# Chapter 3

## Hard tissue applications of biocomposites

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**Chapter 3 Hard tissue applications of biocomposites**

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**Keywords:** Bioactive material, Bone, Composite, Clinical Application, Implant

**Abstract**

Composites were first used clinically in the 1970s, these were based on carbon reinforced epoxy resin and although they progressed to successful clinical applications, none remained in use much beyond their initial clinical trials. The major problems were either the inability to shape the implant to fit the patient, or the method of manufacture being expensive and complex, finally these materials were "first generation" biomedical composites being bioinert. In the 1980s the second generation, that is bioactive composites, were developed and brought into clinical trial. As surgeons have been able to shape these implants to fit their patients the application of these materials has been more successful and being bioactive have lead to stronger bonds between the implant and the supporting bone, thus the implants has progressed to clinical use after their initial clinical trials. However, most of these could only be used in low load bearing applications. Since the early 2000s and the first edition of this book, the number of composite implants in clinical application and the loads to which they are exposed have both increased substantially. Improvements have come from applying engineering composites technologies to increase the mechanical properties and the use of bioactive components and the release of bioactive molecules to increase the bioactivity of the materials and devices.

## 3.1 Introduction

As has been discussed elsewhere this book, there are a variety of reasons to use composites in biomedical applications and a wide range of composites which have been developed. Briefly, the major reason for using composites is that mechanical properties can be tailored for the specific application so that that these properies closely match the stiffness of the natural tissue, preventing stress transfer effects, and can have strength in excess of the natural tissue being replaced. This rationale applies to a wide range of tissues, from soft load bearing tissues including tendons (Amis *et al*., 1984; De Santis *et al*., 2004) and the intervertebral disc (Ambrosio *et al*., 1998), and in hard tissues, that is bone replacement and augmentation (Bonfield *et al*., 1980; 1981) and finally in the replacement of multilayer structures such as surface defects in joints where both the articular cartilage and the underlying cancellous bone are replaced (Lynn *et al*., 2010; Harley *et al*., 2010a; 2010b). This matching of the mechanical properties can include duplication the non-linear behaviour of natural tissues and aims to optimise the load or stress transfer across the implant-tissue interface, thus reducing the risks associated with stress shielding of the natural tissue or stress concentrations at the interface. The second reason is that the biological properties of the composite also can be tailored to optimise the biological response to the presence of the implant thus a strong biological interface can be produced by the body to integrate the implant into the surrounding tissues (Bonfield *et al*., 1980; 1981; Lynn *et al*., 2010; Harley *et al*., 2010a; 2010b; Tanner 2010a; 2010b). The third rationale relates solely to degradable composites, where the degradation of the implants, at the appropriate rate, allows the gradual transfer of load from the implant to the natural tissue (Bos *et al*., 1987).

When we consider the specific requirements for hard tissue replacement or augmentation composites, the stiffness of the device should be similar to that of the bone and no monolithic materials have stiffnesses close to those of cortical bone and very few close to cancellous bone (Currey, 1998). Furthermore, in most cases the strength of the device should be higher than that of the bone it is replacing or augmenting, again a limited number of materials fulfil this requirement. Finally, the implant should be bioactive to bone, thus encouraging bone deposition onto the device, bonding it strongly into the

surrounding tissue. If the device is also degradable then the degradation products must be non-toxic and it would be beneficial to release products that accelerate bone healing (Waris *et al.,* 1994; Tanner, 2010a; 2010b).

While these may sound relatively simple requirements, when we consider the loads on a bone replacement or augmentation device, it can be seen that the mechanical requirements are high. The loads on a hip joint are 3.5 times body weight during slow walking, rising to 9 times body weight during a stumble (Bergmann *et al*., 1983), those on the knee are 2.0 to 2.5 times body weight during normal activities (Mundermann *et al.,* 2008). The peak strains on the tibial shaft are 500με during normal walking and are increased during running to 1200με, which assuming the Young's modulus of bone is approximately 20GPa equate to 10MPa and 24MPa respectively and furthermore include a torsional component during the push-off phase of the gait cycle (Burr *et al.,* 1996). Thus for a typical 80kg person the normal loads can be substantial, for example 2.0kN on the knee and 2.8kN on the hip joint, while for heavy patients the forces will be increased proportionally. Finally, the fatigue resistance needs to be very good, as Wallbridge and Dowson (1982) and Goldsmith *et al*. (2001) found that the average number of load cycles applied while walking drops from 2 million per year for someone in their 20s down to 0.5 million by the time the subject has reached their 80s. They developed equations for number of load cycles per year (N) versus age of the subject in years (A) with able bodied subjects being:

$$N = [3.29 - 0.03A] \times 10^6 \quad \text{Eqn (3.1)}$$

And total hip replacement patients:

$$N = [2.35 - 0.016A] \times 10^6 \quad \text{Eqn (3.2)}$$

It should be noted that these data sets were for people from the UK monitored in the late 1990s, while a similar study in California at about the same time with total joint replacement patients showed only about 2/3 of these activity levels (Schmalzried *et al*., 1998). Similar numbers of load cycles as seen in the legs were predicted for the arms and hands by Joyce and Unsworth (2000), although of course of lower magnitude.

When the first version of this chapter was written for the 2010 edition of this book there were very few bioactive composite materials used clinically in bony applications. At the time I said "it is probably not surprising to see that only a few composite materials have been reported as being used clinically." I hope that in this new edition the changes that have taken place in the first half of the 2010s are obvious and show that what was once a hope is now reality.

## 3.2 Head and Neck applications

### 3.2.1 Maxillo-facial applications

The maxillo-facial region has been the first application of many materials due to the lower mechanical requirements compared to most other skeletal applications. However, if there are problems these will be more obvious due to the more superficial implantation sites and less soft tissue covering, as was reported by Böstman *et al*. (1990) and others when degradable polylactic acid plates were first used clinically.

