inadequate cosmesis can continue

into adulthood and possibly requires many grueling and unnecessary surgeries to properly correct". The features of the described device are unclear and the authors have strong perplexities about the use of a 'growing oil' that allows the implant to fit the anophtalmic socket. Clarification of these crucial issues, which should involve an accurate, serious investigation of the actual suitability of this implant for clinical use and a careful monitoring of its current commercialization, is therefore strongly expected in the next future.

3.1.3. Poly(methylmethacrylate)

Poly(methylmethacrylate) (PMMA) is well-known in ophthalmology mainly as an ideal material to fabricate intra-ocular 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; furthermore, PMMA has been also widely used in oculoplasty. As to 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 6 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. Volume correction was excellent and the motility was apparently comparable with that of quasi-integrated implants; therefore, the authors concluded that the baseball implant had a promising 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, but it should be avoided if the conjunctival fornices were already shallow as a result of previous surgery. 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.

In 1994, Leatherbarrow et al. [36] reviewed 44 patients receiving the baseball implant and reported 6 cases of severe complications (1 case of unacceptable pain, 3 cases of implant migration and 2 cases of implant exposure). In the late 1990s, Christmas et al. [21] implanted the baseball implant in 6 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. The development of a new, cost-effective implant that could be readily available on site was an urgent need for Pakistani ophthalmic surgeons as the most commonly used porous orbital implants have to be imported from abroad through a process that can take several weeks. From 2003 to 2006 Kamal-Siddiqi et al. [37] implanted in 60 enucleated patients the Sahaf implant type I, that was characterized by a 2-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 with multiple sizes to restore different ocular volumes. The anterior part of the implant was wrapped in sclera or fascia lata in some cases. After surgery, three initial cases showed necrosis of the conjunctiva leading to exposure of the implant, which needed reinforcement by autogenous fascia lata, and in one case the anterior part of the implant was extruded; in general, all cases had satisfactory socket filling. These early results were promising but the authors wisely concluded that further studies and long-term follow-up on a broader number of cases were needed to draw definite conclusions about the advantages of Sahaf orbital implant I over the existing ones.

Kamal et al. [38] 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 (Fig. 2a). Most of patients underwent enucleation, but this implant was also used in some cases of exenterated socket, along with temporalis muscle rotation and with 360° fornix reconstruction using mucous membrane graft. Wrapping of donor sclera or autogenous fascia lata was used in most cases. Postoperatively, two cases exhibited initial

necrosis of the conjunctiva leading to exposure of implant, which needed reinforcement by autogenous fascia lata.

Among the recently-developed designs, it is worth mentioning the clever approach reported by Agahan and Tan [39], who hypothesized that implant weight might be a cause for most cases of implant migration; hence, they suggested that a hollow PMMA implant would be expected to be more stable compared with a solid implant of the same size as it would be subjected to less gravitational force. Hollow implants were manufactured by fusing 2 hemispherical elements made from medical-grade PMMA powder. Twelve patients were randomly divided into two equal groups, receiving either the standard solid acrylic implant or the hollow PMMA implant, respectively. The anophthalmic socket was examined postoperatively by serial computed tomography (CT) scanning to detect implant migration. Most of the implants remained in the socket at least 6 weeks in both groups, with 1 case of early implant extrusion in the solid acrylic group. Small degree of implant migration was observed on CT scans in 4 patients in the solid acrylic group and 3 in the hollow PMMA group after a 12-week follow-up. In the solid acrylic group, the implant migrated posteriorly in eviscerated patients and anteriorly in enucleated patients. No pattern was observed in the type of operation and direction of the implant migration in the hollow PMMA group. The authors concluded that hollow PMMA implants were comparable substitutes for solid acrylic implant, but multicenter clinical trials with adequate patients' sample size and longer follow-up are needed to establish the long-term stability of the implant.

In summary, PMMA is an excellent biomaterial for ophthalmic applications; it is also commonly used to manufacture ocular prostheses (as described in the section 4) 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 9 severely-injured patients by implanting CT-based biomodelled, 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 PMMA non-porous sphere (or a silicone one, that is slightly more pliable) rather than a porous device in children and elderly patients [23]. PMMA has been also used for manufacturing the majority of quasi-integrated implants, that are described in the section 3.2.

3.2. Quasi-integrated implants

An interesting approach to provide adequate motility without interrupting the conjunctival lining, with the aim of minimizing discharge and infections related to exposures or pegging procedures, was introduced about 70 years ago with the use of what is known as a quasi-integrated orbital implant design. These implants have irregularly-shaped anterior surfaces that create an indirect coupling mechanism between implant and ocular prosthesis, thereby allowing movement transfer from the implant to the artificial eye and, accordingly, imparting greater mobility to the latter one. The posterior surface of the ocular prosthesis is modified so that it fits in a “lock-and-key” fashion with the anterior surface of the implant, although it remains buried beneath the conjunctiva. Among the various types of orbital implants, the quasi-integrated ones nicely capture the progression of orbital implant design and “philosophy” from the WWII to present.

3.2.1. Early models

In 1946, Cutler introduced the so-called “basket implant” (Cutler implant I), that had four openings through which the rectus muscles were pulled through and sutured together with the patient’s conjunctiva closed over it; the ocular prosthesis had a knob on its posterior surface that fitted into the concavity of the (female) implant without direct contact [41]. Some variations of the quasi-integrated Cutler implant have been proposed in the following years, such as the King implant that

consisted of a pear-shaped tantalum mesh at whose base the rectus muscles were attached with the patient's conjunctiva closed over it [17]. The interested reader can find a comprehensive historical picture about early quasi-integrated models in a valuable paper by Gougelmann [17].

3.2.2. The Allen implant and its evolutions

The original Allen implant, that was developed in the mid 1940s by Prof. James Allen (Iowa University) together with the ocularist Lee Allen, was actually a mechanically-integrated PMMA implant connected by a thin rod (peg) to the aesthetic ocular prosthesis [42]. In the attempt of improving the design of Cutler integrated (female) implant (section 3.4), the Allen design incorporated the peg into the implant (male); each rectus muscle was passed through a peripheral tunnel, split lengthwise to straddle the gold peg and was sutured to its antagonist. Unfortunately, this first model gave less than satisfactory results as these implants were retained only a few months before they extruded or were removed because of infection due to bacterial colonization of implant/tissues [43]. The implant design was therefore modified: the peg was removed, the muscles were sutured together (or "imbricated") through a central 6-mm opening and the Tenon's capsule and conjunctiva were completely closed over the flat PMMA surface of the implant that was thus buried beneath the tissues of the eye socket. Such a design for the Allen implant was widely used for more than 10 years until it was replaced by a modified version developed to address the common complaints of some of the ocularists who were fitting them. For instance, since the flat surface did not well support the weight of the ocular prosthesis against gravity, lower lid droop and exaggeration of the upper lid sulcus were noticeable in some patients [44]. In the late 1970s Jahrling [45] reported an average 19% incidence of exposure among 186 Allen implants; in other long-term studies, however, much lower exposure rates (about 1%) were found and no exposure occurred before 5 years of follow-up [44].

For the redesign, Lee Allen saw the advantage of a differently-shaped motility implant with pronounced irregularity on its anterior surface, in order to connect it more securely to the artificial eye's posterior surface, which was shaped to match the irregular anterior surface of the implant. This next design, first reported in 1959, was referred to as the quasi-integrated Iowa implant I [46]; the Iowa implant II, introduced one year later, was similar in shape but nearly one third larger in volume [47]. The Iowa implants (type I and II), made of PMMA, had four peripheral mounds (height 5 mm) on the anterior surface designed to integrate with four depressions on the back of the ocular prosthesis (Fig. 2b); the rectus muscles were brought together through the valleys between the mounds, overlapped and tied together at a central anterior depression. Holes were also made through parts of the implant in the attempt at promoting fibrovascular tissue in-growth – this concept will be fully explored and applied 25 years later with the development of porous implants (section 3.5). The Iowa implants addressed many of the problems complained about the Allen implant: for instance, the four surface small hills supported the ocular prosthesis and remarkably reduced gravitational effect on the lower lid. Spivey et al. reported a 3.3% exposure rate of Iowa implants over a 10-year follow-up [48]. It was also noted that Iowa implants exposure was usually localized at the surface of the mounds due to pressure-induced necrosis; therefore, the Iowa implants design was modified and the Universal implant, exhibiting lower and more round-shaped mounds (Fig. 2b), was introduced in the late 1980s [49,50]. However, the Universal implant was not widely used because it emerged around the same time that the porous implants begin to greatly spread on the market.

3.3. Magnetic implants

The class of magnetic orbital implants deserves a particular mention. From a historical perspective, the development of orbital implant design seems to be mainly "evolutionary", as surgeons and ocularists progressively tried to improve implant performances and clinical outcomes by

overcoming step-by-step some specific drawbacks which featured the implants proposed by their predecessors; a typical example is represented by the modifications of the Allen implant towards the Iowa and eventually the Universal implant. However, in the authors' view, magnetic implants might be considered – at least partially – "revolutionary" due to the interesting principle behind their action. Essentially, the ocular prosthesis is held in place and the implant movement can be transferred to it by means of the action of magnets with opposite poles incorporated on the posterior surface of the prosthesis and within the anterior region of the implant, respectively; the conjunctiva is sandwiched between the two elements.

This approach was introduced after the WWII and led to the development of a certain number of early models [51-56]. In 1954, Troutman [51] published the results of a 5-year follow-up including 102 patients receiving a magnetic orbital implant and reported an extrusion rate below 4%. Roper-Hall [55,56] developed a magnetic implant deriving from the Allen design and consisting of a PMMA 21-mm hemisphere with a flat anterior face into which a magnet was embedded; a ring of the same material stand forward of the face and had tunnels through which the 4 rectus muscles might be passed. More horizontal than vertical movement of the artificial eye was usually seen, and this could be increased in all directions if additional magnets were placed in the ocular prosthesis. Unlike the mechanically-integrated (pegged) implants developed in the same period, this implant did not have an extreme amplitude of movement, for it was limited to a "conversational" range [57]. In the early 1980s, Atkins and Roper-Hall [58] monitored 66 enucleated patients over a 5-year follow-up: only 1 case of extrusion was reported, together with residual problems of lower lid droop and a deep upper lid sulcus.

Magnetic implants generally had adequate movement, but if the magnet was too strong or misaligned, conjunctiva and Tenon's capsule tissue could become compressed between implant and prosthesis, thereby leading to breakdown and exposure along the outer edges [59]. These implants, although representing a clever approach to the problem of implant-prosthesis integration, exhibited two apparently unavoidable drawbacks. The first issue was recently pointed out by Sami et al. [15],

who clearly recognized local toxicity related to iron ions accumulation within the conjunctival tissues and associated tissue necrosis as an important cause of possible tissue breakdown and late exposure. Over time, PMMA tends to absorb water due to prolonged contact with biological fluids, which may cause magnet rusting (Fig. 2c,d) with subsequent exposures developing over the central anterior surface, as opposed to the peripheral edges which are prone to pressure necrosis [60]. The second issue is common to all metallic implants or prostheses that can be potentially hazardous during magnetic resonance (MR) imaging because of movement or dislodgment of the foreign metal object [61]. Yuh et al. [62] reported a case of a magnetic orbital implant extrusion caused by implant movement during MR imaging at 0.5 T. In recent years, there has been a renewed interest by surgeons, biomaterials researchers and implant producers towards magnetic orbital implants, as demonstrated by some relevant patents deposited in the early 2000s [63,64].

3.4. Mechanically-integrated implants

The evolution of quasi-integrated and mechanically-integrated (pegged) orbital implants was substantially concurrent. In the late 1940s, Cutler described a PMMA “ball-and-ring” implant (Cutler implant type II) whose exposed face had a square (female) receptacle, into which a gold square (male) peg attached to the ocular prosthesis could be inserted; the rectus muscles were looped around and sutured to the ring [65,66]. In the following years, similar implants were developed by other researchers with slight modifications [15,17].

It is worth mentioning that pegged integrated implants were developed not only for enucleation but also for evisceration. In 1951, Young first described a PMMA implant to be inserted in an eviscerated globe; the device was maintained in position by tantalum wires passing through the sclera and the peg passed through a hole in the cornea, thereby acting as an obturator on which the ocular prosthesis rested [67].

