Ceramics for oculo-orbital surgery

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Abstract

Ceramics are an extremely versatile class of materials with an extraordinarily broad spectrum of applications, ranging from building industry to medicine. Ceramics began to be systematically investigated as implantable biomaterials in the 1950s and soon revealed surprising properties. Orthopaedics and dentistry are the preferred areas of surgical applications of ceramics, due to their suitable strength for load-bearing applications, wear resistance (e.g. alumina and alumina/zirconia composites) and, in some cases, bone-bonding ability (e.g. hydroxyapatite and bioactive glasses). Another clinical field where ceramics are playing a significant role is oculo-orbital surgery, a highly interdisciplinary medical area that focuses on the management of injured eye orbit, with particular regard to the repair of orbital floor/wall fractures and/or the placement of orbital implants after removal of a diseased eye. Especially in the latter case, implants are not intended for bone repair but have to be biointegrated in soft ocular tissues; therefore, suitable ceramics for this application are required to go beyond the "traditional" bone-bonding ability. This article provides a picture of the

currently-used ceramics for such applications and explores new emerging perspectives, highlighting the promises for the future disclosed by the recent advances in nanobioceramics science.

Keywords: Calcium phosphates; Alumina; Bioactive glass; Nanoceramics; Orbital floor repair; Orbital implants.

1. Context of application

Oculo-orbital surgery (OOS) is a highly interdisciplinary clinical specialty that involves the tight collaboration between maxillofacial and ocular surgeons, with the aim of treating critical patients affected by orbital diseases. Our face and eyes are often the first card that we present to others; therefore, traumas or pathological diseases involving damage to eye orbit region are associated to important societal and psychological issues, including self-acceptance. Recent advances in surgical techniques and biomaterials science allow even dramatic cases to be successfully treated with excellent postoperative outcomes. In this regard, some types of biocompatible ceramics have been proven to be particularly suitable and effective in OOS for the repair of orbital floor (wall) traumatic fractures and as orbital implants for anophthalmic patients (Fig. 1).

External, traumatic impacts to midface, such as blunt injuries, can lead to orbital blowout fractures in the inferior or medial thin orbital wall (bone thickness within 200-500 μm) as a result of the abrupt increase in intraorbital pressure [1]. A fracture of the orbital floor commonly causes herniation of the orbital content (fat and soft tissues) into the maxillary sinus located underneath, usually accompanied by enophthalmos[1] and/or hypoglobus[2]. Timing of repair, modality of surgical intervention and type of implanted materials used for bone grafting are all critical issues that strongly affect the overall outcomes of orbital floor fracture treatment [2,3]. Basically, the scope of

[1] Recession of the ocular globe within the orbit. This disease may be acquired as a result of trauma (e.g. blowout fracture of the eye orbit bone) or related to postoperative complications of OOS.
[2] Downward displacement of the ocular globe; its aetiology and symptoms are quite similar to those observed for enophthlamos.

the implant is to act as a bone graft ensuring structural support at the bone defect site (fracture); the implanted material is often designed as a porous scaffold to promote bone ingrowth and a safe anchorage to surrounding host tissues [4]. In this regard, porous hydroxyapatite (HA) and HA/polyethylene (PE) composite plates are the most commonly used biomaterials for orbital floor and wall repair.

In the case of severe trauma to the ocular globe, infections non-responsive to pharmaceutical therapy or intraocular malignancy (e.g. retinoblastoma in children), removal of the diseased eye have to be considered [5]. Orbital implants, often designed as porous spheres of HA, alumina or PE, are placed in the patient's anophthalmic socket at the time of evisceration[3] or enucleation[4] in order to allow adequate volume replacement and transmit good motility to the ocular prosthesis [6,7]. Surgical implantation can be facilitated by wrapping[5] the implant within a sheet of a smooth material, which is particularly recommended for the implants, such as those made of HA, characterized by an irregular, rough surface that could erode the conjunctival layer. The motility of the aesthetic ocular prosthesis can be improved by placing a titanium peg in the front of the orbital implant in order to guide the prosthesis movement in accordance to that of the orbital implant. It has been demonstrated that infections following implant exposure[6] are more amenable to treatment in porous implants compared to non-porous ones (e.g. silicone or poly(methyl methacrylate) (PMMA) solid sphere), as vascular ingrowth helps to anchor the implant *in situ* and permits immune surveillance via blood supply.

[3] Evisceration involves the removal of the contents of an eyeball, with the sclera and muscle attachments left intact (the orbital implant is therefore inserted in the scleral envelope).

[4] Enucleation involves the removal of the ocular globe from the orbital socket, together with the scleral envelope and a portion of the optic nerve, while the conjunctiva, Tenon's capsule and extraocular muscles are usually spared; this procedure is necessary in the case of ocular cancer spread to the sclera.

[5] Preoperative strategy that involves the wrapping of an orbital implant within a sheet of a smooth material, with the aim of facilitating its placement within the soft tissues of the eye socket, diminishing tissue drag and helping precise fixation of the rectus muscles to the implant surface. Wrapping is particularly recommended for porous orbital implants in order to provide a physical barrier over their slightly irregular porous surface. Suitable wrapping materials include scleral autografts and allografts, bovine pericardium and synthetic polymeric meshes.

[6] Break in the conjunctiva overlying the orbital implant, which may predispose to extrusion of the entire implant. Poor surgical technique, excessively large implant size and implant infection may all contribute to this postoperative complication.

2. Repair of the eye orbit bone

The goal of an orbital floor (wall) implant is to repair the fractured eye orbit bone, lifting the ocular globe into its correct position and thus avoiding enophthalmos. Simplifying the problem, the repair of orbit bone fractures can be viewed as a special case of bone tissue engineering. An ideal orbital bone implant should be (i) biocompatible, (ii) available in sufficient quantities to produce grafts of proper shape and size, (iii) strong enough to support the orbital contents and the related compressive stress, (iv) easy to be shaped to fit the orbital bone defect, (v) easily fixable *in situ*, (vi) osteoconductive and, if possible, osteoinductive. Progressive degradation in the biological environment can be a desirable feature if the material resorption rate is comparable to bone healing kinetics and the dissolution by-products elicit minimal foreign-body reaction.

To find a proper material for orbital floor reconstruction is not an easy task. The first material to be routinely used for orbital floor repair was silicone in the form of flexible sheets (commercially named Silastic®), introduced in the 1960s by Lipshutz and Ardizone [8]. Since then, a wide number of substances of biological or synthetic origin have been experimented in the hope that a truly functional biomaterial will eventually materialize. A special subset of ceramics and composites appear to be highly suitable due to their favourable physico-mechanical properties and, in some cases (e.g. HA, bioactive glasses), osteogenic potential that promotes bone regeneration (Table 1). Ceramic and composite implants for orbital bone repair can be fabricated in the form of dense plates/sheets or porous structures; in the latter case, pore features typical of bone tissue engineering scaffolds are recommended (porosity above 50 vol.%, macropore size of at least 100 μm, high pore interconnectivity) [9,10].

2.1. Biological ceramics: bone and HA of marine origin

From the materials scientist's viewpoint, bone itself can be considered a natural ceramic-based composite comprising a calcium phosphate matrix (mainly nanocrystalline hydroxyapatite) and an organic phase (mainly type I collagen) [11].

In the field of orbital bone reconstruction, most surgeons consider autografts from patient's hard tissue as the best option [12,13]. Preferential donor sites include split calvarial bone, maxillary wall, mandibular symphysis, antral bone, rib, parietal bone and iliac crest [14-24]; specifically, calvarial bone seems the best material especially due to the adequate mechanical suitability [25,26]. The graft can be placed as-such [27], fixated by titanium screws and/or plates [28], or used in conjunction with a man-made material such as titanium mesh or porous PE [29].

The advantages of autologous bone are its inherent strength and rigidity usually comparable to those of the healthy bone at the fracture site, as well as its vascularisation potential [12]; even most importantly, autografts exhibit excellent biocompatibility after implantation. Autologous bone grafts are incorporated in living tissue without eliciting any immune reaction to self-antigens, which allows foreign body reactions such as infection, extrusion, collagenous capsule formation and ocular tethering to be minimized.

The advantages of using autologous bone in comparison to other options for orbital floor repair have been highlighted in many research reports [12,13,30-33]. Rudagi et al. [22] reconstructed orbital floor fractures in 11 patients by using autogeneous mandibular symphiseal bone grafts. The patients were monitored for 1.5 years postoperatively: a good restoration of the orbital floor was reported and extraocular movements were intact in all cases; there were transient complications, such as enophthalmos and diplopia[7], that resolved spontaneously by few months after surgery. Only one patient exhibited symptoms of postoperative infection, that was not associated to the autogeneous material but to the titanium plates used for graft stabilization.

[7] Commonly referred to as "double vision", it can occur when patient's eyes are not correctly aligned while aiming at an object and, therefore, two non-matching images are simultaneously sent to the viewer's brain.

Sakakibara et al. [23] used 1 mm-thick autogenous iliac crest grafts for repairing orbital floor fractures in 101 patients. Six months after surgery, computed tomography (CT) scanning showed normal orbit morphology and ossification of the transplanted bone grafts; persistent diplopia was observed in 15 patients. The authors emphasized the easiness of shaping and cutting the iliac crest graft to fit the curvature of the orbit, thanks to material softness, pliability and flexibility. Shetty et al. [34] and Ram et al. [35] underlined the particular suitability of autologous bone grafts for the repair of large orbital floor defects that required mechanical support on a wide area.

However, the use of autologous bone is associated with several less favourable aspects. First, it is not always easy to contour the harvested bone according to the desired shape and size, which may depend on graft source. Furthermore, the graft can break if it is bent beyond its natural capacity: therefore, in the case of large defects involving multiple fractures and disruption of bony buttresses, other biomaterials are preferred or combined to autologous bone; in this regard, a better accuracy of reconstruction can be achieved by using titanium mesh rather than cranial bone grafts [36].

Another drawback of autologous bone is its often unpredictable resorption rate, that can vary within a quite wide range (from weeks to months) and depends on the graft origin [28,37-39]; for instance, cancellous bone is less resistant to resorption than cortical bone due to its porous nature [27].

Further problems associated to the use of autologous bone grafts concern the material harvesting from a donor site, including significant increase in surgery duration and patient's time under general anaesthesia, and related postoperative complications for the patient (injury to the healthy tissue) [22].

A partial solution to the drawbacks of autografts is the use of allografts (also called homografts), i.e. the transplant of bone from cadavers [12,18]. Specifically, the advantages over autologous grafts include absence of donor site morbidity, decreased surgery time, opportunity of pre-forming and customizing the implant before surgery, and – at least virtually – unlimited availability of grafting material (banked bone). However, especially in the past, allografts were associated to the risk of disease transmission from donor to patient [40,41] and their use often involved the need for

administration of immunosuppressant drugs. Currently, at least in Europe and USA, a wide legislation exists and the bone sources are carefully checked before the allograft is released for clinical use [42]. A factor that often discourages the use of allografts is their high resorption rate, which is statistically higher than that observed with autologous bone implants [22].