The first application of the hydroxyapatite (HA) reinforced high density polyethylene (HDPE) composite, HAPEX™ developed by Bonfield and colleagues (Bonfield *et al*., 1981; Bonfield *et al*., 1982; Wang *et al*., 1994) was as orbital floor replacement device (Downes *et al*., 1991; Tanner *et al.*, 1994). Here two different designs were developed, the first was a compression moulded disk less than 1mm thick and approximately 15 mm in diameter which was used to close the base of the eye socket after fracture of the orbital floor and prevent extrusion of the soft tissues into the sinus space. The advantages of the composite disk were that the strength and toughness were such that the devices should be cut intra-operatively with either a scalpel or a sharp pair of scissors. The second device was larger, being a space

filling implant for patients who had lost an eye. Here the requirement was that the implant did not change volume and bonded well to the orbital floor. The previously used implants were fat pads, which could resorb with time leading to loss of volume in the orbital cavity, and either glass balls or silicone pads, which did not bond with the orbital floor and therefore could extrude from the socket. In both these groups of patients a close bond of the HAPEX™ implant to the orbital floor could be seen on computed tomography (Figure 3.1) and manual palpation showed an stable interface. However, for commercial reasons, these devices were never used beyond the original cohort of 18 patients, but HAPEX™ progressed to applications in middle ear implants discussed later in this chapter (section 3.2.2).

Törmälä and his colleagues at Tampere University of Technology in Finland developed a series of implants of degradable self-reinforced polylactide (SR-PLLA) rods, screws and plates (Böstmann *et al.,* 1987; Törmälä *et al*., 1988; Suuronen *et al*., 1992; Waris *et al*., 1994; Ashammakhi *et al*., 2001), which have been commercialised. The rods and screws were manufactured by the compression moulding of aligned PLLA fibres. The use of the SR-PLLA screws was extended to fractures in cancellous bone of both the femoral neck and the lateral malleous of the fibula and will be discussed later. The plates were manufactured by extruding the material into a plate, these plates were die-drawn and the thin sheets were then cut to size and moulded together to produce plates that were 0.5mm thick and 12 mm by 40mm in area. These implants were initially used in craniofacial surgery (Suuronen *et al*.,

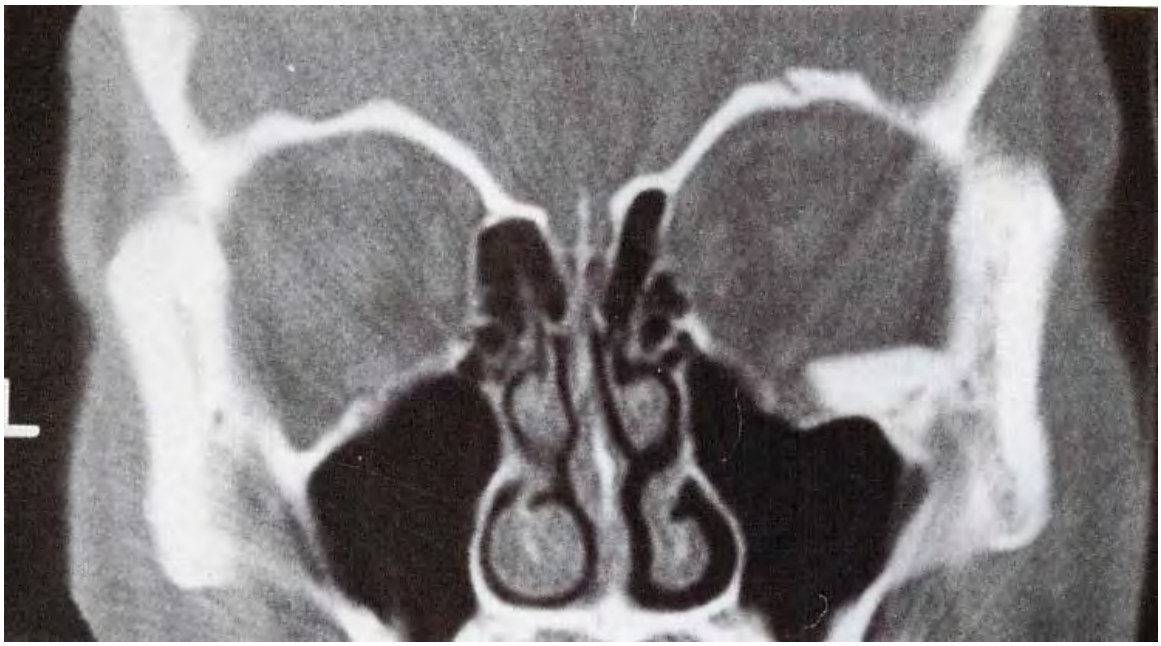


Figure 3.1 Computed Tomography (CT) scan of the head of a patient 6 months after the implantation of a HAPEX™ orbital floor implant showing partial integration of the implant. The CT scan shows the lower part of the brain, two orbital sockets, the nasal cavity in the centre and the two sinus cavities (darker as they are air filled). The implant is to be seen in the right orbital floor (left hand side of the figure) as an additional piece of material with similar radiographic density to bone just above the sinus (From Downes *et al*., 1991).

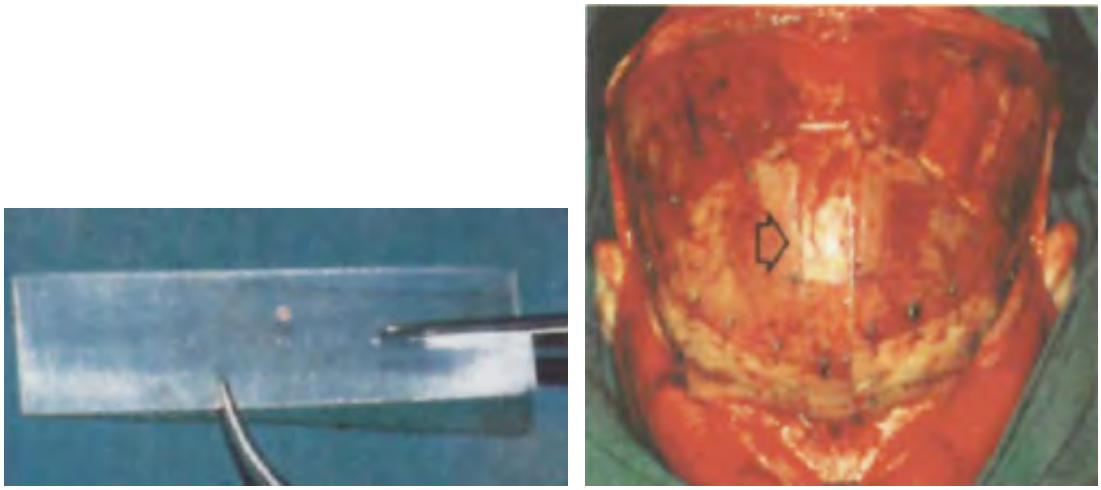


Figure 3.2 showing a) one of the 0.5mm thick self-reinforced PLLA plates used b) to repair the bony defects in the skull of a patient suffering from trigonocephaly treated by cranioplasty (From Waris *et al*., 1994).