All these implants generally gave excellent movement, but their long-term results were unsatisfactory. In a review of the outcomes of 91 patients receiving mechanically-integrated implants, Choyce found that the rate of survival after a 2-year follow-up was from 40 to 50% depending on the implant type; infection due to bacterial colonization of peg/tissues was the reason for extrusion and subsequent removal in 80% of cases [68]. For this reason, the use of mechanically-integrated implants was progressively abandoned and the adoption of quasi-integrated ones was preferred until the diffusion of porous implants widely took place about 20 years ago: the "peg approach" has been re-invented and applied to this new generation of implants that allowed better outcomes thanks to fibrovascular in-growth within the pores.

3.5. Porous implants

From the design style viewpoint, in some ways the porous orbital implants represented a sort of "regression", since the porous sphere could not translate movement to the implant as the irregular anterior surface of quasi-integrated implants did. On the other hand, advantages of porous implants included fibrovascularization with intrinsic decrease of infection risk as well as the capability of a more effective treatment of infections via antibiotic systemic therapy. If porous implants are used for evisceration, scleral windows should be produced by the surgeon to allow fibrovascular in-growth; the same approach is recommended if the implant is covered with wrapping material. Some examples of clinically-used porous orbital implants are collected in Fig. 3. The majority of scientific articles and books dealing with materials for ophthalmolplasty indicate the coralline hydroxyapatite (HA) implant, introduced in the mid 1980s, as the first example of porous orbital devices that have revolutionized anophthalmic socket surgery. However, this statement is only partially correct as porous orbital implants actually have an older but often forgotten history, as shortly summarized in the following two sections.

3.5.1. Bone-derived orbital implants

More than one century ago, in the attempt at overcoming the complications related to the Mules's glass implant, a wide variety of different materials were experimented, including the mineral matrix of bovine cancellous bone first introduced by Schmidt in 1899 [69]. This implant was prepared by heating spheres of cancellous bone to destroy all organic matter, leaving only the calcium phosphate mineral framework [70], that was subsequently shown to consist predominantly of ultramicroscopic crystals of HA with small amounts of calcium carbonate and calcium citrate [71,72]. Schmidt's bone-derived HA spheres were used until 1930 [73] and a variation of this implant, i.e. the so-called Guist's implant constituted by calcined bovine bone spheres [74,75], was widely used and recommended as "the most satisfactory of all orbital implants" before the WWII [76].

Since the 1950s, biologically-inert non-integrated polymeric spheres (silicone and PMMA) progressively displaced the early types of porous implants. In the 1960s, Molteno carefully reviewed the existing literature on orbital implants and noted that the earlier bone-derived HA implants had given good results and that small exposures of the implant during the postoperative period frequently healed spontaneously [76]. This behaviour, which was quite unlike that observed with a smooth surfaced polymeric implant, suggested that the biodegradable microcrystalline HA matrix of bone would constitute a superior orbital implant since, once organized by host connective tissue, it would not migrate through the tissues while any small exposures would heal spontaneously. Furthermore, the mass of host connective tissue incorporating the bone mineral implant would be likely persist unchanged for the patient's whole life. The early trials of this type of implant (M-Sphere, Molteno Ophthalmic, New Zealand; currently it is also produced by IOP Inc., Costa Mesa, USA) were reported in the early 1970s and 1980s [77,78], involved the use of deproteinized (antigen-free) bone of calf fibulae and confirmed that the mineral matrix of cancellous bone was readily incorporated into the tissues and that small exposures were followed by spontaneous crumbling of the exposed bone with healing of the overlying conjunctiva. Other 52

cases with up to 10-year follow-up were reported in 1991 [79], and the long-term successful outcomes of 120 M-Sphere orbital implants inserted after enucleation between 1977 and 2000 were more recently documented [80]. This implant, however, is significantly more porous and, accordingly, more fragile than other available HA implants (described in the section 3.5.3) and may be unable to support a peg [81,82]. Furthermore, its comparatively high cost (500 € or more) may have contributed to its relatively limited diffusion.

3.5.2. Proplast

Unlike what commonly reported in most of the literature, the first porous orbital implant made of an artificial material was introduced more than one decade before synthetic HA and polyethylene (PE) porous implants. In the late 1970s, Lyall [83] pioneered the use of Proplast, an inert felt-like composite material constituted 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 a 18-month follow-up in 16 patients receiving such implants and the motility was generally good. Neuhaus et al. 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 4 patients followed for 2 years and in 6 patients followed for 1 year, with no cases of extrusion or migration in both groups [84]. In recent years, however, the popularity of Proplast has declined because of long-term post-operative complications, primarily late infections, associated with its use [85].

3.5.3. Hydroxyapatite

Porous orbital implants spread worldwide after the introduction of modern HA orbital implants, that are not based on treated bone deriving from animal sources. HA formally belongs to the class of calcium orthophosphates and, especially in form of coralline or synthetic HA, has been widely used since more than 50 years in orthopaedics and dentistry for bone repair thanks to its chemical and compositional similarity to biological apatite of hard tissues; interested reader can find comprehensive pictures about the features and use of HA and calcium phosphates in medicine in a series of reviews published by Dorozhkin [86-88].

Perry experimentally introduced the coralline porous HA sphere (Bio-Eye® Orbital Implants or Integrated Orbital Implants, Inc., San Diego, CA, USA) (Fig. 3a) in the mid 1980s [89] and since the early 1990s it has been commonly adopted in the clinical practice, eventually becoming the most frequently used implant after primary enucleation [90]. Due to this reason, porous HA implants have been widely studied and a lot of retrospective reviews on patients' outcomes are available in the literature [23]. The interconnected porous structure of the HA implant allowed host fibrovascular in-growth, which potentially reduces the risk of migration, extrusion and infection [91]. Apart from discouraging bacterial colonization of implant surface, vascularization also allows the treatment of ocular infection by antibiotic therapy. Extraocular muscles can be securely attached to the HA implant, which in turn leads to improved implant motility [89,92]. By drilling into the frontal region of the HA implant and placing a peg, that can be subsequently 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.

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 raise of the costs associated with enucleation, evisceration and

more generally ophthalmoplastic surgical procedures. In fact, the expenses associated to the placement of coralline HA implant include the intrinsic cost of the implant (600 € or even more, whereas traditional silicone or PMMA spherical implants range within 20-50 €) – which is often the most significant cost –, the need for a wrapping material, the assessment of implant vascularization with a confirmatory magnetic resonance imaging (MRI) study and, even if 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 suitable and less expensive materials for implant fabrication. Synthetic HA implants (FCI, Issy-Les-Moulineaux, Cedex, France) [93], that are currently in their third generation (FCI3), have an identical chemical composition to that of the Bio-Eye®, although scanning electron microscopy (SEM) investigations revealed some architectural differences (lower porosity: 50 vs. 65 vol.%; decreased pore uniformity and interconnectivity; presence of blind pouches and closed pores) [94]. Central implant fibrovascularization in a rabbit model appeared to occur in both Bio-Eye® and FCI3 implants [95]. FCI3 implant has gained increasing popularity over the past 10 years especially as it is significantly less expensive than the Bio-Eye® (approximately 450 € vs. 600 €) and easier to drill for peg placement.

Lower-cost versions of these materials have been developed and are currently in use around the world; however, they exhibit some drawbacks that strongly limit the (economic) advantages over the other available models. The Chinese HA implant (H+Y Comprehensive Technologies, Philadelphia, USA) has been reported to contain some CaO impurities that, after hydration in host tissues, may form $Ca(OH)_2$, which is caustic [96,97]. The Brazilian HA implant, currently available in Brazil only, has higher weight, lower porosity and lower pore interconnectivity than Bio-Eye® and FCI3 implants, with consequent enhanced risk of implant migration and limited fibrovascularization [98]. Other types of synthetic HA implants (75 vol.% porosity, pore sizes ranging from 100 to 300 μm) were also recently used in India leading to patient's good outcomes [99].

Despite the relatively good overall biocompatibility profile, HA generally exhibits certain drawbacks for use in orbital implants. Being a porous ceramic, its brittle nature precludes suturing the extraocular muscles directly to the implant [8,9]. There are convincing evidences that the rough surface of HA implants may adversely impact on biocompatibility, contributing to the development of late exposure due to the abrasion of the relatively thin conjunctiva and Tenon's capsule as the implant moves. Therefore, it is generally recommended that HA implants are placed within a wrapping material (Fig. 3d) before introduction into the orbit [100-102]. 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 [103-105]. In case of orbital implant infections, administration of systemic antibiotics and topical eye drops can solve the problem, but if no symptoms improvement is noticed, implant removal should be considered [106].

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 [107-111]. In order to solve the possible problem of peg extrusion from drilled HA implants due to hole occlusion, Lew et al. proposed a 0.5 mg ml^{-1} mitomycin-C application to the drill hole and obtained good results in an albino rabbit model [112].

The use of porous HA implants in pediatric population has been alternatively advocated and castigated – implant exchange should be necessary later since the patient is growing, but its removal is difficult due to fibrovascularization – and this controversy still lingers on [113,114]; at present, non-porous implants seem to remain the preferable choice in children for the majority of surgeons [23]. In summary, porous HA implants still remain the most commonly used in anophtahlmic surgery and their advantages and suitability, in regard to considering the patient's overall life quality, have been recently underscored by Wang et al. in an interesting paper [115]. However, in the search for an "ideal" porous orbital implants with a reduced complication profile and diminished

surgical and postoperative costs, alternative materials have been also explored over the last two decades.

3.5.4. Polyethylene

Synthetic porous PE implants (Medpor®, Porex Surgical Inc., Newnan, USA) were introduced in the late 1980s for use in the orbit and have been widely accepted as an alternative to the Bio-Eye® HA [116,117]. Furthermore, since then Medpor® thin sheets have been also used for the surgical repair of orbital floor fractures [5].

In an animal model study, Goldberg et al. suggested that porous PE induces less inflammation and fibrosis than HA [118]; similar conclusions were more recently reported by Jordan et al. [119]. SEM investigations showed that porous PE implants exhibit a smoother surface than coralline HA (Bio-Eye®), synthetic HA (FCI3) and even aluminum oxide implants [119,120]. PE implants are also malleable, which permits easier implantation and potentially less irritation of the overlying conjunctiva following placement in comparison to porous HA spheres. On the other hand, the rate of vascularization of porous PE appears to be slower than coralline HA (Bio-Eye®), synthetic HA (FCI3) and aluminum oxide implants [119] as well as dependent on the pore size: PE implants with 400-µm pore size vascularize more rapidly than those having 200-µm pore size [118,121]. In a recent work by Choi et al., gadolinium-enhanced MRI showed that the rate of fibrovascularization was similar for enucleated and eviscerated eyes in rabbits [122].

Medpor® implants may be used with or without a wrapping material and the extraocular muscles can be sutured directly onto the implant, although most surgeons find this difficult without predrilled holes [123]. In a minipig model, acellular dermis wraps were observed to support fibrovascularization of porous PE (and HA) orbital implants without inducing significant inflammation and persisted *in situ* for at least 12 weeks after surgery [120]. A recent retrospective

report by Blaydon et al. suggested similar exposure rates for wrapped and unwrapped porous PE implants (< 5%) [117].

An unusual complication following implant exposure was reported by Robberecht et al., who described a patient with lost eyelashes perpendicular to the extruding part of a porous PE implant due to their entrapment within the implant pores [124]. Infections of porous PE implants are generally rare [125]. Chuo et al. carefully reviewed the histopathologic features of 18 explanted porous PE orbital implants and confirmed that anterior exposure is a risk factor allowing bacterial colonization; furthermore, poor tissue in-growth may limit the penetration of topical or systemic antibiotic therapy, leading to the need for implant removal [126].

Comparative studies about the postoperative problems associated to HA and PE implants did not provide yet definite conclusions. In 2008 Sadiq et al. analyzed 2 groups of 26 patients receiving a HA or porous PE implant, respectively, and reported that the complication rates were identical between the groups; only, the implant motility was better in the PE group [127]. On the contrary, Ramey et al. found that porous PE and aluminum oxide implants were associated with higher exposure rates and higher overall complication rates compared to HA implants [128]. It is worth mentioning that the type of material is certainly a key aspect but, in clinical practice, the choice of orbital implant is often mainly governed by other factors such as surgeon experience, ease of use and cost. Porous PE implants were also used in pediatric population with satisfactory outcomes and relatively low complications rates [129, 130]. Some authors have recently suggested that the risk of exposure can be prevented if the porous PE implant is used in combination with a free orbital fat graft over its anterior surface [131,132]; however, Kim et al. observed in a rabbit model that the fat patch on Medpor® implants was gradually resorbed and the fat-occupied volume was not maintained [133].