Occasionally, bone transplant materials from donor animals (xenografts) have also been used. Morax et al. [43] implanted bovine bone in a series of 20 patients and found it suitable for the repair of orbital fractures: the material was safe and no evidence of biological incompatibility, inflammation or infection was detected in the cases examined. However, the use of xenografts is potentially associated to disease transmission, severe immunogenic response and unpredictable resorption rate, usually higher than that of autologous bone; furthermore, ethical and religious issues may apply by the patient. All these factors have discouraged the use of animal bone grafts in recent years, also considering that a wide range of other materials and implant options are available to surgeons.

Among ceramics of natural origin, sea coral HA has been widely employed to produce non-absorbable bone grafts for orbital floor repair. Elmazar et al. [44] compared the efficacy of coralline HA porous implants (mean pore size of 400 μm) with that of autologous bone grafts and expanded poly(tetrafluoroethylene) (Gore-Tex) for the repair of surgically-induced orbital floor fractures in cats. Gore-Tex was more easily shapable and contourable than HA, that showed high brittleness involving difficult implantation and loss of integrity postoperatively. Nam et al. [45] compared the postoperative outcomes following the use of coral-derived HA (Biocoral®) (191 human patients) and PE (214 cases) implants for orbital floor reconstruction. Postoperative enophthalmos was statistically more frequent in HA-treated patients with respect to those receiving porous PE, but no other significant differences was found postoperatively between the two groups.

Apart from brittleness, the high cost and some ecological issues (damage to sea coral ecosystem due to coral harvesting) are the two other main drawbacks associated to coralline HA implants.

The use of algae-derived HA has been recently proposed as a less expensive and more eco-friendly alternative to coralline HA. Poeschl et al. [46] evaluated new bone formation and remodelling after grafting of the maxillary sinus of 14 patients with an algae-derived HA (AlgOss-C Graft/Algipore) implant, with or without the addition of platelet-rich plasma (PRP). Both as-such and PRP-treated implants showed good efficacy for bone fracture repair, but statistical evaluation of the samples proved significantly better overall resorption of algae-derived HA and increased new bone formation when PRP was used as an adjuvant.

2.2. Man-made ceramic implants

In the attempt to overcome the shortcomings of biological HA (inorganic bone matrix and coralline HA), powders of chemically-synthesized commercial HA have also been used to produce 3-D non-absorbable porous scaffolds for orbital floor repair by advanced manufacturing techniques [47-49]. Custom-made HA scaffolds can be fabricated through the computer-aided design/computer-aided manufacturing (CAD/CAM) approach using the data obtained through CT as a 3-D virtual template with high anatomic accuracy. Simon et al. [49] reported the direct-write assembly of 3-D periodic scaffolds composed of microporous HA rods arrayed to produce macropores that are size-matched to trabecular bone, and highlighted the potential suitability of the produced structures for craniofacial and orbital bone reconstruction (Fig. 2). The CAD/CAM-based approach is very effective even for the treatment of very dramatic cases: Brie et al. [50] recently applied a stereolithographic technique to produce HA custom-made implants for the reconstruction of large craniofacial defects (injured area above 25 cm^2) with satisfactory cosmetic results both in adults and in children. In principle, rapid-prototyped synthetic HA scaffolds represent a good alternative to biological ceramics but, like in the case of coralline HA [44,45], implant brittleness (intraoperative difficulty of implantation, postoperative loss of structural and mechanical integrity) is still an issue.

In order to improve the outcomes following orbital floor surgery, bioactive glasses have also been proposed as candidate materials due to their bone-bonding ability and tissue regenerative potential. In this regard, a series of studies performed in Finland from the late 1980s to the early 2000s on four series of human patients investigated the suitability of cast S53P4 bioactive glass plates (oxide weight composition: 53% SiO_2, 23% Na_2O, 20% CaO, 4% P_2O_5) for orbital bone reconstruction. Suominen and Kinnunen [51] first implanted S53P4 granules and plates at 36 sites in 13 patients and compared the behaviour of these materials with that of bone grafts at 16 sites in the same patients. Bioactive glass granules were used to treat facial bone defects in subperiosteal pockets and to obliterate frontal sinuses, whereas the plates were employed for orbital wall reconstruction. Clinical examination, middle face radiographs and CT scanning showed that the bioactive glass was generally well tolerated by host tissues. The S53P4 plates retained their density, did not change in size and were characterized by tighter contact with the host bone in comparison to glass granules and bone grafts. The clinical outcome showed no relapses after a 1-year follow-up and no further operations were needed to remove or adjust the material implanted.

On the basis of these promising results, the studies were continued by Kinnunen et al. [52] who compared the use of melt-derived S53P4 glass plates with conventional cartilage grafts for the treatment of traumatic orbital floor fractures in 28 patients operated from 1991 to 1995 and evenly split in two groups of 14 people. None of 14 patients receiving the S53P4 plate showed significant evidence of implant-related postoperative complications; furthermore, their clinical outcomes (only 1 case of infraorbital nerve paraesthesia and 1 case of entropion[8] were registered) were better than those of the cartilage group (3 cases of diplopia, 2 case of infraorbital nerve paraesthesia and 1 case of enophthalmos). The authors of this study concluded that the use of bioactive glass plates led to less morbidity as no donor site operation was needed and S53P4 glass provided favourable healing due to its ability to stimulate new bone formation. Aitasalo et al. performed further investigations

[8] Folding inwards of the eyelid (usually the lower eyelid), which causes the eyelashes to constantly rub against the cornea.

and reported a retrospective study of 36 patients operated from 1995 to 1999 [53]. After a 1-year follow-up, the S53P4 glass implants caused no foreign body reaction in the bone or soft tissue as well as no infection, haemorrhage and implant displacement/extrusion[9]; CT scanning qualitatively demonstrated new bone ongrowth around the bioactive glass plates. Peltola et al. [54] reviewed the postoperative outcomes of 49 patients receiving a S53P4 glass plate from 1998 to 2001 (Figs. 3a and b): no signs of implant-related infection, extrusion or displacement were observed over a 2-year postoperative follow-up. Furthermore, the implants caused no foreign body reaction, while new bone formation was observed around the glass plates and only a minor resorption was found on the margins of the implants.

From the data reported in this series of studies, bioactive glass plates appear a promising and reliable solution for orbital floor reconstruction. Specifically, S53P4 glass is biocompatible, able to stimulate new bone growth and slowly soluble in the biological environment (thereby ensuring adequate structural support while bone regenerates); furthermore, if the glass implant size and shape are properly selected, excellent functional and aesthetic results can be achieved.

It is also interesting to mention a recent work by Tesavibul et al. [55] who fabricated 45S5 Bioglass® porous scaffolds via a lithographic method. From the preliminary results reported, the Bioglass® meshes seem to be enough strong and flexible to be implanted in orbital floor defects, as suggested in Figs. 3c and d.

2.3. Composites and mouldable ceramic pastes

Apart from being processed in the form of single-phase macroporous structures, HA was also used for manufacturing HA/PE composite implants, that have been marketed under the commercial name of HAPEX® since more than 20 years and successfully adopted as a bone replacement material in

[9] "Extrusion" is the commonly used surgical term describing the expulsion or spontaneous removal of an (ocular) implant from the host tissue, without any connotation of its meaning in polymer technology.

otology (middle ear ossicles prosthesis) [56] and orbital floor repair (Fig. 4) [57-60]. The combination of stiff, osteoconductive but brittle HA with low-modulus, tough and bioinert PE produces a biomedical composite exhibiting attractive properties for bone substitution [58-60]. These composite implants allow bone ongrowth and ingrowth to occur (if produced as porous scaffolds) but are not reabsorbed by the organism, thus remaining permanently *in situ*.

In 2010, Asamura et al. [61] produced a 4-layer composite construct by joining a periosteum graft to a HA/poly(L-lactic acid) PLLA/polycaprolactone (PCL) sheet. This composite biomaterial was implanted in human patients suffering from orbital floor fractures; autologous iliac crest bone was also implanted in a control group. The anatomical position and movement of the eyeball were postoperatively normal in both groups; therefore, this multilayer composite was suggested as a promising alternative to autologous bone, thereby overcoming the problems of limited autograft availability and possible morbidity at the donor site.

Landes et al. [62] recently treated a group of patients with midfacial bone fractures, including a few cases needing orbital floor repair, with an internal fixation HA/PLLA composite device; bone ingrowth into the implant was observed and minimal postoperative complications were reported over a 67-month follow-up.

Since about 25 years, HA and other calcium phosphates are also commercially available in the form of mouldable pastes, commonly termed as “bone cements”, to be used in the broad field of cranio-maxillofacial reconstruction [63-66]. HA cement is composed of tetracalcium phosphate and dicalcium phosphate (anhydrous); in the presence of water and at physiological pH, the salts react isothermically to produce a dense paste that can then be shaped intraoperatively. The reactants are then reprecipitated until the entire material is converted to finely porous HA, which takes approximately 4 to 6 h *in vivo*. The setting time can be properly modulated according to specific surgical needs; for instance, it was observed that mixing the HA cement in 0.25 M sodium phosphate buffer decreased the setting time significantly [67]. Mathur et al. [68] reviewed the use of HA cements in craniofacial surgery, including orbital floor and wall repair, and concluded that such

materials are excellent options for reconstruction in the clean field. However, the existing literature suggested that exposure to sino-nasal or oral cavity – which is the case of orbital floor repair, as HA cement is exposed to the environment of the maxillary sinus – may predispose the implant to infection (bacteria may migrate from the external environment to the implant surface), and therefore the material should be used cautiously in these situations.

Apart from HA, other calcium phosphates have been occasionally proposed as implantable materials for orbital bone repair. Reyes et al. [69-71] fabricated porous biphasic β-tricalcium phosphate (β-TCP)/HA plates (weight ratio β-TCP/HA = 77 : 23) by the sponge replica method and implanted them in cats as orbital floor grafts. These scaffolds were highly biocompatible and did not elicit any kind of adverse postoperative complications; furthermore, their porous network (mean pores size of 198 μm) allowed fibrovascular tissue ingrowth to occur inside the implant, thereby increasing its stability *in situ*.

Van Leeuwen et al. [72] fabricated β-TCP/poly(trimethylene carbonate) (PTMC) composite sheets (thickness around 1.0 mm) through co-precipitation followed by compression moulding and suggested their suitability as materials for orbital floor repair; specifically, the effect of different amounts of the ceramic component (15 and 30 vol.%) on the properties of the composite was investigated. Lamination of the composites with minimal amounts of poly(D,L-lactic acid) (PDLLA) was also experimented, as the reconstruction of large defects might necessitate the use of more rigid materials (the elastic modulus of PDLLA is above 2500 MPa, whereas that of PTMC is within 5-7 MPa). The flexural modulus of the composites reached 17 MPa when introducing 30 vol.% of β-TCP. A laminate of this composite incorporating a PDLLA sheet (total thickness 1.0 mm) had a flexural modulus of 64 MPa. These results suggested that, from a mechanical viewpoint, these laminated composite sheets can be suitable for orbital floor reconstruction. The authors hypothesized that, after implantation *in situ*, the polymer component resorbs enzymatically without the formation of acidic compounds, while the ceramic phase can induce bone formation.