1992; Waris *et al*., 1994; delCampo *et al*., 1994), where Suuronen *et al*. (1992) suggest using four of the 0.5mm thick plates which are screwed together once each plate has been bent into the required shape. The individual plates can be bent easily, but once the four plates have been screwed together they have the required stiffness and strength for clinical applications. In the study of Waris *et al*. (1994) one to three plates were used (Figure 3.2), in children between 6 months and 8 years old, so lower loads would be expected. Waris *et al*. suggest that ensuring a good covering of "well-vascularised tissue" and not using an excessively large implant will reduce the risk of a sterile inflammatory response due to the presence of the degrading implant. delCampo *et al*. (1994) used these plates to fix osteotomies in the maxilla, that is the upper jaw bone, and found good post-operative stability, without complications. Most of the reports have related to the craniofacial region (Ashammakhi *et al*., 2001), where they have found good responses to the implants. An advantage is that when used in growing children the gradual reduction in the mechanical properties as the implant resorbs leads to less reduction in the growth of the child's face. They are also able to shape the devices intraoperatively by warming the implants above their glass transition temperature (Tg) of approximately 60˚C. However, it should be noted that a self reinforced PLLA plates takes about 5 years to degrade completely compared to 6 to 12 months for self reinforced polyglycolide (PGA) plate (Suuronen *et al*., 1992).

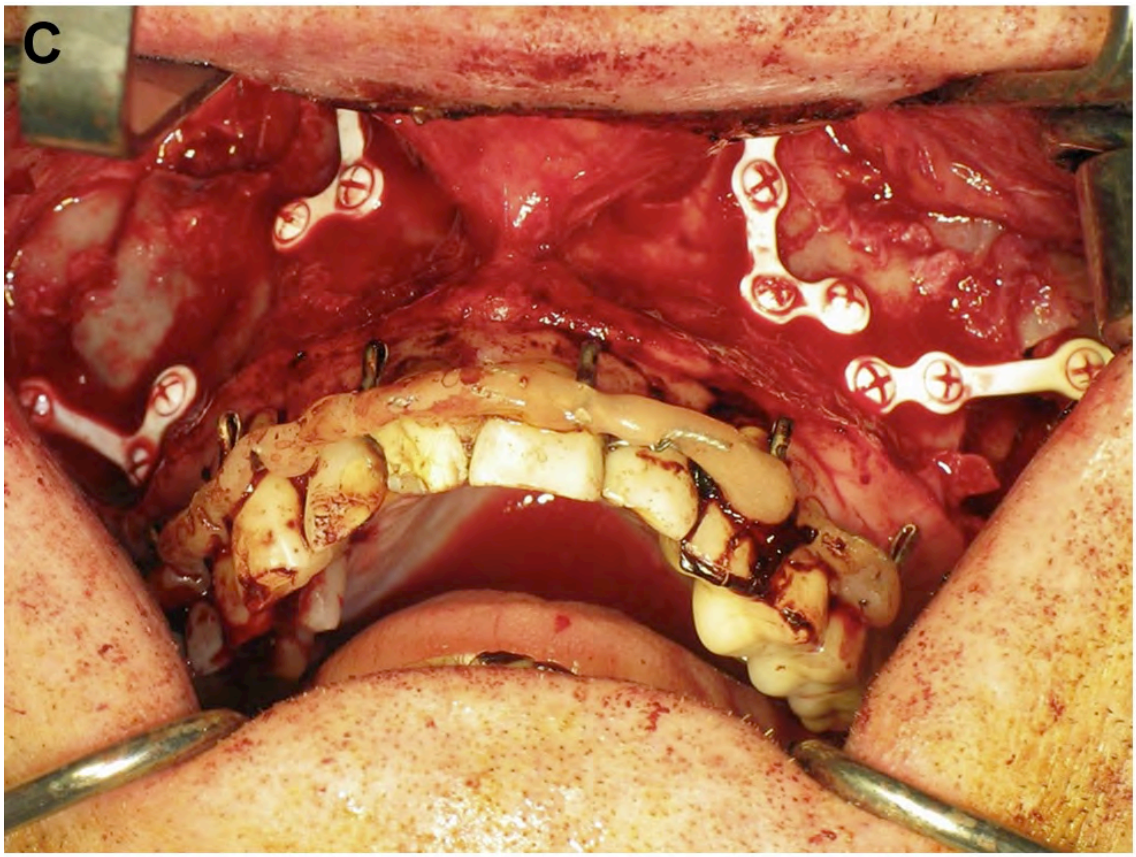
Zanetti and colleagues (Zanetti *et al*., 2001; Zanetti and Nassif, 2003) used a hydroxyapatite in polycaprolactone composite (Piattelli *et al*., 1997) which was manufactured in the form of flexible sheets 0.3 to 1.2mm thick which were used to reconstruct both the wall of the outer ear canal in 42 patients between the ages of 14 and 64 (Zanetti *et al*., 2001) and to repair minor defects of the base of the skull in seven patients (Zanetti and Nassif, 2003). In the ear study, after two years the outer ear was successfully reconstructed in 37 cases (88%) with the outer wall totally re-epithelialised in 33 cases (79%). There was re-occurrence of the clinical problem in three patients and in seven patients the implants extruded, however compared to the results of studies using other implants, this was considered to be a successful series with three quarters of the patients

returning to normal anatomy with no remaining infection. In their skull study, the defects treated were all less than 30mm in diameter and after 18 to 62 months follow-up there was no extrusion or foreign body reaction. In both studies they considered these preliminary results to be encouraging. They also comment on the ease of cutting and shaping the composite implants.