The first generation of spherical porous PE implants had a rough surface like HA – probably this was the reason why a high exposure rate (about 22%) was reported in the early studies [134] – and quite homogeneous pore distribution [123]; since then, implants with gradients of porosity have

been introduced. For instance, the smooth surface tunnel sphere (SST™, Porex Surgical Inc., Newnan, USA) has suture tunnels for easier muscle attachment and exhibits a non-porous anterior surface to prevent abrasion of the overlying tissue while retains a larger pore size posteriorly to facilitate fibrovascular in-growth [135]. Other currently available Medpor® implants (Fig. 3b) include some variations of the standard porous sphere (e.g. egg-shaped implant developed for easier implantation), conical implants with a flat anterior surface and an upward projection to reduce superior sulcus defect [136] and the recent quasi-integrated "quad" PE motility implant (Medpor Quad™ Motility Implant, Porex Surgical Inc., Newnan, USA), which is similar in design philosophy, shape and method of muscle attachment (imbrication) to the Iowa and Universal implants (see the section 3.6). A standard spherical Medpor® implant costs approximately 150 € less than the Bio-Eye® porous HA sphere; new-generation PE implants having complex shape and advanced functionalities are more expensive proportionally.

By looking at the future of PE orbital implants, it is instructive to mention the recent work by Kozakiewicz et al. [137] who fabricated by a CAD-CAM approach and implanted in 3 patients ultra-high molecular weight PE implants for orbital reconstructions. On the basis of CT scanning, the authors prepared a virtual model of both orbits (injured and uninjured); 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 be applied in the future also for designing and manufacturing orbital implants closely mimicking the original shape and size of the anophtalmic socket; issues to be considered concerns the long time required to design and manufacture implants at the pre-operative stage and, accordingly, their high cost.

3.5.5. Polytetrafluoroethylene

The use of expanded (porous) polytetrafluoroethylene (ePTFE or Gore-Tex; W. L. Gore & Associates, Flagstaff, USA) spheres as orbital implants was investigated by Dei Cas et al. in the late 1990s [138]. The left eyes of 6 New Zealand white rabbits were enucleated and replaced with spherical Gore-Tex implants. After a 6-week follow-up, no rabbits developed a postoperative infection and no cases of exposure or extrusion were noted; there was also evidence of inflammatory infiltration and fibrovascular in-growth into each implant to a maximum penetration depth of 500 μm. Histopathologic analyses revealed varying degrees of acute and chronic inflammation surrounding each implant; probably, this is the reason why no other studies on Gore-Tex as an orbital implant biomaterial were carried out in the following year.

It is instructive to mention that, in the ophthalmic field, the problems related to ePTFE-induced inflammatory reactions were also found by Mourtemousque and associates [139,140], who investigated its use as a scleral buckling biomaterial for the treatment of retinal detachment; stiffness mismatch with orbital tissues is probably one of the reasons why these postoperative complications occurred.

3.5.6. Aluminum oxide

Aluminum oxide (Al_2O_3), commonly termed alumina, has been used for decades in orthopaedics thanks to its attractive mechanical properties (high hardness and compressive strength, excellent resistance to wear), biocompatibility and bio-inertness. For instance, the introduction of alumina and, later, alumina-based ceramic composites for manufacturing prosthetic femur heads had a significant impact in the field of hip joint replacement, leading to an improvement of prosthesis duration and performance as well as of patient's life quality [141]. Since the late 1990s, alumina was also proposed in a porous form to fabricate orbital implants to be used in ophthalmoplasty; this type of device was approved by US Food and Drug Administration in April 2000 and has been marketed under the commercial name of "Bioceramic implant" (Fig. 3c).

The first *in vivo* study was reported in 1998 by Morel et al. [142], 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 was confirmed two years later by Jordan et al. [143], who compared the performance of alumina and HA implants in rabbits again. The authors reported that the new alumina implant was as biocompatible as HA, less expensive and its manufacturing did not involve any damage to marine life ecosystems as may occur in the harvesting of coral for coralline HA devices.

A more exhaustive comparison about the proliferation of orbital fibroblasts *in vitro* after exposure to Bioceramic implant and other three implants made of different materials (coralline HA, synthetic HA, porous PE) was documented by Mawn et al. [144], who assessed cell growth with immunocytochemical analysis using bromodeoxyuridine, a thymidine analogue. The proliferation of fibroblasts differed on the various studied implants and, specifically, was maximum on the Bioceramic 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 these debris, which was mainly attributed to its finely crystalline microstructure.

Promising results were also published in 2002 by Akichica et al. [145], who implanted pieces of alumina with 75 vol.% porosity in the eye sockets of albino rabbits. There were no signs of implant rejection or prolapse of the implanted material over a 8-week follow-up; at 4 weeks after implantation, fibroblast proliferation and vascular invasion were noted, followed by tissue in-growth by the 8th week. The first outcomes of Bioceramic implant in humans (107 patients over a 3-year follow-up) were reported by Jordan et al. in 2003 [146]. Postoperative problems encountered with its use were similar to those observed with coralline HA orbital implants (Bio-eye®) but appeared to occur rarely; furthermore, the incidence of exposure associated with the Bioceramic implant was less than that reported for the HA ones, and infection did not occur in any patient. In a following study Jordan and coworkers showed that alumina implant infections are generally rare

[147] 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 [148]. Wang et al. [149] reported that exposures of Bioceramic implants occurred after long-term follow-up 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.

In a recent study, Ramey et al. [128] 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 [147-149]. In case of alumina implant exposure, some strategies can be attempted to avoid removal of the implant and secondary surgery; for instance, Wang and Lai [150] successfully repaired an exposed Bioceramic implant after 4 months after surgery by a retroauricular myoperiosteal graft. This type of autologous graft contained myofibrovascularized tissue, provided durable and vascularized coverage of exposed implant and only required a nearby harvesting site; the exposure completely resolved without recurrence after 2 years of follow-up. Zigiotti et al. [151] recently described a new surgical procedure to reduce postoperative complication following alumina implant insertion in enucleated eyes. The authors initially performed a standard enucleation on 19 patients; then, they covered the Bioceramic implant only partially with the patient's sclera harvested from the enucleated eye, and the implant was finally inserted into the posterior Tenon's space with the scleral covering looking at front. There were no cases of implant extrusion over a 16-month follow-up period and the orbital volume was well reintegrated with good cosmetic result after final prosthetic fitting (a good motility was also documented).

3.5.7. HA-coated aluminium oxide implants

The HA/Al_2O_3 composite porous orbital implant, developed by a group of Korean researchers in the early 2000s, deserves a special mention. A synthetic HA-coated porous alumina implant was fabricated by the polymeric sponge replication method in order to overcome the limitations associated to coralline HA implants; the porous Al_2O_3 skeleton acted as a load-bearing member, whereas the 20-µm thick HA coating layer was advocated to provide biocompatibility and long-term stability in the eye [152]. Seong et al. [153] evaluated the morphologic changes of 12-mm sized HA/Al_2O_3 devices with different pore sizes (300, 500 and 800 µm) after implantation in 18 eviscerated rabbits. Fibrovascularization was noted at the implant periphery in all groups after 2 postoperative weeks and also at the center of the implant after 4 weeks. Fibrovascularization was most predominant in the group of implants having 500-µm pores compared to the other two groups.

In 2002 Jordan et al. [154] reported a comparative study on the implantation of experimental alumina implants coated with HA or calcium metaphosphate in rabbits. Both types of implant had multiple interconnected pores and, in comparison to the uncoated one, the coatings increased the size of the trabeculae from 150 to 300 µm; therefore, the pores appeared smaller but still ranged in the 300-750 µm range. There was no clinical difference in the socket response between coated or uncoated implants and, histopathologically, fibrovascularization occurred uniformly throughout each implant at 4, 8 and 12 weeks after implantation.

Three years later Chung et al. [155] investigated the fibrovascular in-growth and fibrovascular tissue maturation of HA-coated porous alumina implants in comparison with HA sphere in enucleated rabbits over a 24-month follow-up and achieved similar conclusions. There was no significant difference between the two groups, except for the 3^{th} to 4^{th} week postoperative period, during which the composite sphere showed a significantly lower grade of fibrovascular tissue maturation.

To the best of the authors' knowledge, no other studies about HA-coated implants have been reported in the literature. Although these implants showed similar appearance of fibrovascularization, low price and easy manufacture compared to the coralline HA implants (Bio-

eye®), probably the absence of a clear advantage from a clinical viewpoint (HA coatings did not appear to facilitate or inhibit fibrovascular in-growth) and the presence of significant amounts of CaO as a contaminant (related to the coating manufacture) [154] led the researchers to abandon further investigations. As a suggestion for future research, long-term studies could be useful to more clearly determine whether the HA coating actually plays a significant role in the acceptance and retention of the implant.

3.5.8. Polyethylene/bioglass composite implants

As first demonstrated by Hench et al. in the early 1970s [156], bioactive glasses (BGs) exhibit the unique properties to bond to bone forming a stable interface and to stimulate bone tissue regeneration. BGs are recognized as ideal materials for bone substitution with superior performances with respect to HA or other calcium-phosphate bioceramics, have been extensively investigated over the years in form of dense implants, fine particulate and 3-D porous scaffolds by several research groups worldwide [157-163] and some BG-based products are currently available on the market [164]. To date, the application of BGs to orbital implants fabrication is quite limited and the relevant reports are still scarce [165,166].

In 2006, Choi et al. [165] first investigated the *in vivo* suitability of BG for the manufacture of orbital implants; specifically, the authors studied the effects of BG particulate on the fibrovascular in-growth that occurred in porous PE orbital implants. Forty-eight rabbits were divided into 4 equally-sized groups, according to the different surgical techniques and implanted materials used: groups 1 and 2 were implanted with porous PE after enucleation or evisceration, respectively (reference groups), whereas groups 3 and 4 received porous PE/BG composite implants after enucleation or evisceration, respectively. Histological examinations revealed that there was no statistically significant difference with regard to fibrovascular in-growth among the 4 groups after 1, 2, 4 and 8 weeks of postoperative follow-up. Therefore, the authors concluded that inclusion of BG

particulate did not significantly promote the rate of fibrovascular in-growth into porous PE orbital implants.

In 2011, Ma et al. [166] reviewed the clinical outcomes of 170 patients after placement of porous PE/BG composite orbital implants for primary enucleation or secondary implantation. The majority of patients did not experienced any complications (161 cases) and had comfortable socket characterized by good implant motility, without conjunctival thinning or inflammation; excessive discharge and implant exposure occurred in 2 and 7 cases, respectively. All exposures were successfully treated with antibiotics or additional surgery; secondary surgeries were required by some patients but not due to implant-related complications (ectropion repair in 5 patients and volume augmentation in 3 patients). These early results suggest that the porous PE/BG composite orbital implant may be a useful implant for orbital reconstruction, but comparative studies are necessary to definitely estimate their performance with respect to the other available – and routinely used – implants.

3.5.9. Silicone

In a very recent study, Son et al. [167] compared the extent of fibrovascular in-growth of experimental porous silicone orbital implants with that of commercially-available porous PE (Medpor®). Both types of spherical implants were implanted in the left socket of 20 New Zealand white rabbits after enucleation. At 4 weeks after surgery, porous PE implants showed deeper fibrovascular in-growth than porous silicone spheres (42.4% vs. 34.2% of the radius of the implants) and a similar trend was also observed after 8 weeks, although the difference was more moderate (71.6% vs. 63.6%). This preliminary report demonstrates that porous silicone orbital implants exhibit fibrovascular in-growth comparable to that of commercial Medpor® implants and might be therefore low-cost, effective alternatives to current porous implants; long-term studies on a

larger number of subjects are needed to clearly determine the suitability of porous silicone as an orbital implant as well as the advantages/drawbacks ratio.