Chen et al. [73] evaluated a biomaterial combining biphasic calcium phosphate (HA and β-TCP) with single-donor allogeneic fibrin glue in 10 patients with a follow-up of 4 years. The fibrin-rich biomaterial was easy to mould and apply on the surgical site, allowing the surgeon to sculpt accurately the bone defect and providing adequate mechanical stability. No infection of the eye orbit or implant extrusion were observed. Ocular motility was normal, and no diplopia or enophthalmos of the injured orbit was noted. CT scans of the reconstructed orbits revealed good restoration of the orbital floor defect in all 10 patients. On the basis of these promising results, the authors of the study suggested that the use of a fibrin-rich calcium phosphate biamaterial offers a valuable alternative to autologous cranial bone graft or titanium mesh in the reconstruction of orbital floor bone defects.

It is worth pointing out that, unlike HA implants, β-TCP-containing ceramics are characterized by a certain degree of solubility, which should be taken into account in view of the maintenance of an adequate structural and mechanical integrity while new bone tissue regenerates.

Among the ceramic/polymer composites proposed for orbital floor repair, Proplast II (a polytetrafluoroethylene (Teflon) fibres/alumina implant) was also reported with good outcomes in one study by Shah et al. [74]. Specifically, Proplast II was used to manufacture subperiosteal implants for the correction of anophthalmic enophthalmos in 34 patients who had poor orbital volume replacement after insertion of a spherical orbital implant. However, since the late 1990s Proplast II had progressively fallen into disuse because of adverse effects associated to its use in other surgical applications [75].

3. Orbital implants

Since the ancient Roman age a number of materials, including wool, clay, gold and silver, have been used to manufacture orbital fillers, often painted or enamelled to mimic the natural iris of the contralateral eye, with the aim of replacing the anophthalmic socket volume and restoring an

acceptable aesthetic appearance to the patient's face [7]. Serial production of artificial eyes dates back to the end of the 18th century, when Venetian glassmakers began to fabricate implantable blown glass spheres, that however were brittle and had poor fit and little comfort [76].

The modern era of anophthalmic socket surgery started in 1885, when Mules first described in detail the surgical placement of a hollow glass sphere into an eviscerated globe [77]. In the early 1900s, orbital implants coupled with external ocular prostheses (both made of glass) began to be adopted due to better postoperative outcomes and overall comfort of the patient. The prosthesis was a coloured glass shell placed between the closed conjunctival surface covering the orbital implant and the eyelid. The battle casualties of the First World War increased the need for artificial eyes, and from 1920 to 1940 Germany became the main supplier of glass orbital implants due to the superior glass blowing techniques [7]. A study involving 52 human patients and published by Burch in the mid 1940s estimated failures in less than 10% of cases using glass orbital implants [78]. The battle casualties of the Second World War (WWII) caused again a large demand of artificial eyes, but the wartime shortage of glass eyes imported from Germany led to the development of PMMA orbital devices in the USA. Acrylic implants overcame the drawbacks of glass implants (brittleness and chemical etching by body secretion) and permitted custom fitting at a relatively low cost as well as better motility of the prosthesis due to a new design for improved attachment of extraocular muscles [79]. Since the 1950s till now, a variety of biomaterials have been experimented in the search of an ideal orbital implant; among them, porous ceramics of biological or artificial origin seem to be particularly suitable (Table 2).

An ideal orbital implant should display a number of characteristics, including (i) material biocompatibility, (ii) adequate socket volume replacement, (iii) good motility transmitted to the ocular prosthesis, (iv) adequate support to the ocular prosthesis, (v) low cost, (vi) easiness of implantation and (vii) non-degradability over time. The presence of an interconnected network of macropores in the 300-500 μm range is a highly desirable feature that allows implant fibrovascularization, defined as the postoperative ingrowth of viable vascular connective tissue.

Tissue growth into a porous orbital implant offers several key advantages including a very low extrusion rate and a reduced risk of implant infection due to the presence of an adequate blood supply. It was also observed that, with sufficient time for fibrovascularization to occur, any exposure due to the abrasion of the conjunctiva by the implant surface may heal spontaneously due to the good blood supply within the implant.

Moreover, fibrovascularization carries an additional advantage. Looking at the historical evolution of orbital implants, previous attempts to establish a direct mechanical connection between non-porous orbital implants (e.g. a simple polymeric sphere) and the aesthetic ocular prosthesis had been invariably met with the development of infections (due to bacterial colonization of the implant region connected with the prosthesis), exposure and other complications. Thanks to the fibrovascularization of porous implants, it is possible to drill a hole in the implant and to insert a peg between implant and ocular prosthesis. The presence of a good blood supply allows the drilled area to re-epithelialize with conjunctiva: thus, the implant remains separated from the external environment by the living conjunctival layer but retains a direct connection to the prosthesis, thereby providing enhanced motility (the ocular prosthesis can more closely follow the movement of the contralateral eye) without exposure of the implant and relevant complications. Significant improvement of both vertical and especially horizontal excursion of the artificial eye has been reported for pegged HA implants with respect to unpegged ones [80].

3.1. Implants based on apatites of biological origin

As an alternative to brittle glass implants, small spheres of natural ivory from elephant's tusks were experimented as orbital implants in a few human patients in the first half of the 20th century [81]. Formally, ivory is a ceramic-based biocomposite made of nano-sized apatite crystals (about 70 wt.%) hold together by a complex network of type I collagen fibres that are eliminated after the animal's death. This type of non-porous orbital implant was rapidly replaced by porous spheres of

bovine cancellous bone, that were heat-treated to destroy all organic matter, thereby leaving only the calcium phosphate mineral framework [82-84]. These porous apatite implants were widely used before the WWII and recommended as "the most satisfactory of all orbital implants" in the Spaeth's treatise [81].

After a hiatus of about 30 years, corresponding to the development and spreading of polymeric orbital implants, in the 1970s a group of researchers coordinated by Dr. Molteno and working in New Zealand resurrected the idea of an implant based on natural bone apatite. Reviewing the available literature, Molteno and co-workers noted that the postoperative exposures of bone-derived HA spheres used till the WWII were generally rare, small and frequently tended to heal spontaneously, which did not occur upon implantation of a polymeric device. This behaviour suggested that the biodegradable nano-crystalline 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 likely remain unchanged for the patient's whole life. The early trials of this type of implant (the so-called "Molteno M-Sphere") involved the use of deproteinized bone of calf fibulae and confirmed that the mineral matrix of cancellous bone was readily incorporated into the tissues; furthermore, small exposures were followed by spontaneous crumbling of the exposed bone with healing of the overlying conjunctiva [85,86]. A study involving 52 human patients with good follow-up over a 10-year period was reported in 1991 [87], and the long-term successful outcomes of other 120 M-Sphere orbital implants inserted after enucleation between 1977 and 2000 were later documented [88]. This implant is significantly more porous (around 80 vol.%) than other available HA orbital spheres (50-65 vol.%); the use of a lighter device is an advantage leading to decreased stress on the lower lid and associated ectropion[10] formation. However, due to the high porosity (Table 3) the M-Sphere orbital implant is brittle and may be unable to support a peg [89,90]. This drawback, together with

[10] Turning out of the lower eyelid with exposure of its inner surface.

the high cost (around 500 €, significantly higher than that of polymeric implants) and ethical issues by some patients who did not accept an animal-derived implant, may have contributed to limit its diffusion.

In the last 1980s, Perry [91] and Dutton [92] independently pioneered the use of coralline porous HA spheres (Bio-Eye®) in anophtalmic surgery with excellent postoperative outcomes. The interconnected porous structure of the HA implant (Table 3) allowed host fibrovascular ingrowth, which potentially reduces the risk of migration[11], extrusion and infection [92]. Furthermore, coralline HA is strong enough to support a peg in the frontal area of the implant, thereby ensuring connection to the aesthetic ocular prosthesis with more life-like motility.

However, the use of coralline porous HA implants is associated to some drawbacks [5,6,79], including damage to marine ecosystems due to the harvesting of natural corals and high cost (around 600 €) compared to other options such as non-porous silicone or acrylic spheres (around 50 €). Furthermore, being a porous ceramic, its brittle nature precludes suturing the extraocular muscles directly to the implant [6,93]; therefore, pre-operative placement of the HA implant within a sheet of soft material (e.g. donor sclera, polymeric meshes) is necessary for muscles attachment. Furthermore, there is convincing evidence that the rough surface of coralline HA implants may contribute to the development of late exposure due to the abrasion of the relatively thin conjunctiva and Tenon's capsule as the implant moves. Therefore, also for this reason HA implant wrapping within a sheet of soft material is strongly recommended [94,95]. On the other hand, it was also 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 [96-98]. In case of orbital implant infections associated to exposures, administration of systemic antibiotics and topical eye drops should be carried out; if no symptoms improvement is noticed, implant removal should be considered [99]. Other reported complications include

[11] Postoperative change in position of the implant.

conjunctival thinning (followed or not by exposure), socket discharge, mid-term to chronic infection of the implant, persistent pain or discomfort, and peg extrusion from drilled HA implants [100-104]. In the search for an "ideal" porous orbital implants with a reduced complication profile and diminished surgical and postoperative costs, alternative materials such as porous synthetic HA and alumina have been investigated over the last two decades.

3.2. Synthetic ceramic implants

Orbital implants made of chemically synthesized HA, such as the so-called FCI3 sphere, began to be commercialized in the early 1990s as a less expensive alternative to coralline HA (Fig. 5). These implants have analogous chemical composition to that of the Bio-Eye® [105], although scanning electron microscopy (SEM) investigations revealed some differences in terms of porous architecture (lower porosity: 50 vs. 65 vol.%; decreased pore size uniformity; presence of blind pouches and closed pores [106,107]) and size of the surface crystals (Table 3); nonetheless, implant interconnectivity (Fig. 6) is still sufficient to allow central implant fibrovascularization [108]. FCI3 implant is less expensive than the Bio-Eye® (400 vs. 600 €) and easier to drill for peg placement (due to lower porosity); however its shortcomings, in terms of risk of conjunctival abrasion and postoperative exposure, are substantially analogous to those of coralline HA.