In Japan Hayashi *et al*. (2013) used degradable plates developed by Shikinami and colleagues (Shikinami and Okuno, 1999; 2001; Shikinami *et al*., 2005) produced by "compression forging" of non-sintered hydroxyapatite particles, 3-5μm in diameter, in poly-L-lactic acid (PLLA) and known as F-u-HA/PLLA to treat 86 facial fractures in 17 patients. The plates were 1mm thick and could be bent through 60˚ at room temperature, but for further contouring the plates were heated to 65-68˚C for 10 to 60 seconds. Follow-up was for 6-60 months (mean 21.6 months) with computed tomography pre and post-operation and annually thereafter. Two plates were involved in complications, one patient had excess bone formation at a single fracture site, but normal healing at their other three fractures and another patient developed a swelling around one of their three implants, due to the development of granular tissue. The authors comment that the PLLA has gone by 4-5 years and the HA particles by 5.5 years. They also comment on due to the presence of the HA that the radiographic density of the plates and the bone are similar, so difficult to differentiate on CT scans or radiographs.

In parallel Landes *et al*. (2014a; 201b) in Frankfurt, Germany used the same plates for two different studies. Landes *et al*. (2014a) treated orthognathic surgery patients, that is the correction of facial deformities, and compared 25 patients treated with 120 F-u-HA/PLLA plates with 25 patients treated with 124 conventional titanium alloy plates and followed them up for a mean of 22 or 24 months, respectively. A large range of clinical analyses were performed and no substantial differences were seen between the two groups. In parallel they treated a group of 29 patients with midface or malar factures using F-u-HA/PLLA plates and screws without a control group (Landes *et al*., 2014b). The rationale for the exclusion of a control group was that showing the patients their post-operative radiographs would immediately display whether they had been given composite or metal implants, due to the differences in the radiographic density. Follow-up was performed at 1, 2 and 4 weeks and 1, 3 and 5 years, by clinicians who had not been involved in the original surgery. The authors state that "all the patients healed well", but about half failed to attend after 4 weeks, but said that as they had no problems they had not seen the need to return. In the patients who did attend at 5 years, some remaining material was present, but without any problems (Figure 3.3). One patient had further surgery at 28 months, to correct a scar, and a biopsy was taken which showed the surrounding bone was in direct contact with the implant (Figure 3.4). They conclude that all the fractures were successfully stabilised and with limited foreign body reactions. More recently Sukegama *et al*. (2016) also reported the use of these plates under the commercial name OSTEOTRANS MX in 35 patients. All patients healed their fractures "satisfactorially" with three complications, two due to plate exposure and one where the patient complained of discomfort, all these plates were removed at times between 4 and 12 months and examined. Scanning electron microscopy showed direct bone contact with all three of these plates, the molecular weight of both the plates and the screws decreased between 4 and 8 or 12 months.

a)

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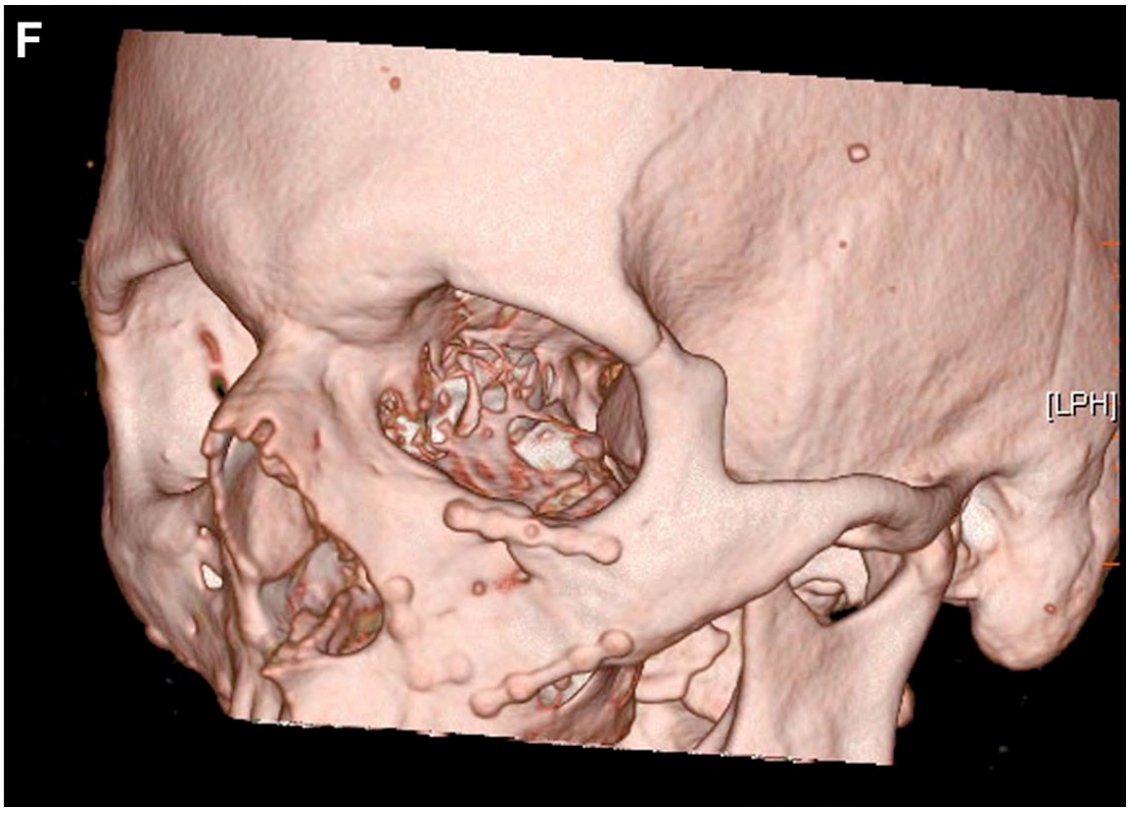



Figure 3.3 a) F-u-HA/PLLA plates and screws implanted in a 56 year old male with a sports injury and b) reconstructed CT scan at 53 months post surgery showing the integration of the implants into the bone (from Landes *et al*., 2014b).