3.6. Porous quasi-integrated implants

The advantages of porous and quasi-integrated implants, in terms of fibrovascular in-growth and motility, respectively, was merged for the first time by Girard and co-workers [168,169] who described a porous quasi-integrated enucleation implant made of Proplast II (Vitek, Inc., Houston, TX). It differed from Proplast implant I in its composition, being constituted by 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 in-growth. Proplast implant II was completely buried maintaining a nipple on its anterior surface that could integrate with a depression on the posterior surface of the ocular prosthesis. Several Proplast implants II required subsequent removal because of poor motility and, over histopathological examination, were found to be completely avascular and surrounded by a pseudocapsule [170]. Use of Proplast II has been still reported later as a subperiosteal implant for the correction of anophthalmic enophthalmos in patients having poor orbital volume replacement despite the prior insertion of an adequately-sized spherical implant within the orbital socket [171].

In the same years, Guthoff and associates [172] developed a composite implant constituted by a semispherical anterior part made of synthetic porous HA to guarantee tissue integration joined to a posterior part that was manufactured using silicone rubber; the horizontal and vertical eye muscles were sutured cross-wise in front of the implant to ensure better stability and motility. Overall implant biocompatibility was excellent and the transmission of the motility to the prosthesis was moderate to good [173,174]. To date this implant is commercialized and considered a good option especially in Europe; however, its diffusion is quite limited as standard porous implants seem to be generally preferred by surgeons.

The more recent evolution of this type of devices is represented by the Medpor Quad™ implant, that is conceptually similar to the Iowa implant but fully made of porous PE instead of solid PMMA. A preliminary study on 24 patients showed no cases of the "quad" implant extrusion or migration; only, 2 patients required deepening of their inferior fornix to accommodate the increased motility of their prosthesis [175]. 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 [176].

3.7. Comparison of the present strategies and crucial issues

After presenting in the previous sections an overview of the different types of orbital implants that are currently available in the marketplace or have been recently proposed for experimental studies, some crucial questions will reasonably raise: first of all, is there a class of orbital implants univocally superior to the other ones? And then, more specifically, what is the role of surface chemistry and topography of the implant? Are the porous implants truly superior to the other orbital implants, including the last generation of PMMA quasi-integrated ones (the Universal implant)? Are the clinical outcomes of wrapped implants superior to those of unwrapped ones? Should the pegging procedure be clearly recommended to improve the ocular prosthesis motility?

On the basis of the existing literature, it is almost impossible to give definite responses to this complex set of questions; nonetheless, some indications can be presented, together with a series of challenges for the future. It is worth underlining once more that, in general, the choice of an "optimal" orbital implant is influenced by many factors, including the specific characteristics of the injury, cost, the patient's clinical history and age and the experience/opinion of the surgeon. For the reader's benefit, it is instructive to report part of the results of a recent questionnaire addressed to UK ophthalmologists to evaluate current clinical practice in the management of the anophthalmic socket [177]. The surgeons' responses indicated that 55% used porous orbital implants (PE, HA or

alumina) as their first choice and 42% used PMMA quasi-integrated implants; most porous implants were spherical (diameter 18-20 mm) and only a minority were egg-shaped or conical; 57% wrapped the implant after enucleation using salvaged autogenous sclera (20%), donor sclera (28%) and synthetic Vicryl or Mersilene mesh (42%); only 7% placed motility pegs in selected cases, usually as a secondary procedure; 14% of respondents reported implant exposure for each type of procedure and extrusion was reported by 4% after enucleation and 3% after evisceration. In summary, this survey highlights that most UK surgeons use porous orbital implants with a synthetic wrap after enucleation and only few perform motility pegging. The validity of these results may be reasonably extended to the whole European context; however, in other areas of the world, different options may be preferred. For instance, as declared by some local surgeons [37], in Pakistan it is quicker and less expensive to use the Sahaf quasi-integrated PMMA implant (produced on site) than to import porous orbital devices from abroad.

3.7.1. Material features

Looking at the chemical, physical and structural characteristics of orbital implants, comparative studies on such topics are actually quite rare in the literature. It has been recognized that adequate fibrovascularization is vital for achieving a long-term success of a porous implant: chemical composition, microstructure and mechanical features are all factors playing a role, but there is a high variation in these characteristics among the available materials. Perhaps the most comprehensive study was carried out by Mawn et al. [94], who compared the microstructural and architectural features (assessed by SEM) of six porous orbital implants made of HA (coralline Bio-Eye®, synthetic HA (FCI) and Chinese HA implant), porous PE (Medpor®; two implants with nominal pore size of 150 and 400 µm were examined) and alumina (Bioceramic implant). The Bio-Eye® had multiple interconnected pores in the 300-700 µm range; coarse-appearing 2-µm sized HA crystals were also observed. The FCI implant showed similar interconnectivity of the pores but with

fewer pores ranging within 300-500 µm; hexagonal HA crystals (size 1-5 µm) were detected. The Chinese HA implant had multiple interconnected pores ranging from 200 to 700 µm in size; the HA crystals were a bit smaller and more granular than those of Bio-Eye®. The 150-µm pore size Medpor® implant had irregularly-shaped pores in the actual 100-500 µm range, whereas the 400-µm pore size implant had channel-like pores actually ranging from 125 to 1000 µm; in both cases the surface showed a woven texture of PE. In the alumina implant the pores (size about 500 µm) were well interconnected and evenly distributed inside the material volume; the material showed a cobblestone-like pattern of crystals ranging from 4 to 5 µm. Therefore, there were marked variations of crystal size/shape and surface topography of porous implant biomaterials, and the authors suggested that such variations could influence the inflammatory response after implantation and hence the overall biocompatibility. From the viewpoint of micro-scale features, crystal size, for example, could determine the material-induced phagocytic response: biomaterials with crystal size above 3 µm showed greater tissue reaction, which was probably due to increased phagocytic activation by crystals of this size. Moreover, smooth HA crystals have been associated with less inflammation than sharp-edged crystals [178].

In a recent study, Choi et al. [179] examined the surface of non-porous PMMA, porous alumina and porous PE intact implants by atomic force microscopy (AFM). The surface of the non-porous PMMA implant showed nodule nanostructures in the 160-260 nm range, the alumina implant exhibited a porous structure with crystals ranging from 400 nm to 1.1 µm and the porous PE implant had the highest roughness with severe surface irregularities. 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-/nano-scale topography on bacteria, since cells have to compete with bacteria in many environments. In a fascinating scenario, surface topography could be purposely designed to encourage cells colonization while limiting bacterial adhesion [180]. The currently-available evidences indicate that

the relationship between the microstructural features and the clinical performance of orbital implants deserves future investigation, which could lead to develop novel design and manufacturing strategies. Looking at the macro-scale, 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 3-D tissue engineering scaffolds [181]. Rubin et al. [121] studied the vascularization in porous HA and PE orbital implants with small and large pore size and suggested that pore size should be greater than 150 µm and preferably around 400 µm in order to encourage favourable tissue in-growth. Another issue deserving investigation concerns the material surface chemistry and response to biological fluids through ion-exchange mechanisms, that are expected to play a key role for porous implants fibrovascularization; the challenge of the chemical design of orbital implant biomaterials, for instance by using BGs [165,166], will be discussed in the section 5.2.1.

A final interesting issue, which has been almost totally neglected in existing reports, is related to the mechanical properties of the implants that, especially if made of ceramic materials (HA, alumina), are remarkably stiffer than the original ocular globe as well as the surrounding orbital tissues. The use of stiff biomaterials carries some advantages from an operative viewpoint – e.g. the surgeon can easily handle and place the implant within the orbit with a great control over its position – but compliance mismatch between implant and overlying conjunctiva/soft tissues, in combination with repetitive movement of the implant by the extraocular muscles, might contribute to inflammation and soft tissue necrosis leading to implant exposure. Therefore, future research directions towards an ideal orbital implant might consider the use of more compliant biomaterials; potential options might be adapted, for instance, from the field of experimental vitreous substitutes, such as some selected hydrogels – biocompatible, porous and able to absorb water for having similar physical properties to living tissues [182] – or the capsular artificial vitreous, constituted by a 10-µm thick capsule made of a silicone rubber elastomer with a silicone tube valve system filled with physiological solution [183].

3.7.2. Motility

From a theoretical viewpoint, one of the major advantages of porous implants (e.g. porous HA, PE, alumina) in comparison to the non-integrated ones (e.g. silicone and PMMA sphere) should be the improved motility, even without the placement of a peg due to implant fibrovascularization. However, to date, no objective difference has been documented in terms of motility associated to porous or non-porous spherical implants. In a study on 55 patients, Colen et al. reported no statistical difference between the motility of unpegged porous HA and non-integrated PMMA or silicone spherical orbital implants (both types were wrapped within a scleral sheet) [184]. Analogous conclusions were formulated by Custer et al. in another report involving 107 patients receiving sclera-wrapped porous HA or non-integrated spherical implants [185].

It has been demonstrated that placement of a peg in porous implants may improve horizontal excursions [186] but this procedure is associated with some complications including chronic discharge, pyogenic granuloma formation, peg extrusion and audible "click" [96] – this is the reason why many surgeons and patients generally prefer to avoid peg placement [177]. Peg systems are generally designed for peg placement by additional surgery once fibrovascularization of the implant has been completed, since drilling into an avascular area may predispose the implant to infection [187]; assessment of the extent of implant vascularization can be performed by gadolinium-enhanced MRI [122]. Fibrovascular in-growth may occur at varying rates in different patients, but implant drilling and peg placement is generally deferred until 5 to 6 months after implant insertion. Several titanium peg systems are currently available for use with porous orbital implants: for instance, the Medpor® Motility Coupling Post (MCP) (Porex Surgical, USA) is a titanium screw that can be screwed directly into porous PE implants [188]. In summary, implant pegging seems to improve motility at the expense of a second procedure with related imaging studies, postoperative diseases and further costs. In order to overcome these drawbacks, some surgeons have experimented the peg insertion at the time of orbital implant placement (Fig. 3e), but

this practice still remains controversial [189-192]. Pegging has been sometimes experimented in non-integrated silicone spheres with good results [27].

A quasi-integrated implant, such as the Universal Implant, can be a valuable alternative to porous devices if pegging is not under consideration. From a theoretical viewpoint, the mounded surface of quasi-integrated implants should reasonably offer improved motility over a non-integrated sphere as a result of the partial coupling that occurs between the mounds on the implant and the posterior surface of the ocular prosthesis; however, the report by Smit et al. [193] showed no significant difference in prosthesis motility between Allen and sclera-wrapped PMMA baseball primary implants (18-mm sphere).

As far as the authors are aware, to date no motility comparison between quasi-integrated and porous orbital implants have been reported in the literature. From these relatively few data from the existing literature, it is evident that systematic comparative studies are still needed to draw definite conclusions about the superiority of a class of orbital implants over the other ones, at least as far as motility is concerned. The quasi-integrated design in a porous form, such as the Medpor Quad^{TM} Motility Implant, might at least partially overcome the drawbacks associated to pegging (costs and postoperative complications).

3.7.3. Exposure and clinical outcomes

Although comparisons are difficult due to different implant sizes, surgical techniques and follow-up periods, there are convincing evidences that the exposures occurring in porous implants are more amenable to conservative management without a second operative procedure; on the contrary, the exposures in non-integrated and quasi-integrated implants, unless very limited, almost certainly require implant removal [15,194]. Implant wrapping is useful to decrease the risk of exposure, since the smooth wrapping material acts as a barrier between the overlying soft tissue and the micro-/macro-rough surface of the implant, which is particularly helpful in the case of HA implants having

a rougher surface than other implants [91,100]. It has been demonstrated that the rough surface of unwrapped HA implants appears to be associated with a higher exposure rate when compared to non-integrated implants, and also sclera-covered HA implants seem to have higher late exposure rates than sclera-covered non-porous silicone implants [91,100] – but the former ones can be more successfully treated. Exposure rates for porous PE implants wrapped in absorbable material were found similar to those of unwrapped porous PE [117].

From a general viewpoint, implant wrapping carries some additional advantages as it enables easy attachment of extraocular muscles for better prosthesis motility, entails a smooth external surface thus making the process of implant insertion easier and helps volume augmentation by adding 1 to 1.5 mm of material to the implant diameter. Human donor sclera is the most commonly used wrapping material, but specially-processed bovine pericardium, human fascia lata and acellular dermis are also commercially available. Especially in the past, allografts and xenografts were associated to the risk of disease transmission from donor to patient, such as human immunodeficiency virus (HIV), hepatitis B or C and prions (Creutzfeldt-Jakob disease). Currently, at least in Europe and USA, extensive legislation exists and the donor sources are carefully checked before a graft is released for clinical use. Autologous sclera can also be used if enucleation is performed but its use must be avoided in case of ocular tumour. Alternative autografts include temporalis fascia, fascia lata, rectus abdominus sheath and posterior auricular muscle complex grafts, but the use of these tissues requires a second operative site, extra-surgery time and carries the risk of morbidity at the harvesting site; therefore, synthetic wrapping materials such as polyglactin-910 mesh are often preferred [8,9]. If non-absorbable wrapping material is used, the surgeon should consider the creation of holes through the wrap to allow a good vascularization of the porous implant.