A new type of synthetic HA orbital implants with 75 vol.% porosity and macropore size ranging from 100 to 300 μm was recently experimented by Kundu et al. in India [109-112]. HA powder was synthesized by a wet chemical method, calcined at 800 °C and then intimately mixed with an appropriate quantity of naphthalene particles (mean size of 300 μm). The powder blend was compacted by cold-isostatic pressing to form cylindrical "green" bodies that were subsequently machined to fabricate the orbital implants. By heating at 80 °C, the naphthalene was driven off from the green samples with great care to prevent cracking and, finally, a thermal treatment at 1250 °C allowed the HA particles to sinter and the mechanical properties to increase (compressive strength

around 10 MPa) [109,112]. A detailed investigation of the mechanical properties and *in vitro* biocompatibility (L-929 mouse fibroblasts cells and rabbit corneal epithelial cell line) was carried out with encouraging results [112]. The implants were also tested *in vivo* in Mongrel dogs [110] and human eviscerated/enucleated patients [111]. The available results from clinical trials are promising, but these studies are still too limited (30 patients in all, 2.5 years of follow-up [110,111]) to draw definite conclusions on their long-term safety and efficacy.

Low-cost versions of synthetic HA orbital implants are also available on the market, especially in some emerging countries; however, they exhibit a number of drawbacks that strongly limit their economic advantage over the other commercially-available options. Some of these implants have been reported to contain CaO impurities that, after hydration in host tissues, may form $Ca(OH)_2$, which is caustic [113]. Other implants have higher weight, lower porosity (below 50 vol.%) and lower pore interconnectivity than FCI3 devices, with consequent limited fibrovascularization and enhanced risk of implant migration [114].

Porous alumina (Al_2O_3) orbital implants (the so-called "Bioceramic sphere"), approved for clinical use by FDA in 2000, seem very promising in overcoming the drawbacks of porous HA devices. Although the cost of an alumina orbital implant is still quite high (slightly higher than that of FCI3 sphere), it has a lower tendency to exposure/extrusion due to the smoother surface with submicrometric grains (Table 3), which results in a diminished risk of postoperative complications.

Alumina implants were first experimented in 16 eviscerated rabbits by Morel et al. [115], who observed only one postoperative infection without conjunctival breakdown; furthermore, fibrovascular ingrowth started 15 days postoperatively, reached the core of the implant and was complete after 1 month. These promising results were confirmed in a subsequent study by Jordan et al. [116], who compared the performance of alumina and coralline HA implants in rabbits and highlighted 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 case of BioEye®.

An accurate 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 reported by Mawn et al. [117]. The proliferation of fibroblasts differed on the various implants studied and, specifically, was maximum on the Bioceramic implant. Furthermore, the fibroblasts growing on the Bio-Eye®, FCI3 and PE 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 (Table 3). These findings were later substantially confirmed by Choi et al. [118]

Promising results were also published in 2002 by Akichica et al. [119], 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; four weeks after implantation, fibroblast proliferation and vascular invasion were noted, followed by tissue ingrowth after 2 months.

The first outcomes of Bioceramic implant in humans (107 patients over a 3-year follow-up) were reported by Jordan et al. in 2003 [120]. Postoperative problems encountered with its use were substantially similar to those observed with HA orbital implants but appeared to occur rarely; the incidence of exposure associated with the Bioceramic implant was significantly lower than that reported for the HA ones, and infections did not occur in any patient. In a following study the same research group further confirmed that alumina implant infections are rare [121] 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 most exposures occurring after a 3-month follow-up period [122]. Wang et al. [123] reported that exposures of Bioceramic implants occurred only 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. Successful treatment of exposures, without the need for implant removal, were performed by covering the exposed alumina

area with appropriate patches of biological origin (e.g. retroauricular myoperiosteal graft containing myofibrovascularized tissue) [124,125].

In recent years, bioactive glasses and glass-ceramics were also experimented as candidate materials in the manufacturing of porous orbital implants. A group of Chinese researchers implanted bioactive glass-ceramic porous orbital implants in enucleated rabbits and observed no rejection during a 6-month postoperative follow-up [126]. Ultrasound examination revealed a venous-flow-like spectra in the implants after 3 months and histological analysis showed that around 90% of the implant pores were filled by fibrovascular tissue after 6 months from operation. Encouraged by these promising results, the same authors implanted glass-ceramic orbital devices in 102 human patients, declaring a success rate of 96.1% (98 cases) [127]. In 4 cases the conjunctiva was torn partly when suture stitches were taken out of the wound, and 1 patients needed the implant removal. There were no reported complications after a follow-up of 6 months to 2 years and all patients were satisfied with their cosmetic appearance, even in those cases in which implant pegging was not performed as a secondary procedure to further improve the motility of the ocular prosthesis.

The use of bioactive glass to fabricate orbital implants was also cited by Richter et al. in a patent deposited in 2009 [128], but no manufacturing or clinical studies have been reported yet on this type of implant.

A special mention has to be dedicated to Biosilicate®, an interesting set of bioactive glasses and glass-ceramics belonging to the SiO_2-CaO-Na_2O-P_2O_5 quaternary system [129,130]. Biosilicate® was originally developed by the Zanotto's research group in Brazil (late 1990s) and proposed as a multipurpose biomaterial with a number of possible applications that range from bone/dental repair to orbital implants. A study published in 2012 by Brandao et al. [131] aimed to assess the biocompatibility of Biosilicate® and 45S5 Bioglass® in rabbit eviscerated sockets. Fifty-one Norfolk albino rabbits underwent evisceration of the right eye followed by implantation of dense (pore-free) cones made of 45S5 Bioglass® (control group) and two types of Biosilicate® into the scleral envelope. The Biosilicate® materials implanted were two glass-ceramics containing one

($1Na_2O{\cdot}2CaO{\cdot}3SiO_2$, Biosilicate® I) or two crystalline phases ($1Na_2O{\cdot}2CaO{\cdot}3SiO_2$ and apatite, Biosilicate® II). During the experimental period (180 days), no animals presented orbital infection or implant migration/extrusion, and the morphological analysis revealed pseudocapsules around all of the implants. The 45S5 Bioglass® and Biosilicate® I implants induced lower inflammation and less pseudocapsule formation than the Biosilicate® II. Seven days after the surgical procedure, the inflammatory reaction reached the maximum and then gradually diminished throughout the experiment for all groups, especially the 45S5 Bioglass® group. The same researchers obtained analogous results in a second study carried out in 45 eviscerated rabbits [132]. On the basis of these findings, it was suggested that 45S5 Bioglass® and Biosilicate® implants could be alternative materials to manage the anophthalmic socket, the best responses being obtained with 45S5 Bioglass® and single-phase Biosilicate® cones with no signs of systemic or local toxicity in the orbit of eviscerated rabbits.

Clinical studies in human patients are currently on going in the framework of a research project coordinated by Dr. Artioli Schellini (FAPESP grant no. 13/00131-8) in Brazil (Faculdade de Medicina de Botucatu and Faculdade de Medicina of the USP Sao Paulo). Sixty patients who underwent evisceration or enucleation are being recruited; the study was designed in such a way that 40 patients receive Biosilicate® cones, while the control group (20 patients) is implanted with PMMA cones. After surgery, patients are being subjected to follow-up after 7, 15 and 30 days, and thereafter at two-month intervals for a period of six months. Systemic parameters to be evaluated include clinical examination (evaluation of the orbital cavity and changes in vital organs), biochemical and toxicological tests, and CT analysis of the orbit. Clinical trials are expected to conclude by 2015; at present, mid-term results have not yet been published.

Heringer and Ng also reported an interesting use bioactive glass to fill old peg tracts and permit re-pegging of porous HA orbital implants, if the initial drilled tunnel was not perpendicular and central to the implant surface [133]. This strategy has been applied in 3 human patients who had persistent problems with their pegged HA orbital implants and did no longer respond to conservative

treatment. After removal of the old peg, the hole was partially filled with bioactive glass and, after 2 months, 2 patients also underwent successful re-drilling of the implant followed by insertion of a new titanium peg, with satisfactory connection to the ocular prosthesis and absence of complications over a 3-year follow-up.

3.3. Composites and coatings

From the surgeon's viewpoint, the use of stiff orbital implants, such as the ceramic ones, is helpful during the operation as the implant can be easily handled and placed into the anophthalmic socket with high precision and control on its position. However, compliance mismatch between the orbital implant material and the surrounding soft tissues, in combination with the repetitive movement of the implant by the extraocular muscles, can contribute to inflammation and necrosis of conjunctival/scleral layers, which eventually lead to implant exposure.

In the attempt to overcome these problems, orbital implants fully made of polymeric material (e.g. porous PE sphere) as well as ceramic/polymer composites have been proposed over the years and, in some cases, clinically tested in human patients.

In the late 1970s a felt-like composite, called Proplast I, gained a certain popularity in maxillofacial and orbital surgery due to its easy pliability and shapability. Proplast I was constituted of polytetrafluoroethylene and carbon fibres and, once implanted, could be invaded by fibrovascular tissue thereby diminishing the risk of implant extrusion [134]. The clinical studies carried out in patients who received Proplast I hemispherical orbital implants were promising, with no cases of migration or extrusion after a 2-year follow-up [135]. In recent years, however, Proplast I has progressive fallen in disuse because of long-term postoperative complications, primarily late infections, associated with its use [136].

In the 1980s, the implantation of porous enucleation implants made of Proplast II, an evolution of Proplast I, was reported. This new device was different from its predecessor in the composition

(Proplast II was an alumina/polytetrafluoroethylene composite) and in having a pore-graded structure (a porous anterior portion and a siliconized non-porous posterior surface to allow smoother movements) [137,138]. Proplast implant II had a nipple on its anterior surface (lined by the patient's conjunctiva) that could integrate with a depression on the posterior surface of the ocular prosthesis. Several Proplast implants II required removal by few postoperative months because of poor motility and, over histopathological examination, were found to be completely avascular and surrounded by a thick fibrous pseudocapsule [139]; therefore, in recent years the use of Proplast II to fabricate orbital implants has been abandoned.

In the early 1990s, a group of German researchers developed a composite orbital implant comprising a hemispherical anterior part made of synthetic porous HA to guarantee tissue integration joined to a posterior part of silicone rubber; the horizontal and vertical eye muscles were sutured cross-wise in front of the implant to ensure better stability and motility [140]. Overall implant biocompatibility was excellent and the transmission of the motility to the ocular prosthesis was generally acceptable [141,142]. At present this implant is mainly employed in Europe; its diffusion is limited due to the high cost and complex surgical procedures needed for its implantation compared to porous spheres made of HA, alumina or PE.

In a couple of recent reports, bioactive glass-coated PE porous spheres were experimentally implanted in enucleated rabbits [143] and human patients [144] to investigate the effect of bioactive glass on the fibrovascular ingrowth within the implant pore network. In both studies, the inclusion of bioactive glass particulate did not seem to significantly promote the rate of fibrovascularization, and probably this is the reason why the investigations were apparently discontinued.