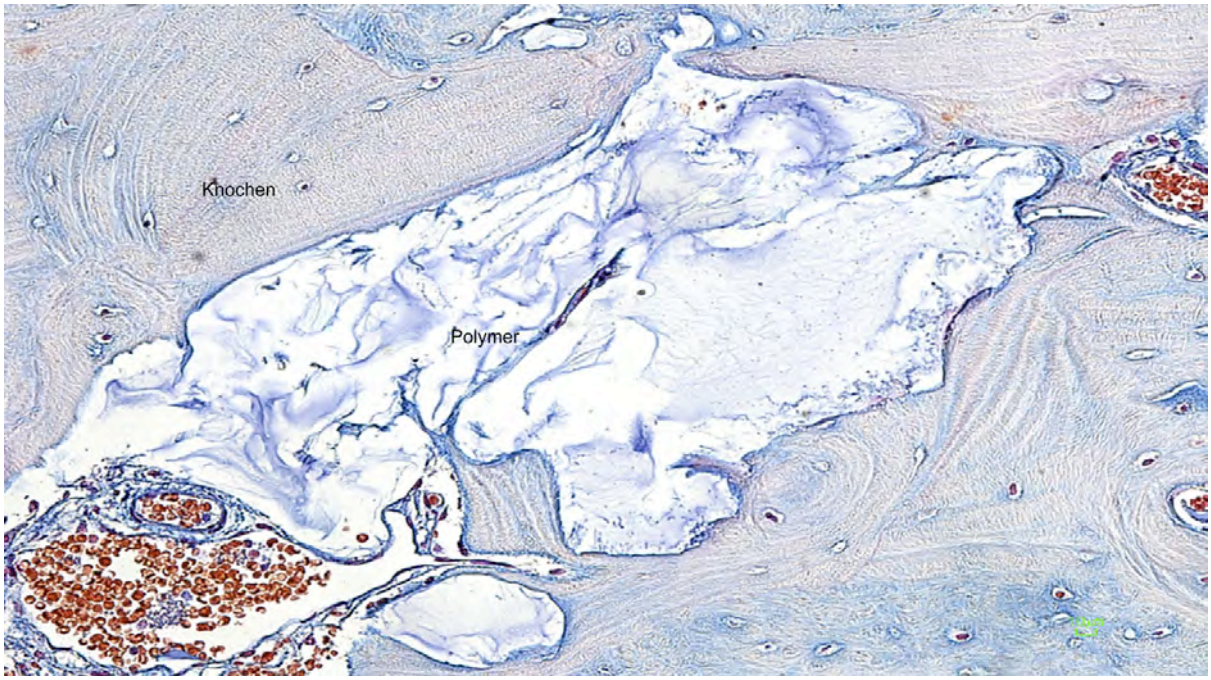



Figure 3.4 A F-u-HA/PLLA plate and screw after 28 months implantation showing direct contact between bone (Knochen) and the plate (Polymer). Heidenhain azan stain, original magnification ×400 (from Landes *et al*., 2014b).

Aitasalo *et al*. (2016) from Turku, Finland developed a non-degradable bilayer composite skull defect implant, based on an outer layer of woven E glass fibres in a bisphenol-a-glycidyl methacrylate and triethyleneglycoldimethacrylate (pBisGMA-pTEGDMA) acrylic co-polymer with bioglass particles providing a porous inner layer. Each device was designed using CT data and rapid prototyping to produce a model for the implant. Then the woven glass fibre composite was hand laid down to provide control of the fibre orientation and to give an approximately 1.1mm thick, relatively smooth, outer layer with high strength that overlapped the defect by 6 to 8mm all round. Below this outer layer was a typically 3.5mm thickness porous layer containing bioglass particles and filling into the actual defect. The monomers were cured with visible light followed by heat and then the device was sterilized using hydrogen peroxide. They report the results from 12 adult patients, from 26 to 78 years old, with large skull defects followed up for between six months and four years (Figure 3.5). All implants remained in position and no patients showed inflammatory or toxic responses. Also in Turku Piitulainen *et al*. (2015) implanted the same design in skull defects in seven children between the ages of 2.5 and 16 years, mainly after skull fractures. Interestingly, they comment that the porosity of the inner layer of the device encourages blood to be absorbed when implanted. Follow-up was for 14 to 53 months, there were some complications, including two infections at the surgical site and leak of the cerebrospinal fluid, but at no higher a level than other studies of similar patient cohorts. They conclude that the implants were safe, but longer follow-up and more patients are needed for definitive conclusions on the biomaterial.

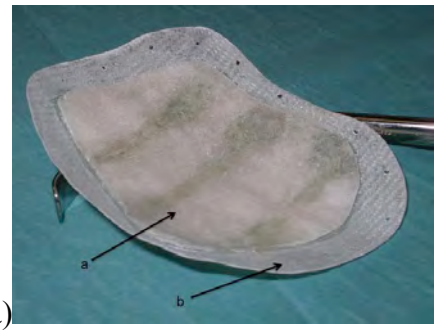
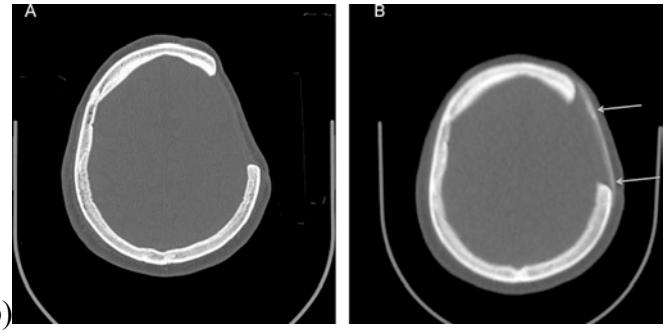
a)  b) 

Figure 3.5 a) internal view of a and b) the CT scans per-operatively and at 9 months post operation (from Aitasalo *et al.*, 2014)

An application in sinus repair of a composite of collagen reinforced with anorganic bovine bone, that is after removal of the protein phase, has been reported by Alayan *et al*. (2016). They compared the composite with a mixture of anorganic bovine bone and autogenous bone. The anorganic bovine bone was used as granules with the aim of encouraging vascular ingrowth and was the commercially available Bio-Oss® granules combined with an equal volume of autogenous bone, while the second implant studied was blocks of anorganic bovine bone had 10% porcine type I collagen added, known as Bio-Oss Collagen®. There were twenty patients were in each group and after 5 months they were given an implant at the operation site and at this time a histological section was taken. Undemineralised histology showed very few differences in the response to the two materials, both showed good bone ingrowth and the authors considered that either material could be used in this application.