In summary, it appears that the incidence of implant extrusion and socket infection is lower with porous implants; this supports the theoretical considerations that vascular in-growth helps to anchor the implant and permits immune surveillance. In case of implant exposure, implant savage by the

placement of frontal patches represents a successful approach [105]. Therefore, from the viewpoint of exposure-related complications porous implants seem to be preferable to other implant types, at least when surgery is performed in adults. When eye removal is performed in infancy, implant exchange may be necessary to stimulate adequate orbital growth; therefore, the use of porous implants in children is controversial, since implant exchange is more difficult once a porous implant has been vascularized.

By looking at the commercially-available porous orbital implants, it is impossible to univocally claim one porous material as clearly superior to the others, even though alumina, exhibiting excellent biocompatibility and favorable microstructural features [94], seems a promising candidate. The search for "ideal" orbital implant design and materials continues to progress due to significant improvements in analytical techniques for materials/implants analysis and patient monitoring. A robust comparison of currently-available orbital implants, as well as the clear detection of what features might be selectively improved, is difficult due to the relative scarcity of large randomized controlled trials in this area, the significant variations in patient populations, the differences in surgical technique, the wrapping option and the length of follow-up, as complications may not be apparent until 5 or more years post-operatively [44]. The results of well-designed, longer-term studies on the orbital implants performance could contribute to clarify some of these issues in the next years.

4. Ocular prostheses

Over the centuries, different models of ocular prostheses were tested and described, including metal (usually gold) shells with the iris painted in coloured enamel and thin, fragile glass shells that often had poor fit and little comfort [16]. Generally, all these prostheses were not supported by an orbital implant placed in the socket (there was no volume replacement), which was clearly reported by Mules only in 1885 [2]. At the end of 19th century, a thick but hollow glass artificial eye (the so-

called Snellen reform eye), that better compensated for volume loss after enucleation and reduced the sunken appearance of post-enucleation prostheses, was introduced and remained the standard until WWII [16]. Since the 1940s, the introduction of PMMA revolutionized the field of both orbital implants and ocular prostheses [18].

4.1. Post-surgical conformers

A final artificial eye (ocular prosthesis) is manufactured as soon as the postoperative inflammation has settled, usually within 6-12 weeks after surgery. During this time, a temporary acrylic conformer, commonly made of PMMA, is worn to keep the fornices formed and to prevent socket contracture [195,196]. Two holes are usually present in the conformer to allow the drainage of discharge from the socket and to make easier the application of medication (e.g. therapeutic drops) [196]. Standard conformers do not resemble a natural eye and often do not fit very well the correct ocular dimensions – they are too large or too small. Low-cost, pink acrylic resin for dentistry is often employed to make postoperative standard conformers.

Cosmetic conformers, exhibiting a variety of sizes, iris colours and scleral colours, are also available to patients. While they do not provide as good a fit or cosmetic appearance as the custom-made ocular prosthesis, however they are a valuable temporary option. A study published by Patil et al. showed that the majority of patients was pleased to wear a cosmetic conformer instead of a standard conformer, although the latter was less expensive [197]; the authors also highlighted that this early cosmetic improvement seemed to be very important in the emotional rehabilitation of patients following the loss of an eye.

4.2. Definitive ocular prostheses

The ocular prosthesis, as previously mentioned, fits over the orbital implant – with or without coupling by a peg – and sits just behind the eyelids. Professional ocularists are responsible for the overall fabrication and fitting of ocular prostheses (creation of the impression, shaping and painting the prosthesis); they also have to instruct the patient on how to place and care for the prosthesis, providing long-term support and help.

From a historical standpoint, before the WWII the majority of ocular prostheses were made of glass – hence they were popularly referred to as "glass eyes"; however, artificial glass eyes were brittle and prone to implosion with acute changes in temperature, as already discussed about the Mules orbital implant [2]. Furthermore, over time the glass prosthesis became etched from exposure to body secretions and usually lasts only about 2 years [197]. The battles of WWII created a large demand for artificial glass eyes, that were mainly produced in Germany; the unavoidable wartime shortage of ocular prostheses imported from this country led to the development, especially in the USA, of a new generation of artificial eyes based on acrylic resin. Interestingly, the introduction of PMMA ocular prostheses mirrored the advances of orbital implants, as the early models of quasi-integrated and mechanically-integrated PMMA orbital implants were also proposed in the mid 1940s.

Today, most of available prostheses are either stock or custom-made PMMA devices. With respect to glass, PMMA is more durable and has a longer life expectancy as well as better tissue compatibility [197]; however, glass is still used in selected cases. Stock, or ready-made, prostheses are advantageous when time and cost are limited because they can be fabricated rapidly with acrylic materials found in any dental office; furthermore, they do not require an artist to complete the painting of the iris and the sclera. However, stock prostheses are available in a limited range of sizes and iris colours. The size limitation is a concern because an improperly-fitting prosthesis may not only distort the lid and socket but it could also create an air pocket between the prosthesis and the socket, which provides a good medium for bacterial overgrowth. Moreover, rough fitting of the prosthesis may leave pockets where fluids stagnate; as a result, trapped fluid may gush forward in

response to firm eyelid closure – which is a socially unpleasing situation. The colour limitation of stock prostheses is also a concern for many patients because the iris colour of the prosthesis is often noticeably different from that of the healthy eye, which is aesthetically displeasing.

The preferred ocular prostheses are then the custom-made PMMA prostheses, fabricated through a multi-step processing schedule. To ensure that the artificial eye sits in a natural position and does not fall back into the socket and to minimise any space in which infected debris could collect, the device should be shaped to match the contours of the orbital tissues. Therefore, an impression of the socket is taken using a quick-setting material such as dental alginate; once set, the alginate is removed and a plaster of Paris mould is made from it. The mould is used to cast a wax shape, which is then trimmed to fit the socket. A further mould is made from the modified wax shape, and the PMMA prosthesis is finally cast in this mould. A hand-painted iris button is placed on the front of the eye, scleral features (e.g. veins) are painted on and clear plastic is laminated over the top (Fig. 4). Of course, the prosthesis should be tested in the patient's eye during the manufacturing process for proper fit and aesthetic appearance: symmetry of the iris in the palpebral opening and the alignment and plane of the irises in both the artificial and healthy eye are determined with the use of a corneal-iris button. Correct position of the iris is also ensured by measuring the distance from the facial midline and pupillary light reflex in the healthy eye and duplicating this measurement for the prosthesis.

The use of silicone as an alternative for the manufacture of ocular prostheses has been alternatively advocated or castigated over the years, and this controversy still lingers on. Since the mid 2000s, a silicone ocular prosthesis together with the so-called "Flexiglass system" – a kit for making the prosthesis – has begun to be marketed in the USA by the same producer. On the product website [31], silicone was claimed superior to PMMA as the latter was considered responsible of adverse reactions in certain patients and due to the toxicity of the catalyst used for PMMA production; it is textually reported that "the Flexiglass™ System is also now available globally. All of the products in the system comply with the medical device directives for a class 1 customizable medical device

and are CE compliant". However, as far as the authors are aware, the USA Society of Ocularists maintain the position that the quality of silicone prostheses is poor compared to that of acrylic-based ones, and therefore PMMA still remains the material of choice for the majority of ocularists, ophthalmologists and patients. Serious, comparative studies would be useful to give ultimate conclusions and full clarification to this issue.

The patients should receive precise instructions regarding the proper care and use of their own ocular prosthesis. It is strongly recommended to wear eye prostheses overnight during periods of orbital growth, and they may be worn overnight even later especially to prevent eyelashes turning in and irritating the conjunctival surface; however, if conjunctival inflammation develops, it is better not to wear the prosthesis during sleep. Cleaning can be performed by hand with a simple liquid surfactant; the ocular prosthesis should be then dried at air as paper tissues or towels could scratch the surface or allow bacterial contamination. Bacterial colonization of the posterior surface of the artificial eye in contact with the patient's conjunctiva or with the orbital implant's peg could be a crucial issue during the follow-up and lead to the development of infections; interesting strategies to overcome this problem are discussed in the section 5.2.3.

4.3. Cosmetic contact lenses

The removal of an eye is an extreme surgical option and not all painfully disfigured, atrophic, often blind ocular globes undergo such a fate; in many cases, pharmaceutical treatments can be administered to reduce pain and cosmetic solutions alternative to surgery are explored. Cosmetic contact lenses can be considered, at least to some extent, a particular subset of ocular prostheses and are intended to disguise eyes with unacceptable appearances; the lenses fall into three groups, i.e. scleral shells, soft corneoscleral contact lenses and rigid corneal contact lenses.

PMMA scleral shells are indicated when a blind eye is shrunken or its surface is very uneven; the thickness of the shell can be varied to properly fill out the volume deficit that accompanies ocular

atrophy. Scleral shells should be worn only while awake as the shell occludes the cornea, placing it under metabolic stress and thereby increasing the risk of ulceration; even more scrupulous care should be taken over the maintenance and cleaning (by an appropriate surfactant) of a scleral shell than over a whole eye prosthesis, behind which a "living" ocular globe does no longer exist.

Soft corneoscleral lenses are made of different types of hydrogels and can be recommended to hide corneal scars (due to trauma or infections) and iris defects (due to trauma or congenital diseases) in normal sized eyes that have a fairly regular surface. Soft lenses cannot be used if the eye is so misshaped that the lens will not centre or if the tear film is deficient. These lenses can be fully occlusive, with both pupil and iris coloured to match the fellow eye, or can have a clear pupil if the eye is sighted. Soft lenses should be worn only while awake for the same reasons that apply to scleral shells.

Rigid lenses are made of PMMA and their fabrication process and external features are analogous to those of definitive ocular prostheses.

5. Future perspectives and research challenges

5.1. The potential of advanced imaging techniques

Periodic monitoring of composition, density, volume and shape changes of orbital implants *in vivo* is essential to gain key information about the postoperative outcomes; in particular, the assessment of fibrovascular in-growth is extremely important when porous implants are used. Over the years, several imaging techniques have been developed and are currently at the surgeons' disposal. Medical source CT (MSCT) scanning has been widely used [121,198,199] but has the disadvantage of a significant radiation dose with each examination. Other imaging options to verify implant vascularization include gadolinium-enhanced MRI [122,200-202] and technetium 99m bone scintigraphy [203-205].

Intraorbital implant examination with cone beam CT (CBCT), having lower radiation exposure than MSCT, may be a simpler, less expensive and reliable alternative for the detection of soft and hard tissues which still has to be fully evaluated. CBCT was first described in the early 1980s and since then applied to dentomaxillofacial diagnostics [206,207]. In the past CBCT was less accurate than MSCT in tissue density measurements, but recent advances allowed to achieve a voxel resolution from 400 to 70 μm, whereas MSCT voxels are generally larger than 250 μm. However, image noise is generally higher with CBCT [208], while the dose of radiation is much lower [206].

In a recent work, Lukats et al. [209] highlighted the potential of CBCT in tissue engineering applications wherein long-term monitoring of scaffolds in a noninvasive manner with the lowest possible doses of radiation is required, and applied this technique to evaluate 30 enucleated patients receiving polyglactin-wrapped HA and alumina orbital implants over a mean follow-up of 3.2 years. Implant volume, orientation and shape estimations were possible while density evaluation was more complicated compared to MSCT and required careful calibration procedures. This approach is interesting and would deserve further investigations in next years to achieve definite conclusions about CBCT suitability in the ophthalmoplastic field.

As a final remark, it is worth mentioning that advanced imaging techniques associated to CAD/CAM systems for implant prototyping could disclose a great potential to fabricate ever more accurate, custom-made implants able to successfully fulfill the patient's anatomic and cosmetic needs; this issue will be further discussed in the section 5.2.1.