The clinical effects of a calcium phosphate coating on the struts of porous alumina implants were also investigated in a few studies over the last 15 years. A group of Korean researchers first fabricated this new type of implant by means of the polymer sponge replication method: the porous alumina skeleton acted as a load-bearing structure, while a 20-μm thick HA layer deposited on it was advocated to provide superior biocompatibility and better long-term stability in the eye [145].

Animal studies in eviscerated rabbits receiving 12-mm sized HA-coated alumina spheres with different pore sizes (300, 500 and 800 μm) revealed peripheral fibrovascularization of the implant in all groups after 15 postoperative days and also at the center of the implant after 28 days; fibrovascularization was more predominant in the group of implants having 500-μm pores compared to the other two types [146].

In 2002 Jordan et al. [147] 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 device, 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 fibrovascularization occurred uniformly throughout each implant over a 12-week follow-up.

A few years later, Chung et al. [148] investigated the fibrovascular ingrowth and fibrovascular tissue maturation of HA-coated porous alumina implants in comparison with commercial HA spheres in enucleated rabbits over a 24-month follow-up without finding any significant difference between the two groups.

No other studies about HA-coated implants have been published; probably, the absence of a clear advantage from a clinical viewpoint (HA coatings did not appear to facilitate or inhibit fibrovascular ingrowth with respect to uncoated implants) and the presence of significant amounts of CaO as a contaminant (related to the coating manufacturing) [147] discouraged the researchers from performing further investigations in this direction.

4. Emerging perspectives: the role of surface nanostructure and the potential of nanoceramics

Many experimental studies have demonstrated that cell-substrate interactions at the micro- and nano-scale can be regarded as one of the major factors ultimately determining the long-term

performance of biomaterials once implanted *in vivo* [149]. A valuable publication by Jones provides interesting insights on the importance of bioceramic and composites nanostructure [150]. Most studies on the topography of biomedical materials have been carried out in the context of bone tissue engineering, and there is convincing evidence that osteoblasts preferentially adhere to and spread on finely microrough surfaces [151,152]. In this regard, implants made of biological or synthetic HA appear to be very suitable for the repair of orbital bone fractures as their micro-/nano-crystalline surface can favour colonization by bone cells. New perspectives could emerge from bioactive glasses, as their surface roughness can be tailored, for instance, by changing the size of the starting glass particles and/or the sintering parameters to modulate the crystal size. Recent studies have also demonstrated that cells directional growth and alignment can be also induced and properly modulated by means of a nanogrooved surface, as schematically illustrated in Fig. 7 [153].

In the field of orbital implants, The group of Dr. Jordan [106] and Choi et al. [118] used SEM to investigate the microstructural features of coralline HA, synthetic HA and alumina porous spheres; they also provided a comparison with other polymeric devices available on the market. As shown in Table 3, the materials analysed reveal marked variations of crystal size/shape and surface topography. The authors of these studies suggested that surface roughness could influence the inflammatory response after implantation and crystal size could determine the material-induced phagocytic response. It was observed that ceramics with crystal size around 2-3 μm (coralline and synthetic HA) showed greater tissue reaction in comparison to implants with finer grain (alumina). In this regard, it was suggested that surface crystals of larger size increased phagocytic activation, consistently with the findings by Nagase et al. [154] who showed that smooth HA crystals are associated with less inflammation than sharp-edged crystals. From these results it is still impossible to unequivocally claim that one porous ceramic implant is clearly superior to the others, even though alumina, exhibiting excellent biocompatibility and favourable microstructural features, seems a promising candidate.

An additional issue to consider is the effect of micro- and nano-scale topography on bacteria, since cells may have to compete with pathogens in the ocular environment. Some studies suggest that the surface topography of ceramic implants could be purposely designed to encourage cells to colonize while limiting bacterial adhesion and risk of infection [149]. This strategy could involve the use of micro- and nano-fabrication techniques and/or the optimization of sintering temperature and time to develop crystals with a specific size, thus creating a customized surface roughness. On the other hand, it has been widely showed that, especially in the case of orbital implants, surface macro- and micro-roughness is responsible of conjunctival abrasion, which may lead to implant exposure with the associated risk of bacterial colonization. In this regard, the use of non-crystalline ceramics with a smooth surface, such as bioactive glasses, could be highly desirable. Usually, bioactive glasses are processed to obtain macroporous scaffolds through a high-temperature thermal treatment of sintering, accompanied by partial devitrification of the material occurs with formation of a superficially rough glass-ceramic [155-161]. However, few interesting exceptions can be found in the literature: for instance, Fu et al. [162] produced 13-93 bioactive glass scaffolds by heat treatment at 700 °C to densify the glass network, thus forming strong porous constructs without crystallizing the material.

Bioactive glasses can be a very valuable resource in OOS, but their composition should be carefully designed: if a bioactive and even resorbable glass can be desirable for the repair of eye orbit bone fractures, a glass with minimal chemical/biological reactivity *in vivo* and able to persist *in situ* indefinitely should be used for orbital implants [163].

In a few recent studies, the use of nanoceramics and nanocomposites, also in the form of coatings on pre-existing devices, has been experimentally proposed in the context of OOS. Patel et al. [164] incorporated HA nanoparticles (size in the 20-70 nm range) within cyclic acetal hydrogels to create nanocomposites that were used to repair surgically-created orbital floor defects in rabbits. Some evidence has shown that nano-sized HA particles exhibit superior osteoconductive ability compared to conventional microcrystalline HA [165], which would be a highly desirable property for the fast

healing of critical orbital defects. Histomorphometric results indicated that the nanocomposite material elicited a positive *in vivo* response in terms of bone growth; however, in this preliminary study complete restoration of orbital floor defects was not achieved after 28 days of implantation.

Ye et al. [166] coated macroporous HA orbital implants with a thin layer of CuO-containing mesoporous bioactive glass (Cu-MBG) (Fig. 8). The aim of this research was to combine the antibacterial effect of released Cu^{2+} ions [167] and the local drug delivery capacity of the mesoporous glass coating [168]. Cu-MBG coatings with 0, 2 or 5 mol.% of CuO were prepared by dipping the porous HA implants into the sol precursor of the mesoporous glass, followed by evaporation, ageing and calcination. With the peculiarity of releasing antibacterial ions as the Cu-MBG degrades (viability of *S. Aureus* and *E. Coli* was inhibited *in vitro*) and good drug uptake/delivery ability (in this study ofloxacin), Cu-MBG coating could be a promising, multifunctional tool for the prevention of implant-related infections.

In a recent patent, Baino et al. [169] proposed the deposition of an antiseptic silver nanoclusters/silica composite layer on the surface of orbital implants and ocular prostheses to limit the problems of intra- and postoperative bacterial colonization. This nanocomposite oxide-based coating is produced by co-sputtering from silver and silica targets, and its thickness can be properly modulated in the 1-1000 nm range. A few studies demonstrated that this type of coatings generally exhibits a good adhesion on a wide range of substrates (glasses, crystalline ceramics, polymers) and allows a prolonged release of silver ions to be maintained in a biological environment (up to 1 month) [170-172]. In comparison to antibiotics administration, the use of metal ions as antibacterial agents (in this case silver) makes it possible to overcome the problems of bacterial resistance and could be effective also against antibiotic-resistant bacterial strains. However, the ocular environment is highly complex and a number of parameters should be taken in account, such as the long-term solubility of the coating, the interaction of metal ions with the tears, the fate of the released ions and the possibility of ion-induced tissue necrosis. The strategy of depositing a slowly soluble antibacterial coating will deserve further investigation as it could be particularly useful for

those ceramic devices, such as porous orbital implants, that should possess a non-absorbable skeleton and maintain adequate structural/mechanical integrity over time.

5. Conclusions

The role of ceramics in medicine is traditionally associated to the repair of hard tissues in orthopaedics and dentistry; however, they can have a great potential also in other clinical areas, such as OOS, due to a set of unique properties that can be successfully exploited for these unconventional applications. Unlike metals and polymers, calcium orthophosphates and bioactive glasses can bond to host bone and promote new tissue regeneration, which is a key feature for implants devoted to the repair of eye orbit bone fractures. Porous ceramics such as HA and alumina have been shown to allow fibrovascular ingrowth, which is a fundamental characteristic to ensure a safe stability of orbital implants *in situ* and to reduce the risk of postoperative infection. Novel perspectives could raise from the use of nanoceramics such as nano-sized HA, exhibiting an enhanced bone-bonding ability compared to conventional clinically-used HA, and mesoporous glasses for *in situ* drug release. Furthermore, bioactive glasses doped with proper metal oxides (e.g. CuO) could be exploited to elicit a local antiseptic effect via the release of antibacterial ions. Deposition of antiseptic oxide-based coatings on orbital implants could also be a valuable option to discourage bacterial infections, which represent a serious problem in OOS. As witnessed by the history of biomaterials science, cross-fertilization between different disciplines (materials science, cell biology, mechanical engineering, medicine) is essential so that research can proceed; therefore, in the next years an increasing collaboration among ceramic scientists, biologists, ophthalmologists and maxillofacial surgeons is more than desirable to accelerate the development of new, once unexpected strategies to improve the performances of medical ceramics and, consequently. the life quality of the patients.

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Figure legends

Fig. 1. Overview of biocompatible ceramics used in oculo-orbital surgery.

Fig. 2. Synthetic HA scaffolds fabricated by direct ink writing for potential use in craniofacial surgery and orbital floor reconstruction: (a) macrophotograph showing the gradient of porosity of the implant, (b) ordered porous pattern of stacked HA rods, (c) fracture surface showing the connections between two HA rods in adjacent layers, (d) higher magnification view of HA rod surface showing an interconnected (partially sintered) network of HA particles (roughly 2 μm in size) with intervening fine-scale porosity (images adapted from Simon et al. [49] © Elsevier).

Fig. 3. Bioactive glasses in orbital bone reconstruction: (a) cast S53P4 glass transparent plates with their corresponding ‘‘kidney-shaped’’ and ‘‘drop-shaped’’ stainless steel moulds and (b) CT scan taken 2 years after orbital floor reconstruction with a 25 mm × 2 mm S53P4 glass implant (white arrow) (images adapted from Peltola et al. [54] © American Association of Oral and Maxillofacial Surgeons); (c) 45S5 Bioglass® cellular structure fabricated by lithography-based additive manufacturing after sintering and (d) proposal for a customized implant for orbital floor repair (images adapted from Tesavibul et al. [55] © Elsevier).

Fig. 4. HA/PE composites: (a) HAPEX® implant in the orbital floor of a patient who has lost the right eye (the implant is shown with the same radiographic density as the bone to which it is bonded, while the spherical black object is a glass ball implanted earlier to restore the volume of the orbital socket) (adapted from Tanner [60] © The Royal Society); (b) optical cross-section of sintered HA (20 vol.%)/PE composite showing the porous structure with interconnected pores (infiltrated by resin) after selective laser sintering (the particles are well fused to each other and formed strong boundaries between them); (c) and (d) show the microstructure, at higher

magnification, of the areas marked by the rectangles in (b) and (c), respectively (scale bars 50, 50 and 10 μm respectively) (images adapted from Zhang et al. [59] © Wiley Periodicals).