Another hydroxyapatite-collagen composite was prepared in theatre by D'Agostino *et al*. (2016) and used to reshape the zygomatic bone (also called the malar bone or the cheek bone) in 430 patients. After mixing the composite of HA granules with collagen microfibrils and sterile saline under sterile conditions and shaping, it was heated using a 150W lamp for at least 2.5 hours to stiffen the material before implantation into pockets formed in the periosteum. Follow-up was 3 to 10 years and all patients were radiographed to check position and integration of the implants. Smaller groups underwent more extensive analysis, 110 patients had cone beam tomography after at least 36 months, 76 patients used a visual analogue scale to evaluate their view of the restoration of their face shape and 8 patients who subsequently had a screw removed agreed to core biopsies for histological analysis. The complication rate was 1.56%, mainly malpositioning of the implant or resorption of the implant. At 6 months the composite graft was still visible as granules, but without migration and by 24 months the granular structure was less obvious and becoming incorporated into the supporting bone. Histologically, 70% of patients had new bone formation and immunohistochemistry showed osteoclastic activity on the granules.

Thus a range of bioactive composites, many biodegradable, have been introduced recently for maxilla-facial surgery and have been at least as successful as early devices in these low load bearing applications.

### 3.2.2 Aural applications

The clinical success of the HAPEX™ orbital implants encouraged Smith & Nephew ENT to use HAPEX™ in middle ear implants in the 1990s. At the time they were producing a range of middle ear implants, such as those designed by Goldenberg (1994) and Dornhoffer (1998), with hydroxyapatite heads that contacted

the tympanic membrane (ear drum) and had ultrahigh molecular weight polyethylene (UHMWPE) shafts. These shafts were cut intra operatively to the required length to fit on the staples, the last bone of the train of three bones that transmit and amplify sound vibrations from the outer ear to the inner ear. Hydroxyapatite was used for contact with the tympanic membrane as other materials are extruded out of the ear, while the UHMWPE was used as it could be cut easily in the operating theatre to enable the implant to be tailored to fit the patient. HAPEX™ was used to replace the UHMWPE as there was considered to be increased possibility of the stapes bonding with an HAPEX™ shaft, increasing the long term stability of the implant, the presence of the HA particles in the polyethylene made the material easier to trim intra operatively and finally the increased density of HAPEX™ compared with UHMWPE should increase the transfer of sound through the shaft and thus improve the patients hearing. Goldenberg and Driver (2000) in the US considered the clinical success of these implants, reviewing the results for 233 patients of whom 77 had their implants *in situ* for more than 5 years. Overall, the hearing success rate was 56.8% with implant extrusion occurring in 5.3% and visible slippage of the implant in 7.7% of patients. They concluded that the implant provided good hearing which was stable with time and that the extrusion rate was low. Meijer *et al*. (2002) in The Netherlands reviewed the histological response to 11 of these HAPEX™ implants which were retrieved 2 to 20 months after implantation due to re-occurrence of the original clinical problems. They found a fibrous tissue layer covering all the implants (Figure 3.6) but, in no cases did they find a foreign body response, which they comment is in contrast to similar implants manufactured using Proplast® or Plastipore® used in the middle ear. More recently Hahn and Bojrab (2013) in Michigan, USA, compared the clinical results of 46 patients who had been treated with HAPEX™ implants with 176 patients where again the implant head was hydroxyapatite but the shaft was titanium with an adjustable length. For the HAPEX™ implants the mean follow-up was 42.9 months compared with 28.9 months for the titanium shaft implant in patient groups with mean ages of 36.3 and 36.2, respectively. The clinical results were similar with the air-bone gap dropping from 33.2 to 14.0 dB in the HAPEX™ implants and 34.0 to 14.7 with the titanium stem, similarly a “successful outcome”, that is an air-bone gap of less than 20 dB, was seen in 80.4 and 81.3% patients, respectively. For commercial reasons these devices are no longer available.