5.2. Smart biomaterials and implants with advanced and multipurpose properties

5.2.1. Bioactive glass-based orbital implants

BGs have been commercialized worldwide for almost 30 years mainly for bone defect and dental repair [164]. In the specific context of oculo-orbital surgery, BGs have been implanted in humans as

small plates for orbital floor repair [5,210-212] and introduced as particulate in experimental PE/BG composite porous orbital implants [165,166]; moreover, Lloyd and associates recently proposed the use of porous BG as an osteo-odonto-keratoprosthetic skirt material [213]. Hence, there are increasing evidences that BGs could have a great potential also for ophthalmic applications and the authors wish to report here some remarks to emphasize their possible impact in the development of a new generation of orbital implants with advanced properties that only few years ago would have seemed impossible.

BGs have not only the ability to bond to bone [156], but they were also found to stimulate new bone growth and to bond to soft tissues *in vivo* [159]. It was observed that ionic dissolution products from BGs play a key role in affecting the biological response of such materials *in vitro* and *in vivo*, stimulating the expression of several genes of osteoblastic cells towards a path of regeneration and self-repair [214]. Since many trace elements (e.g. Sr, Cu, Zn) present in the human body are known for their anabolic effects in bone metabolism, a new approach for enhancing the bioactivity of BG and BG-derived products could imply the introduction of therapeutic ions into the BG formulation. The subsequent release of these ions after exposure to a physiological environment is believed to exhibit possible antibacterial [215] or anti-inflammatory [216] effects and to selectively affect the response of human cells towards angiogenesis [217,218]. As to the type of orbital implant that might be fabricated by using BGs, porous spherical devices (scaffolds) conceptually similar to those made of HA or alumina would seem the most likely candidates; clearly, cell response will depend not only on chemical composition, but also on surface micro-/nano-roughness, porosity, topography, grain size and crystallinity (if a final glass-ceramic material will be obtained) of the implant [180,218].

Considering the particular application, it is worth pointing out an important aspect: osteogenesis stimulation and bone-bonding ability seem not to be desirable features for an orbital implant, but the added values to be pursued are the enhanced angiogenesis and fibrovascularization that may be induced by BGs. In fact, it has been recognized that vascularization is a desirable characteristic of

orbital implants since it discourages bacterial colonization of the surface and permits treatment of low-grade ocular infection with systemic antibiotics. Hence, an accurate design of BG composition should be performed to synthesize materials suitable to stimulate angiogenesis and fibrovascularization without inducing bone cells recruitment and bone in-growth. Furthermore, the dose effect also seems to play a key role: in a recent study, it has been observed that BG exhibits proangiogenic potential at low concentrations and significant osteogenic potential at higher concentrations [219]. It was reported that the BG surface reactivity, which is so critical in bone adhesion, does not imply a toxic effect in non-osseous tissues [220] and BGs were shown to be able to bond also to soft tissues [159,164].

A detailed overview of the studies investigating the BG effect on angiogenesis *in vitro* has been recently reported by Gorustovich et al. [221]. From a general viewpoint, *in vitro* experiments have shown that BGs stimulate the secretion of angiogenic growth factors in fibroblasts, the proliferation of endothelial cells and the formation of endothelial tubules [217,222]. Day et al. [217] found that L929 fibroblasts cultured on the surface of poly(L-lactic-*co*-glycolic acid) (PLGA)/Bioglass® discs with 0.01%, 0.1%, and 1% (w/v) of 45S5 Bioglass® particles (size < 5 μm) secreted increased amounts of vascular endothelial growth factor (VEGF) compared with cells cultured on PLGA alone. Keshaw et al. [222] recently reported that microporous spheres of PLGA containing 10 wt.% of 45S5 Bioglass® particles (mean particle size = 4 μm) stimulated a significant increase in VEGF secretion from CCD-18Co fibroblasts consistently over a 10-day period compared with neat PLGA microporous spheres.

In vivo results have confirmed that BG is able to stimulate and to promote neo-vascularization, as highlighted by Gerhardt and Boccaccini in a recent review [223]. Leu and Leach [219] filled calvarial defects in Sprague-Dawley rats with 45S5 Bioglass®-impregnated collagen sponges, using unloaded empty sponges as a control; after 2 weeks of implantation, histological analyses of calvaria demonstrated significantly greater neo-vascularisation and vascular density within the defects treated with the BG/collagen composite sponges as compared to collagen controls alone. In

a recent study, Gerhardt et al. [224] investigated the angiogenic potential of poly(D,L-lactide) (PDLLA)/45S5 Bioglass® porous composites wherein micro-sized and nano-sized BG particles were used. The authors observed that human fibroblasts produced 5 times higher VEGF if cultured on BG-containing (20 wt.%) composite in comparison to pure PDLLA; furthermore, after 8 weeks of implantation in Sprague-Dawley rats the composites were well-infiltrated with newly formed tissue and demonstrated higher vascularization and blood vessel-to-tissue percentage (11.6-15.1 %) than PDLLA scaffolds (8.5%). Following an interesting approach, Vargas et al. [225] used the quail chorioallantoic membrane as an *in vivo* model to evaluate angiogenesis and observed that addition of 10 wt.% of silicate BG nanoparticles to collagen films induced an early angiogenic response, which makes these composites promising matrices for tissue engineering and regenerative medicine.

Apart from the advantages from a biological viewpoint, BGs also have other attractive properties. BGs are very versatile as they are synthesizable in form of powders, granules or 3-D porous scaffolds of various size and shape including the spherical one typical of orbital implants (Fig. 5a). Macroporous scaffolds can be obtained by a variety of methods such as foaming techniques [226], organic phase burning-out [227] and sponge replication [157,161]. If glasses are processed in form of mesoporous materials (Fig. 5b), they can also easily incorporate specific molecules, for instance anti-inflammatory drugs, to be released *in situ* postoperatively to elicit an appropriate therapeutic effect [228-230]. Custom-made BG-derived porous orbital implants could be fabricated by using rapid prototyping techniques [231]: CT- and MRI-derived files can act as input data for CAD/CAM manufacturing systems in order to produce scaffolds matching exactly the dimensional features of the anophtahlmic socket. Recent studies have demonstrated that advanced manufacturing techniques such as lithography-based methods [232] or selective laser sintering [233] can lead to the production of high-quality porous scaffolds of complex shape with an accurate control of pore size and interconnectivity. Furthermore, BG-derived products can be easily, quickly and effectively sterilized, for instance by β- or γ-irradiation, without undergoing degradation.

Specific added values can be imparted to BG-derived products by appropriate surface treatments [163]: for instance, use of silver-doped glasses [234] to produce orbital implants exerting antibacterial properties could be a promising strategy for the future (an example of silver-doped layer on the surface of a bioactive glass, obtained by ion exchange, is reported in Fig. 5c); this topic will be treated in more detail in the section 5.2.3.

A further opportunity to improve the biological performances of bioactive glasses involves their surface functionalization. Silica-based glasses easily expose reactive hydroxyls groups on their surface by simple water treatments, and these functionalities can be employed for the grafting of appropriate biomolecules/drugs eliciting specific responses/therapeutic actions. For instance, Verné and associates successfully coupled biomolecules and drugs to different bioactive glasses and glass-ceramics for bone regeneration and cancer treatment [235,236]. In this way, the idea of grafting specific growth factors to enhance vascularization, or drugs to reduce inflammation and infection, could be of interest also in the field of orbital implants.

Comprehensive reviews dealing with the recent advances on bioactive porous glasses and glass-ceramics have been published in last years and are available to interested readers [163,223,237].

In the light of the above-discussed properties of BGs, in the next future a 8^{th} type of orbital implant could be included in Table 2, as BG-based porous implants are expected to fall under the definition of "bioactive orbital implants". In biomaterials science and regenerative medicine, the term "bioactivity" refers to the ability of a biomaterial to perform a desired, appropriate function generating the most appropriate beneficial cellular or tissue response in a specific situation. Of course, bioactivity implies biocompatibility (that is a sort of pre-condition), i.e. the ability of a biomaterial to perform its function without eliciting any undesirable local or systemic effects in the recipient, according the definition provided by Williams [238]. In the context of anophtalmic surgery, as previously mentioned one of the most important functions to be performed by the (porous) orbital implant biomaterial is the promotion of fibrovascularization, which could be actually enhanced by *in situ* release from a BG implant of suitable metal ions eliciting an

angiogenetic effect [218]. The possibility of making porous orbital implants fully constituted by BGs was disclosed by Richter et al. in a recent patent [239] but, as far as the authors are aware, no manufacturing or clinical studies have been reported yet in the literature on this type of implants; early studies on BG/PE composite orbital implants have been carried out [165,166] but further investigations are needed to obtain more substantial conclusions.

Few closing remarks on the concept of orbital implant bioactivity need to be presented. In this work, BG-based orbital implants are defined "bioactive" as BGs were shown to intrinsically exert an active role, mainly by the deliberate release of appropriate ions, in stimulating and directing angiogenesis at the cellular and genetic level; therefore, the term "bioactive" is equivalent to "angio-inductive". On the other hand, fibrovascular in-growth has been observed also in commercially-available HA, PE and alumina orbital implants from which no release of "angio-stimulating" ionic species occurs. In these cases, however, the vascular in-growth is possible due to the presence of a 3-D porous network in the implants; therefore, these porous biomaterials should be defined "angio-conductive" instead of "angio-inductive" (i.e. "bioactive" in a strict sense). Alternatively, adopting a remarkable simplification and focusing the attention only on the final effect (i.e. the fibrovascular in-growth inside the implant), all porous orbital implants might be defined as potentially "bioactive", but in this way the peculiar, intrinsic features of the different biomaterials would be no longer taken in account.

5.2.2. Absorbable orbital implants

All orbital implants developed over the years have been designed to be permanent, i.e. they should remain *in situ* indefinitely during the patient's whole life without undergoing resorption, degradation or partial/total replacement by surrounding tissues. An interesting exception has been proposed in a patent deposited in the late 1990s by Durette [240], who disclosed an approach in partial countertendency with respect to the established perspective. The Durette orbital implant was

provided with a passageway extending from the anterior surface inwardly to receive a peg prior to implantation; the peg should be made of non-porous material so that the surrounding tissue would encapsulate it without a tight contact. A cap of absorbable biomaterial was placed in front of the implant in order to create a "cushion" between implant and overlying ocular prosthesis, that would be later coupled to the implant by means of the peg without the need for a second drilling procedure for peg placement. Durette specified that the implant should be preferably made of biodegradable material having a matrix with random voids throughout to enhance tissue in-growth [240].

The ideas suggested by Durette are fascinating and would deserve careful experimentation in the next years. A partially absorbable implant able to increase its porosity *in vivo*, thereby allowing improved fibrovascularization, could represent a clever approach; however, the use of a fully biodegradable orbital implant poses several issues, especially concerning the kinetics of socket volume replacement by tissue during implant degradation and the ocular prosthesis motility in absence of an implant that can transfer movement to it.

5.2.3. Antibacterial devices

Bacterial issues in ophthalmic applications, with particular reference to postoperative infection of ocular implants, can cause significant problems followed by post-surgery additional treatments that are both expensive and stressful for patients [104,106,125,126,147,241-242]. Over the years, some strategies have been experimented to limit the risk of bacterial colonization at the time of surgery; for instance, it is a common practice to impregnate porous HA orbital implants in antibiotics prior to implantation in the orbital socket [244]. This approach is certainly useful intraoperatively, but a key challenge of modern ophthalmology is to develop smart biomaterials able to exert a long-term antibacterial activity in order to limit late bacterial colonization and infection of the implant. Moreover, the widespread and increasing use of antibiotics led to the development of antibiotic-

resistant bacteria and, therefore, there is the need for investigating alternative strategies and approaches.

Attempts at imparting intrinsic antiseptic properties to the devices for ophthalmoplasty (ocular prosthesis and orbital implant) are very rare in the literature. In a recent patent, Jun et al. disclosed an antibacterial ocular prosthesis produced by incorporating small amounts of silver, gold or platinum nanoparticles in the acrylic resin (PMMA) or silicone used to fabricate the prosthesis; the patent also related to a conformer produced by the same method and having antibacterial properties in itself [245]. Following a similar approach, Yang et al. produced a PMMA-based ocular prosthesis dispersing silver nanoparticles in the resin (concentration from 300 to 700 ppm), tested its antibacterial properties *in vitro* against *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* and reported that the antimicrobial activity of the Ag-containing artificial eye was 4.8-6.2 times stronger than that of controls [246]. Both approaches, however, pose some problems associated to the release of nano-sized silver, which could be a crucial issue for the implant applicability since tissue toxicity of metal nanoparticles has been reported in several *in vitro* and *in vivo* studies [247,248].