Fig. 5. Synthetic HA orbital implant: (a) appearance of a porous sphere and (b) planar reconstruction of its microstructure by micro-CT (courtesy of Lukats et al. [107]); (c) SEM micrograph of a HA implants obtained by using naphthalene as a pore former (the macropores are in the 100-300 μm range) (images adapted from Kundu et al. [110] © Indian Academy of Science).

Fig. 6. Reconstruction by cone beam computed tomography (CBCT) of a synthetic HA porous sphere implanted in the right orbit of a human patient where the red zones represent the areas of fibrovascularization that starts at the implant periphery; the vitreous body of the contralateral eye is represented as a grey sphere (courtesy of Lukats et al. [107]).

Fig. 7. Model for cell alignment on a nanogrooved substrate. (a) Actin filaments parallel to the grooves form wide focal adhesions at filament terminations. On the other hand, termination of perpendicular filaments is fragmented because focal adhesion is formed only on the ridge. (b) Filopodia movements are isotropic, i.e. no specific direction is observed for their extension and retraction against the nanogrooved structure. This finding suggests that filopodia probing does not play a major role in cell alignment. Cell protrusions extend isotropically, but some that are perpendicular to the nanogrooved pattern retract more rapidly than those parallel to the nanogrooved pattern. These cell protrusion dynamics force a cell to elongate and align along the nanogrooved pattern (image adapted from Fujita et al. [153] © The Royal Society).

Fig. 8. MBG-coated porous HA scaffolds for possible use as orbital implants: (a) SEM micrograph of the surface and (b) detail of the HA/Cu-doped (5 mol.%) MBG interface; (c) TEM picture of the mesoporous texture of the coating (images adapted from Ye et al. [166] © Springer).

Tables

Table 1. Ceramics and composites used to produce orbital floor grafts (the implant are often cut and contoured by the surgeon just before operation to match the defect size and shape).

Class of ceramics	Material	Type of implant	Recipient	Remarks	References
Natural ceramic-based materials (apatites of biological origin)	Autologous human bone	Shapable sheet	Human	Resorption rate depending on bone type (cancellous, cortical) and source (harvesting site).	[14-35]
	Bone homograft	Shapable sheet	Human	Allogenic bone banks are available to surgeons.	[12,18]
	Bovine bone	Shapable sheet	Human	Resorpton rate faster than human host bone.	[43]
	Coralline HA porous plates	Porous plate	Human	Commercial product: Biocoral®. Problems of brittleness upon implantation.	[44,45]
	Algae-derived HA	Porous plate	Human	Commercial product: AlgOss-C Graft/Algipore) implant	[46]
Synthetic calcium phosphates	Synthetic HA	Porous plate	Human	Problems of brittleness during implantation.	[47-50]
Bioactive glasses	Melt-derived S53P4 glass	Solid plate	Human	Slowly resorbable.	[51-54]
	45S5 Bioglass®	Mesh	-	No biological studies are available yet.	[55]

Composites	HA/PE	Porous plates	Human	Commercial product: HAPEX®	[57-60]
	Periosteum joined to a HA/PLLA/PCL sheet	Sheet	Human	Absorbable implant.	[61]
	HA/PLLA	Plate	Human		[62]
	HA cements	Mouldable paste	Human		[63-66,68]
	β-TCP/HA biphasic calcium phosphate	Porous plate	Cats		[69-71]
	β-TCP/poly(trimethylene carbonate)	Sheet	-	No biological evaluation has been reported yet.	[72]
	Fibrin-rich β-TCP/HA biphasic calcium phosphate	Mouldable paste	Human		[73]
	Alumina/PTFE (Proplast II)	Sheet	Human	Currently abandoned.	[74]
	HA nanoparticles/cyclic acetal hydrogels	Sheet	Rabbit		[164]

Table 2. Ceramics and composites used to produce orbital implants.

Class of ceramics	Material	Type of implant	Recipient	Remarks	References
Biological apatites	Ivory	Solid sphere	Human	Used till the WWII and then abandoned.	[81]
	HA derived from heat-treated bovine bone	Porous sphere of charred cancellous bone	Human	Used till the WWII and considered an excellent alternative to blown glass orbital implants.	[81-84]
	Bovine bone-derived HA	Porous sphere	Human	Commercial product: Molteno M-Sphere.	[85-90]
	Coralline HA	Porous sphere, egg-shaped porous implants	Human	Commercial product: Bio-Eye®.	[91-104]
Synthetic calcium phosphates	Synthetic HA	Porous sphere, egg-shaped porous implants	Human	Mostly used commercial products: FCI3. Few less expensive implants are available worldwide, especially in emerging countries (with problems associated with low purity of HA).	[105-114]
Bioinert ceramics	Alumina	Porous sphere	Human	Commercial product: Bioceramic implant.	[115-125]
Glasses and glass-ceramics	Common silicate glass (non-crystalline ceramic)	Blown sphere	Human	First implant used by Mules in evisceration procedures (1885). The "Mules implant" and its evolutions were the most commonly used devices till the WWII.	[77]
	Porous glass/glass-ceramic	Porous sphere	Human	Promising results.	[126-128]
	Biosilicate®	Dense (pore-free) cones	Rabbit, human	Early clinical trials in humans are currently on going in Brazil.	[131,132]

	Bioactive glass	Additive in HA implants to fill old peg tracts	Human	Good outcomes	[133]
Composites	Carbon/PTFE composite (Proplast I)	Hemispherical implants	Human	Despite the fibrovascular ingrowth and generally good outcomes, it was abandoned in the 1980s due to the risk of late infections.	[134,135]
	Alumina/PTFE composite (Proplast II)	Porous implant having a siliconized non-porous posterior surface to allow smoother movements	Human	It was abandoned due to poor motility and absence of fibrovascular ingrowth.	[137-139]
	HA/silicone	Implant comprising a hemispherical anterior part made of synthetic porous HA and a posterior part made of silicone rubber	Human	Commonly known as "Guthoff implant". It exhibits good postoperative outcomes but has high cost and requires complex surgical procedures of implantation.	[140-142]
	Bioactive glass/PE	Porous sphere	Human	Absence of a clear improvement in implant fibrovascularization with respect to porous PE.	[143,144]
	HA-coated alumina	Porous sphere	Rabbit	Absence of a clear advantage over bare alumina orbital implants.	[145-148]
	HA coated with Cu-containing mesoporous	Porous sphere	*In vitro* tests	Encouraging antibacterial results against S. Aureus and E. Coli	[166]

	bioactive glass				

Table 3. Major characteristics of today's commercially-available ceramic porous orbital implants (many sizes are available to meet the patient's needs; sphere diameters are typically in the 10-22 mm range).

Commercial product (material)	Porosity (vol.%)	Pore size (μm)	Surface characteristics	Remarks	References
Molteno M-sphere (bovine bone-derived HA)	> 80	> 300	Nanocrystalline structure of bone apatite.	Problems of brittleness upon implantation, difficult pegging.	[89]
Bio-Eye® (coralline HA)	~65	300-700	Irregular micro-crystals of HA with size around 2 μm.	Problems of conjunctival abrasion and associated implant exposure.	[106]
FCI3 (synthetic HA)	~50	300-500	Hexagonal micro-crystals of HA with size within 1-5 μm.	Problems of conjunctival abrasion and associated implant exposure.	[106]
Bioceramic implant (alumina)	> 75	500	Cobblestone pattern of ultrafine micro-crystals in the 0.4-1.1 μm range.	Promising results; very limited problems of conjunctival abrasion due to the small size of surface crystals.	[118]

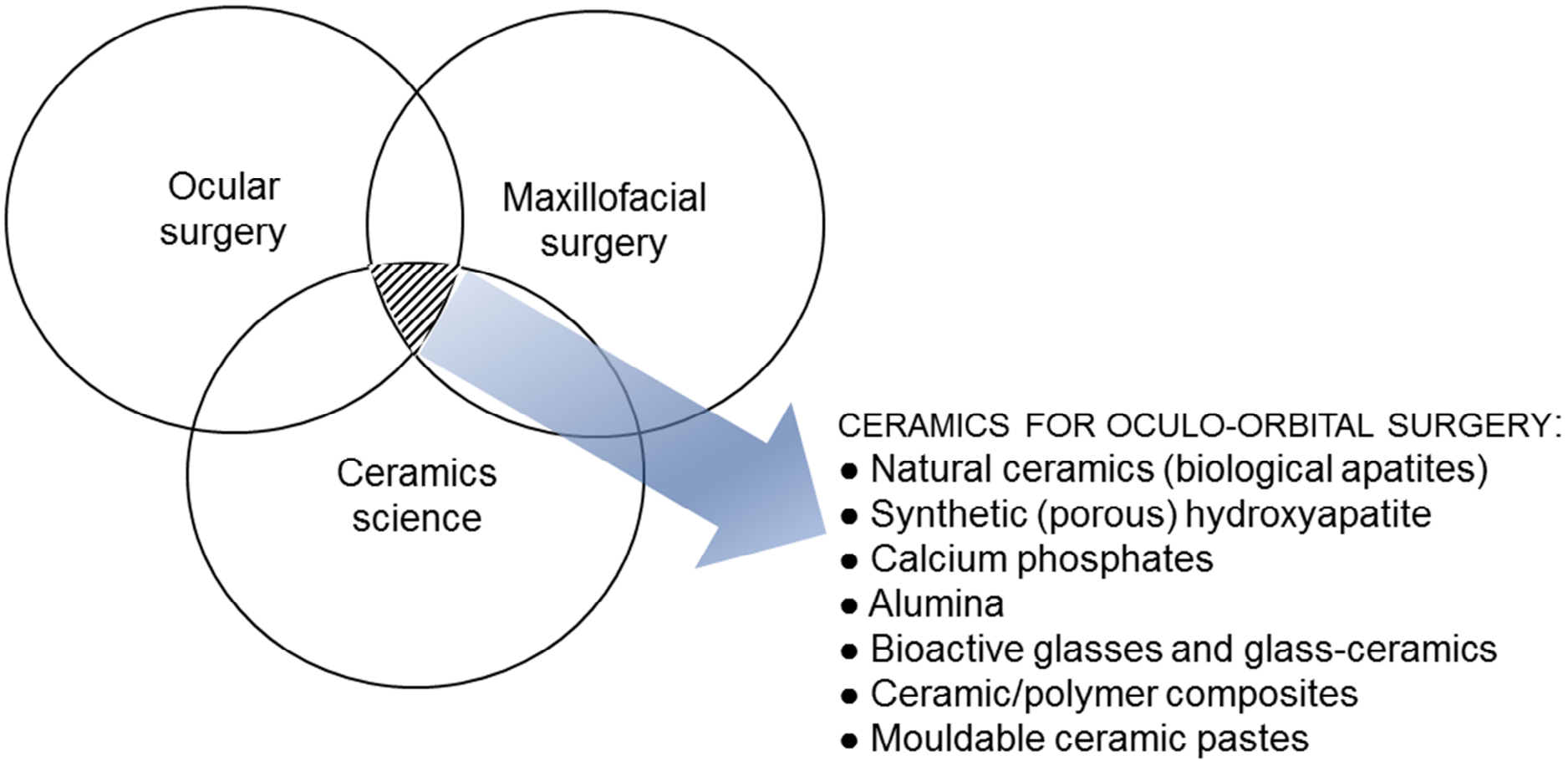
Ocular surgery
Maxillofacial surgery
Ceramics science
CERAMICS FOR OCULO-ORBITAL SURGERY:
• Natural ceramics (biological apatites)
• Synthetic (porous) hydroxyapatite
• Calcium phosphates
• Alumina
• Bioactive glasses and glass-ceramics
• Ceramic/polymer composites
• Mouldable ceramic pastes