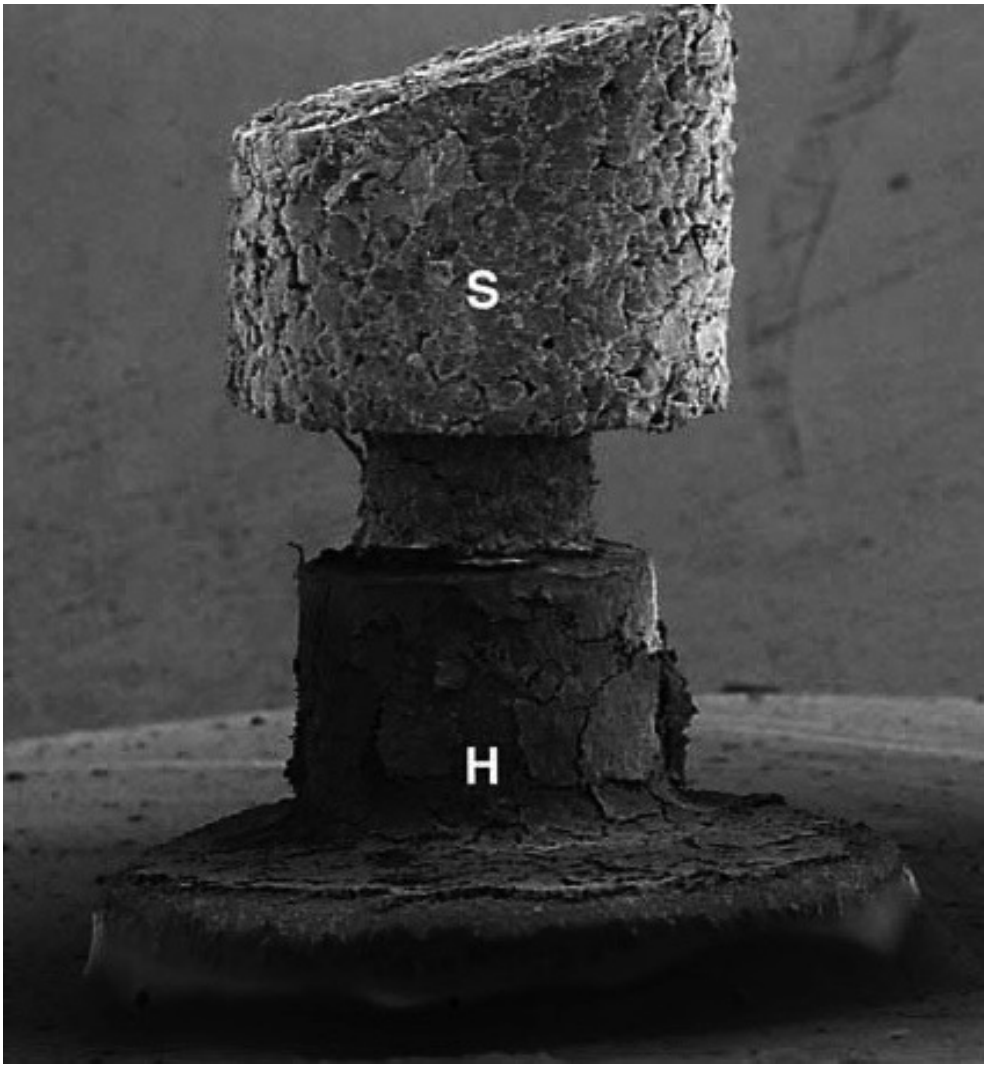



Figure 3.6 Scanning electron microscopic appearance of a HAPEX™ middle ear prosthesis consisting of a hydroxylapatite head (H) and a hydroxylapatite-polyethylene shaft (S). The shaft has been trimmed intra-operatively to fit to the appropriate size in the middle ear. The shaft is composed of sintered hydroxylapatite and polyethylene which gives a smooth but irregular surface (From Meijer *et al*., 2002).

### 3.2.3 Dental Applications

As with many other activities in the field of biomaterials, dental applications have lead the surgical applications of biomaterials. The major dental use of biocomposites, that is as tooth filling materials to replace dental amalgam, will not be considered in this chapter. However, implantable composites have been used as posts for tooth replacement to provide support for either natural or artificial teeth or on the tongue side of teeth to support, either temporarily or permanently a tooth where the anchorage has been weakened (Chan *et al*., 2006).

While the Brånemark titanium tooth root replacement and similar designs are now used almost exclusively, in the past composites have been used to treat such problems. Hodosh *et al*. (1976) manufactured their own implants by mixing polymethylmethacrylate (PMMA) with vitreous carbon (VC). After extraction of one or more teeth, they produced moulds of the gaps in their patients' alveolar ridges and filled these moulds with a mixture of 95% PMMA and 5% VC, presumably these are weight percentages although this is not stated, with MMA monomer and then heat

polymerised. The implants were sand blasted to remove the surface layer and expose the VC. After ultrasound cleaning and sterilisation these were implanted into their patients and used to provide supports for fixed partial dentures. The authors say that they obtained rapid healing with minimal discomfort, which seems surprising given their statement that the composite "is a mildly irritating, strong implant material". In their study of 15 patients also found minimal bone loss with retention of the alveolar ridge height. They do comment that the use of a material with lower modulus than bone produces better load transfer from the implant to the supporting bone.

Kawai *et al*. (2014) have used a collagen-calcium phosphate composite developed by Kamakura *et al*. (2006), although in this case the calcium phosphate is octocalcium phosphate ($Ca_8H_2(PO_4)_6.5H_2O$) combined with porcine skin origin collagen, thus presumably a mixture of Type I and Type III collagen. Their first study (Kawai *et al*., 2014) looked at two patients with radicular cysts (defects at the base of incisor teeth) of 8mm diameter and 5×5×10mm respectively and these healed well with some bone formation visible in the graft from 3 months and increased bone formation by 6 months. Thereafter they (Kawai *et al*. 2016) extended the study to give a total of 10 patients, who either had similar cysts (5) or had impacted teeth extracted (5). The defects were filled with their composite material in the form of discs 9mm diameter and 1 mm thick prior drying and sterilisation, although the size of the final implants is not given. As many discs as could be fitted, were implanted in each defect to fill the space, resulting in 4-22 discs used per patient. There were two minor complications, one case of material extrusion and pus discharge in a patient with a radicular cyst and the excess material was removed and the area washed daily with local antibiotics for the next 5 days, the other patient had a tooth extracted and there was "insufficient closure of the wound" and again local washing with an antibiotic wash and the wound healed. CT scans at 3, 6 and 12 months showed an increases in radiographic density to 3 and then 6 months, but the density then levelled off between 6 and 12 months. Haematology and biochemical studies performed at 1 day, 1 week, 1, 3, 6, 9 and 12 months post operation showed nothing remarkable beyond an increase in the white blood cell count at 1 day which had dropped to normal levels by 7 days.