A promising strategy, that was very recently proposed in a patent by the authors [249], involves the deposition of an antibacterial composite coating on the surface of ocular prostheses and orbital implants. The coating is preferentially constituted by silver nanoclusters embedded in a silica matrix and can be produced by radio-frequency (RF) co-sputtering of silver and silica used as targets (an example of TEM cross-sectional image is reported in Fig. 5d). Previous papers demonstrated that these coating can be successfully deposited on wide variety of substrates (e.g. silicate glasses, polymers) and are able to retain their mechanical stability and antibacterial characteristics even after heating above 500 °C [250-252]. Other matrices (e.g. alumina, TiO_2, polymers) and antibacterial metal agents (e.g. copper, zinc) may be experimented to find the best solution depending on the type of substrate material to be coated and on the biological environment wherein the antibacterial device will exert its function. The proposed coatings are generally thin (from few tens to thousands

of nanometers) in order to maintain bulk properties of substrates and, in particular, possible flexibility of polymeric materials.

The co-sputtering technique has the advantage to allow the tuning of the antibacterial metal concentration through the control of the deposition parameters (e.g. power, pressure in the deposition chamber) and the metal nanoclusters size by using thermal treatment following the sputtering process [250]. In such a way, in a fascinating scenario it would be possible to tailor and to properly design the antibacterial effect in terms of both efficacy (amount of released antibacterial agent) and persistency (more or less prolonged kinetics of release). Considering the silver/silica composite coatings produced by this method in preliminary studies, it has been observed that the as-sputtered coatings contained small silver nanoclusters (diameter of 5-10 nm) that increased their size by heating up to 600 °C [250]. Moreover, it has been also demonstrated by leaching test in different conditions (water or simulated body fluid at 37 °C) that the obtained coatings were able to exert an antibacterial activity for at least 1 month [250]. Furthermore, there are preliminary evidences suggesting that silver is released in ionic form instead of nanoparticles: this is a significant added value overcoming the toxicity issues related to metal nanoparticles delivery. Moreover, the use of metals as antibacterial agents instead of antibiotics, commonly employed in therapy and prevention of implant-related infections, could overcome the problem of bacterial resistance and can be effective also on resistant bacterial strains.

In the case of ceramic orbital implants, such as the HA or alumina ones, ion exchange techniques for surface silver-doping are also suggested in the patent [249], on the basis of the good results obtained with surface treatment of glass and glass-ceramic substrates (Fig. 5c) [234,253].

Exploitation of appropriate metal ions release from biomaterials surfaces for antiseptic purposes is certainly a valuable and promising strategy, and not only in the ophthalmic field [218]. However, it cannot be ignored that ocular environment is particularly complex and several parameters should be taken in account for designing really suitable implants; for instance, the interaction of metal ions with the tears, the fate of released ions and the possible ion-induced eye tissue necrosis are all

aspects deserving careful consideration. Being such topics very new, the existing literature is very scarce but it is instructive to mention a significant case recently documented by Hau and Tuft [254], who described corneal argyrosis associated with silver nitrate-coated cosmetic soft contact lenses that a 67-year-old woman wore for 17 years for the management of intractable diplopia: this is a typical example of an apparently unexpected side effect detectable only after many years of follow-up. In the next years an ever increasing cooperation among materials scientists, chemists, biologists, oculo-orbital surgeons, ocularists and researchers in the medical implant industry would be desirable in an attempt to select and market more suitable and cost-effective biomaterials for the management of the anophtalmic socket, in order to further improve the patient's quality of life.

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Disclosures

The authors have no conflict of interest with one or more companies whose products are mentioned in the manuscript.

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Figure legends

Fig. 1. Sagittal sections of a human orbit after enucleation surgery followed by placement of a spherical implant that replaces the volume deficit created by eye removal. In these pictures, the extraocular muscles are sutured directly to the implant. The ocular prosthesis is designed to fit in between the eyelids and the conjunctiva/implant in order to mimic the normal appearance of a healthy eye. The connection between orbital implant and ocular prosthesis can be indirect, due to the interposition of the conjunctiva (a), or direct, by the use of a peg (b). Pegging procedures are normally performed only in porous orbital implants. After some months from primary surgery, a hole can be drilled into the anterior section of the implant; a peg is then inserted in the hole. Use of pegged implants leads to a greater transmission of movement of the implant to the artificial eye, giving a more life-like appearance.

Fig. 2. Use of PMMA for manufacturing orbital implants: (a) pear-shaped implant (Sahaf implant type I) (image adapted from Kamal et al. [38]); (b) comparison between the Iowa implant (upward) and the Universal implant (downward), showing that the latter has softer mounds in comparison to the Iowa predecessor (image adapted from Sami et al. [15] © Elsevier); (c) magnetic orbital implant and (d) associated ocular prosthesis exhibiting magnet rusting in both components, which may induce late exposures over the central surface of the implant associated to tissue necrosis due likely to iron toxicity (images adapted from Sami et al. [15] © Elsevier).

Fig. 3. Porous orbital implants: (a) coralline HA sphere (Bio-eye®); (b) some examples of porous PE implants (Medpor® line): simple sphere, conical, egg-shaped, "quad" motility implants (courtesy of Porex Surgical); (c) SEM micrograph showing the porous structure of an alumina implant (Bioceramic implant) (image adapted from Jordan and Klapper [23] © Springer); (d) HA spherical implant wrapped within polyglactine 910 mesh prior to surgery (image adapted from Lukats et al.

[209]); (e) vicryl mesh-wrapped HA orbital implant with a titanium sleeve placed before surgery (primary placement) (image adapted from Liao et al. [192] © Nature Publishing Group).

Fig. 4. Typical PMMA ocular prosthesis: (a) hand painting of the iris button, so that it can be as similar as possible to the aesthetic appearance of the healthy eye (b); (c) frontal appearance (with painted capillary vessels) of the final prosthesis after polishing for optimal fit to the patient's anatomy; (b) posterior convex surface.

Fig. 5. Smart biomaterials and strategies for the possible development of future orbital implants with advanced properties: (a) SEM micrograph showing the porous structure of a bioactive SiO_2-based glass scaffold fabricated by sponge replication method: its 3-D interconnected pore network is similar to that of Bioceramic implant (Fig. 3c); (b) TEM image showing the ordered mesoporous structure (parallel channels with diameter of about 5 nm) of a mesoporous bioactive glass (ternary system SiO_2-CaO-P_2O_5) wherein therapeutic agents, drugs or suitable organic moieties could be incorporated for subsequent controlled release *in situ*; (c) silver diffusion profile (the surface is on the left) on the cross-section of a silver-doped glass (ternary system SiO_2-CaO-Na_2O) estimated by compositional analysis (EDS) (image adapted from Verné et al. [234] © Elsevier); (d) high-resolution TEM image showing the cross-section of a silver nanocluster/silica composite thin coating deposited on silica substrates by radio-frequency co-sputtering (image adapted from Ferraris et al. [250] © Elsevier). The approaches illustrated in (c) and (d) are potentially useful to impart antiseptic properties to the orbital implant material [249].

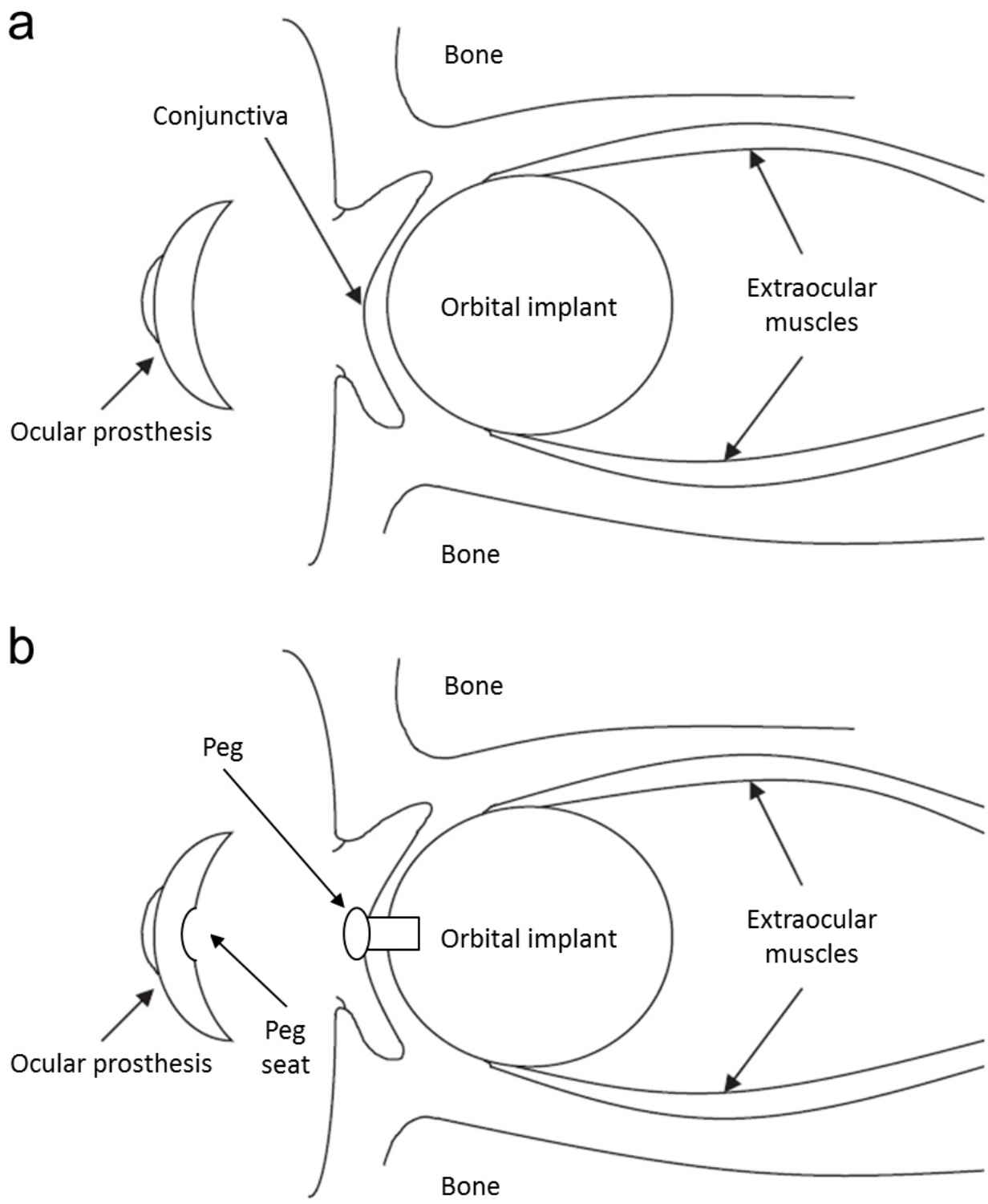
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Fig. 1