Fig. 1

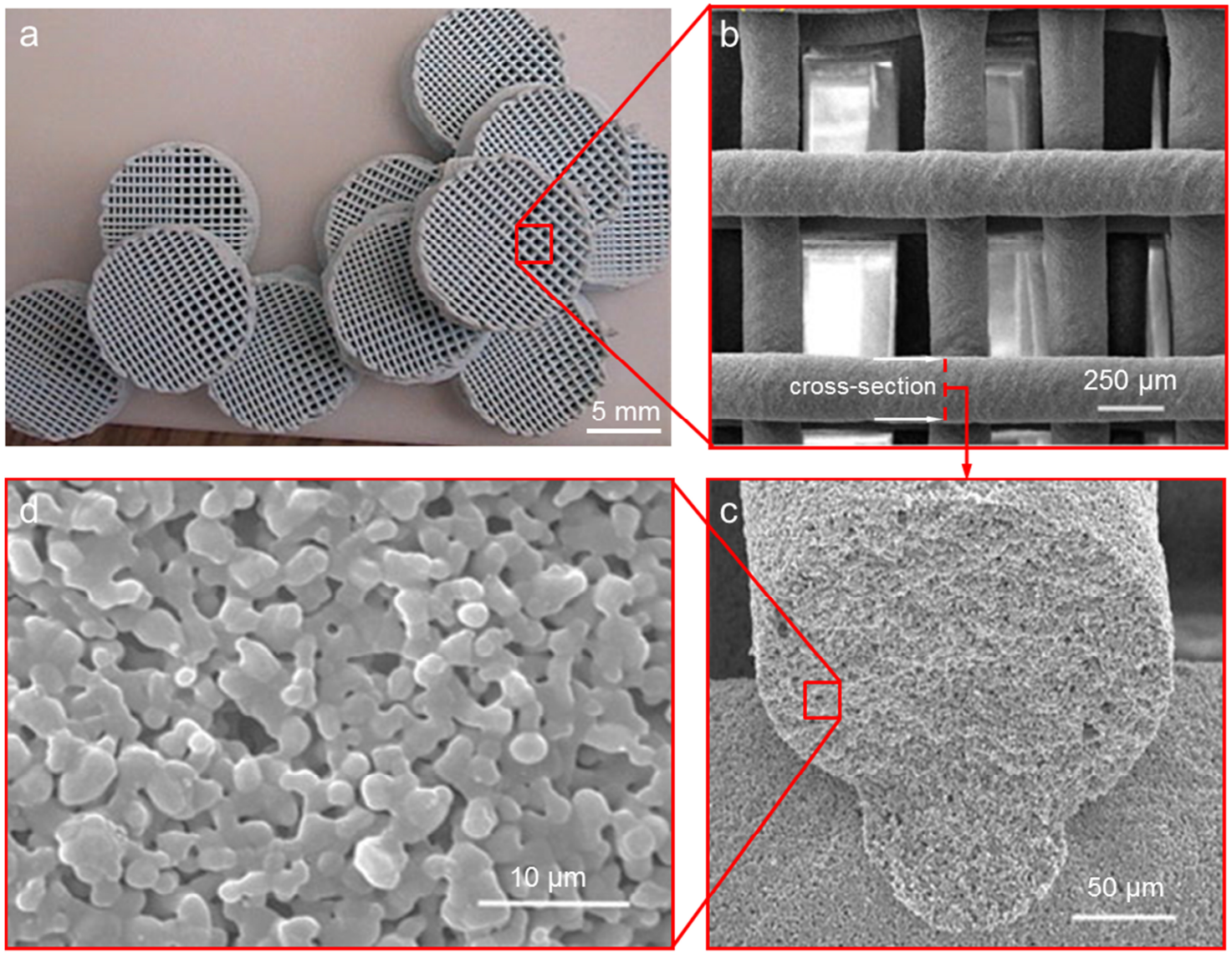

Fig. 2

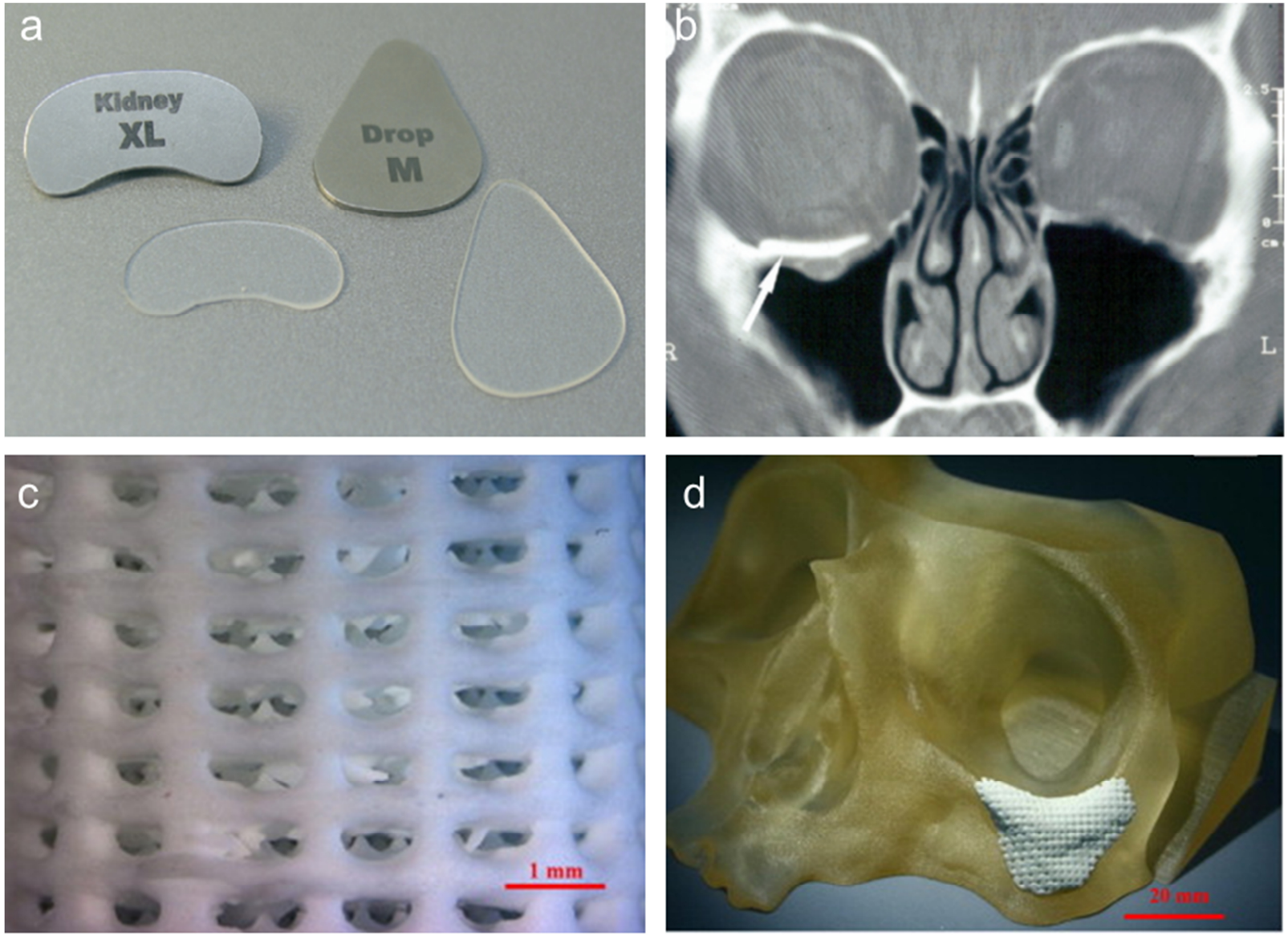

Fig. 3

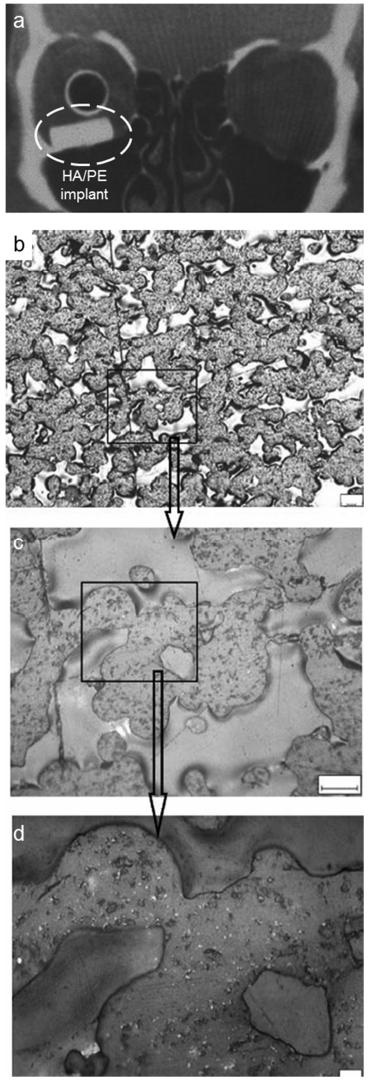

Fig. 4

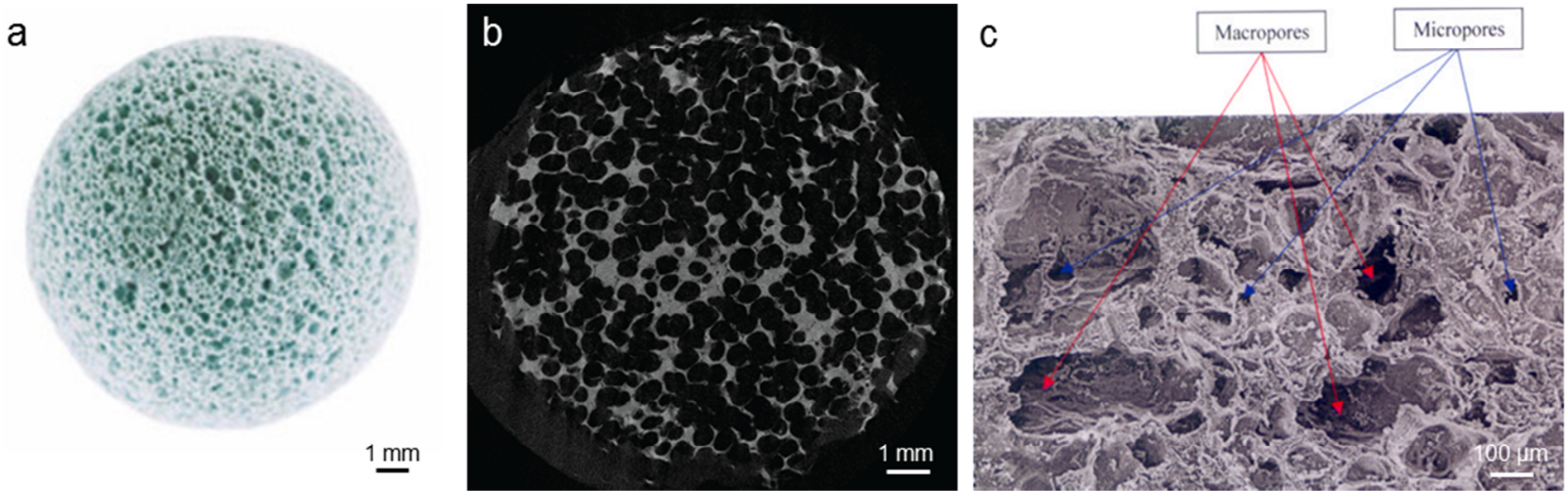

Fig. 5

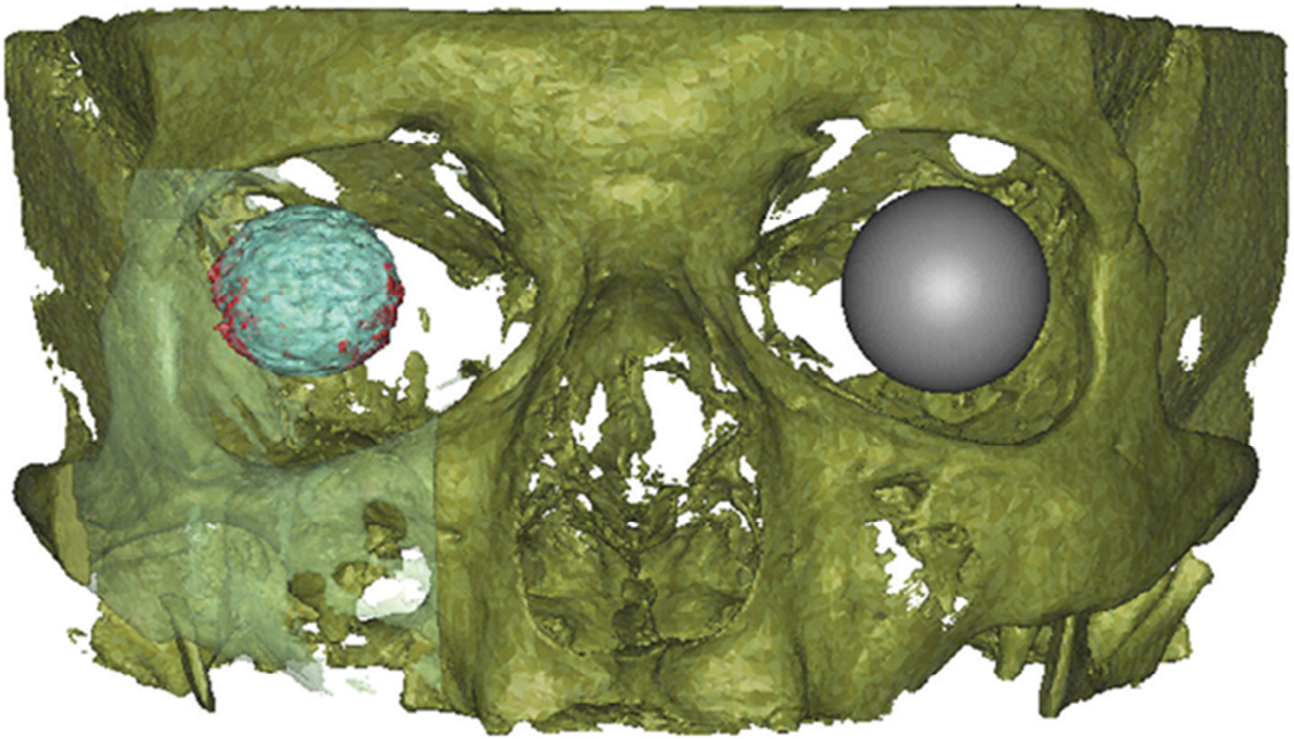

Fig. 6