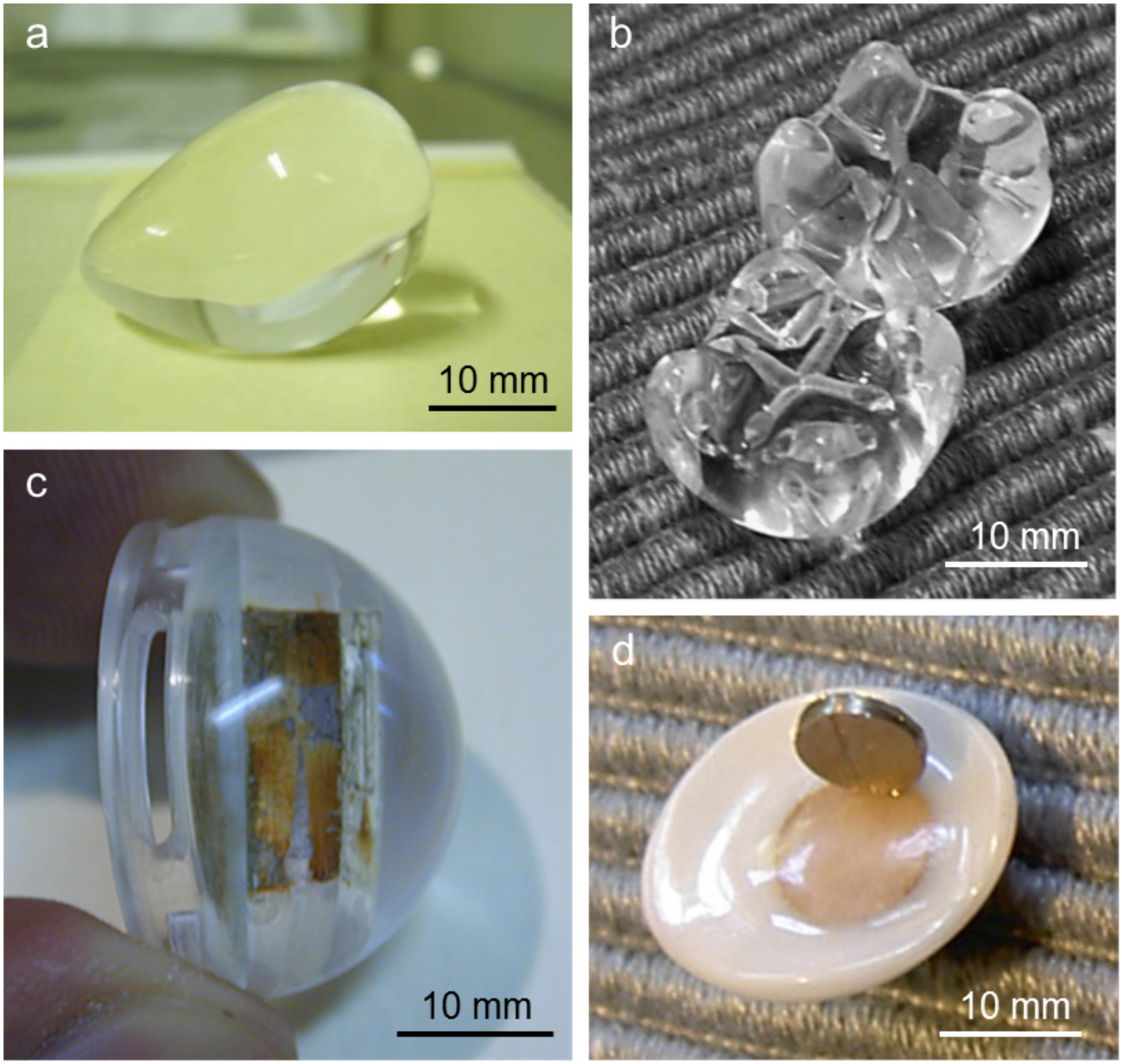

Fig. 2

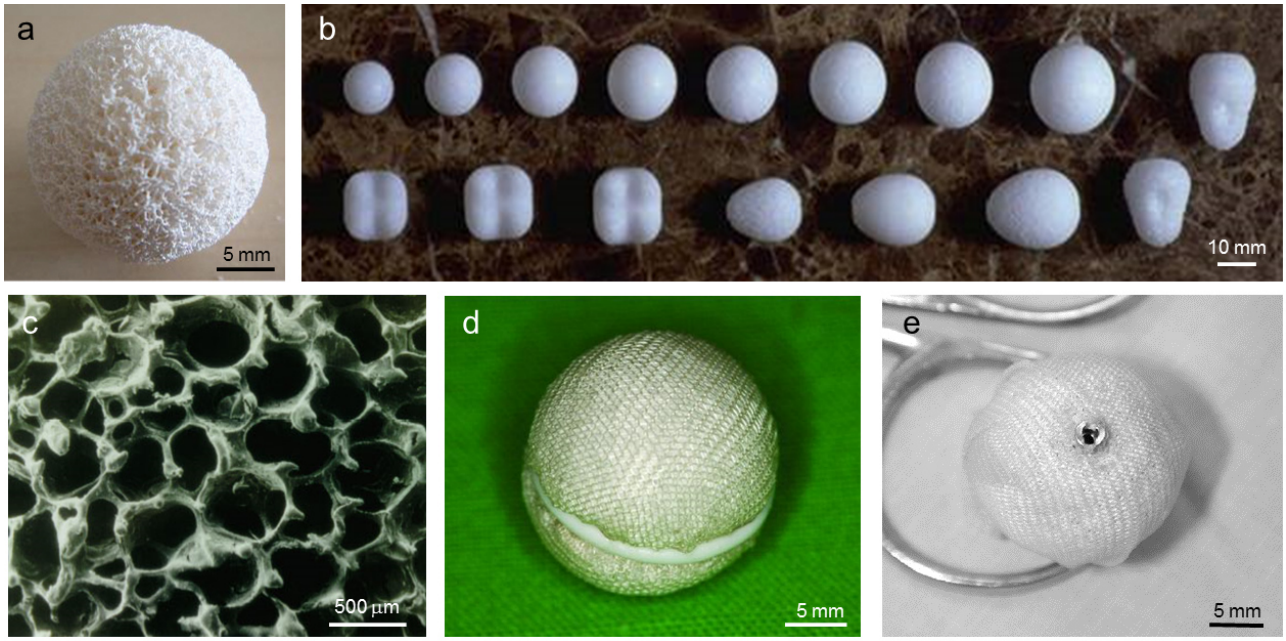

Fig. 3

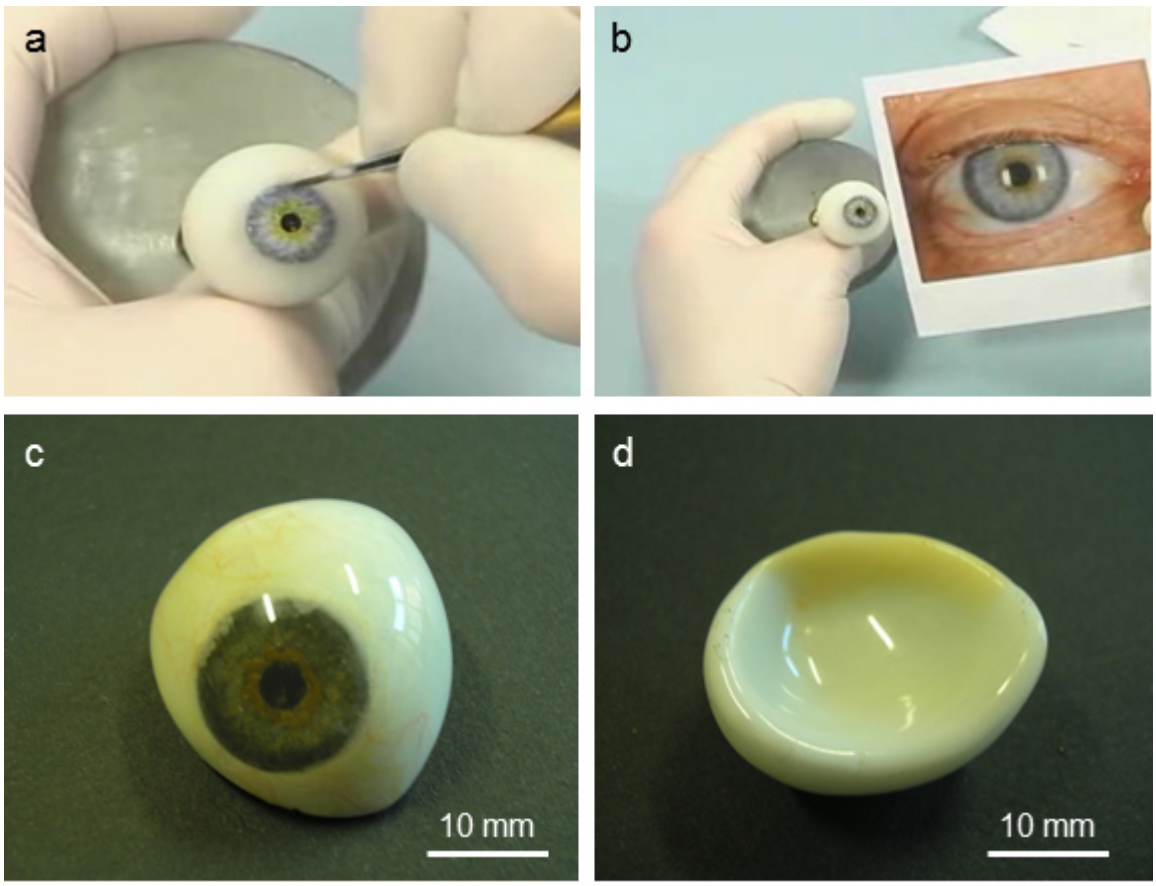

Fig. 4

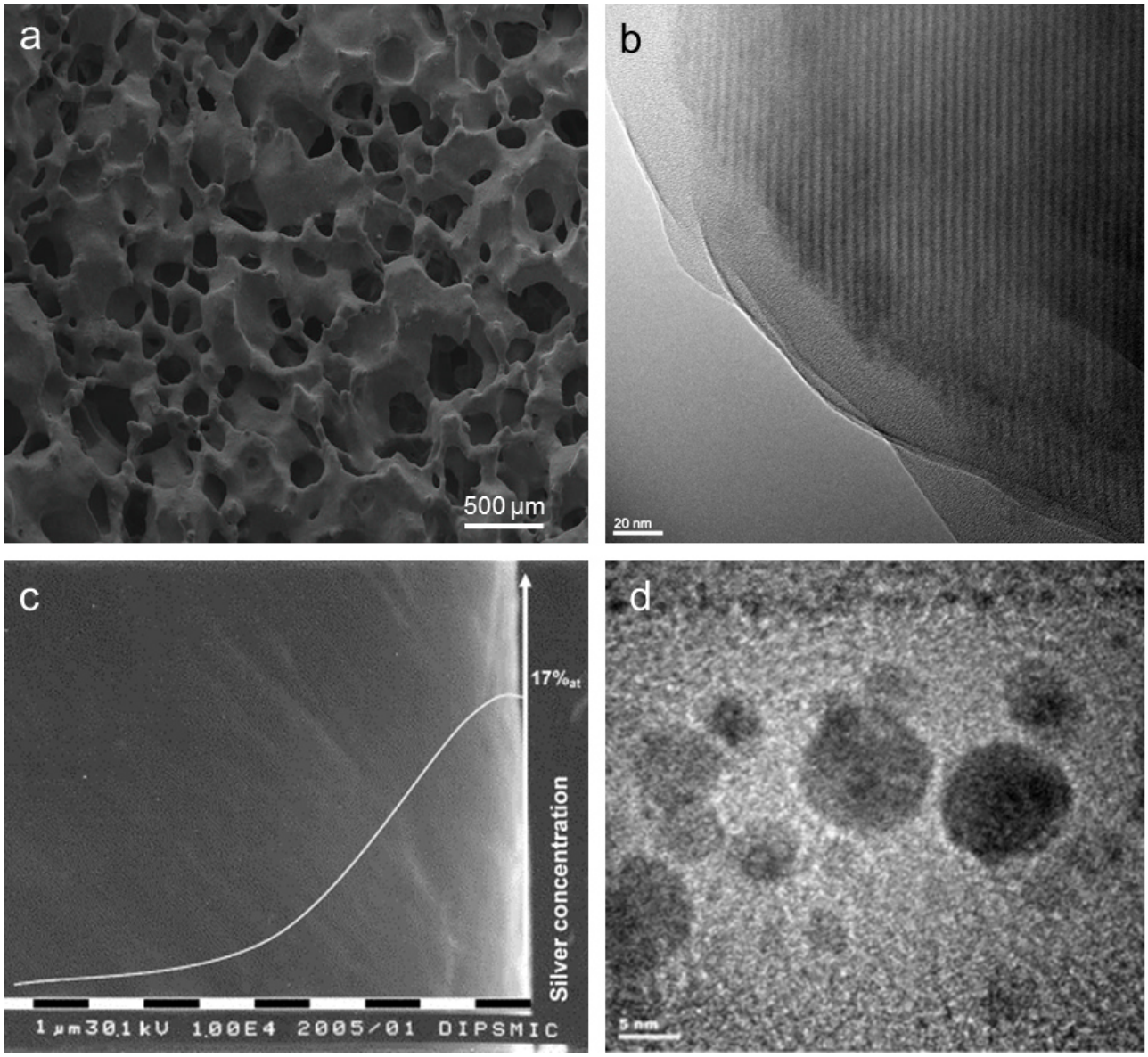
a
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Fig. 5