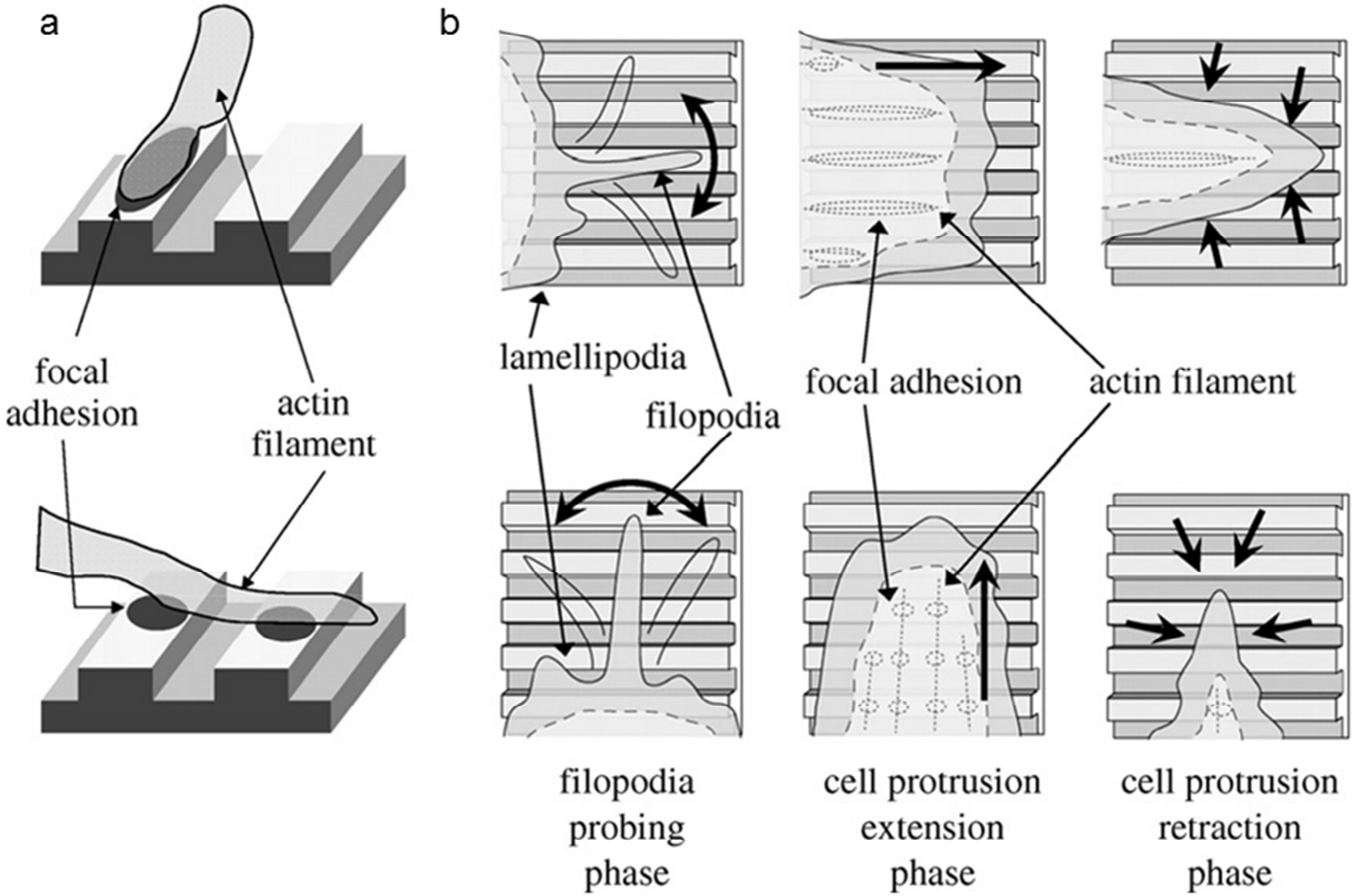
a
focal adhesion
actin filament
b
lamellipodia
filopodia
focal adhesion
actin filament
filopodia probing phase
cell protrusion extension phase
cell protrusion retraction phase

Fig. 7

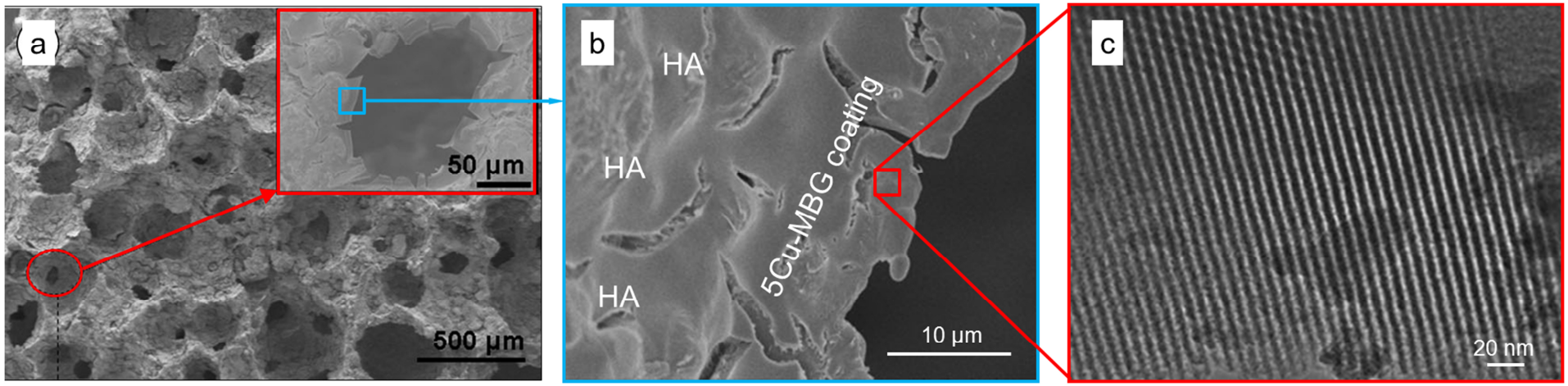

Fig. 8