### 3.3 Axial skeleton applications

#### 3.3.1 Internal applications

The first composite device to reach axial skeletal clinical application was a carbon fibre in epoxy resin composite fracture fixation plate developed by Hastings and colleagues (Hastings, 1978; Bradley *et al*., 1980; Ali *et al*., 1990) where carbon fibres were used to reinforce epoxy resin. The devices were manufactured by a combination of heat and pressure applied to 21 layers of carbon fibres in epoxy pre-preg with fibre directions along and at 45˚ to the long axis of the plates. Once the plates were manufactured screw holes were drilled and countersunk with the size and shape of the implant being identical to a typical metal fracture fixation plate of that time. These plates had a bending stiffness approximately one quarter that of the equivalent metal plates, yet the both fatigue limit and angulation at failure were 60% higher. The biocompatibility was assessed by *in vivo* implantation in mice both in bone and with muscle contact. These plates were used in 40 forearm fractures in 29 patients (Ali *et al*., 1990). The application was limited to the forearm as these plates could not be bent to fir the patient needed for application elsewhere in the body, unlike metal implants. Clinically the patients used their arms earlier than those treated with equivalent metal implants and in 70% of the cases the healing process was secondary healing with callus formation (Figure 3.7) rather than primary healing with minimal callus

formation, that was considered desirable at that time for internally fixed fractures. Primary healing occurs where the motion at the fracture site is less than approximately 100μm, whereas secondary healing occurs with limited motion at the fracture site and is a substantially faster process. All the implants were removed after healing was complete. Histological analysis showed minimal response in all but 6 fractures, although some carbon particles were found in the soft tissue surrounding the implant. In the other cases the responses were minor, except in two patients and in one of these, the implant was found to be infected. As a result of the histological studies the authors suggest that there was no reason to remove the implants in future studies. The limit on the use of these devices was their inability to be bent to fit the patient, thus limiting their use to the forearm and this constraint resulted in them being discontinued. However, thermoplastic and thermoset polymer matrices reinforced by carbon and glass fibers have been used to produce composite hip joint prostheses as discussed elsewhere in this book.

More recently the self reinforced poly-L-lactide (SR-PLLA) materials developed by Törmälä and his colleagues (Böstmann *et al.,* 1987; Törmälä *et al*., 1988; Suuronen *et al*., 1992; Waris *et al*., 1994; Ashammakhi *et al*., 2001) have been used in internal fixation of the ankle and in femoral neck fractures. In an early study of displaced medial and lateral malleolar fractures (Böstman *et al*., 1987) they compared the results of treatment with cylinders of self-reinforced polylactide-glycolide (SR-PLGA) fibres with conventional metal screws. They found no differences in the anatomical and functional results with similar levels of complications in each group. In a later study also in the ankle, Joukainen *et al*. (2007) compared screws manufactured of self reinforced polylactide with 70%L and 30%LD (SR-PLA70) with those made from 100% L PLA (SR-PLLA) for the treatment of ankle fractures in 62 patients. There was minimal difference in the mechanical properties of the two devices, but the co-polymer reduced the time that the implants kept their strength *in vitro* from 36 weeks to 24 weeks. They found that the patients with the co-polymer implants (SR-PLA70) had 65 days sick leave compared with 60 days for the SR-PLLA treated patients, but no other statistically significant differences. In both

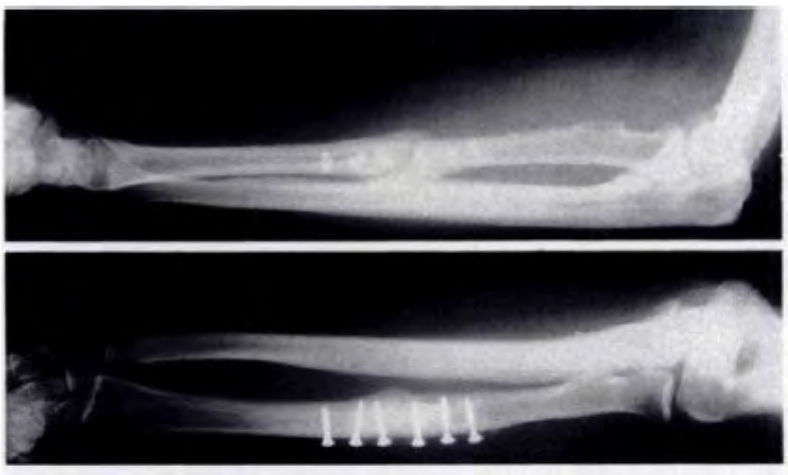


Figure 3.7 Clinical response to the carbon fibre reinforced epoxy resin fracture fixation plates used by Ali *et al*. (1990) in the forearm showing the "healing by close-knit callus which was seen in 70% of cases" (From Ali *et al*., 1990).

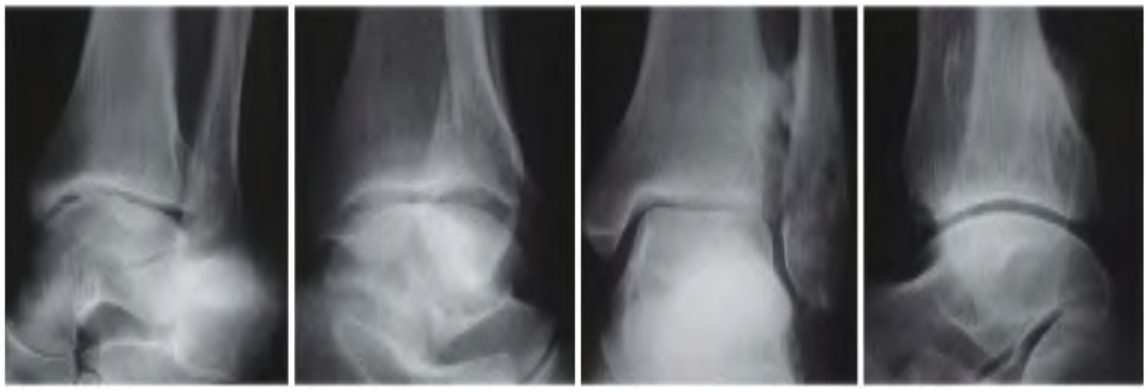


Figure 3.8 Fracture of lateral malleolus preoperatively (a,b) and at the 1-year follow-up (c,d) treated with two SR-PLA70 screws. Note the syndesmotic ossification between the tibia and the fibular. The patient did not report any problems at the 1-year follow-up (From Joukainen *et al*., 2007).

groups the screw track was still visible at one year (Figure 3.8). In the femoral neck study Jukkala-Partio *et al*. (2000) treated 40 patients with subcapital fractures using three 6.3mm diameter SR-PLLA screws per fracture and the results were compared with 38 patients treated with 3 metal screws each 7.0mm in diameter. The groups were similar in age and clinical problems and there were similar numbers of re-dislocations in each group, however the ability to walk and long term range of movement were greater in the patients treated with the degradable implant.

In joint replacement Field and Rushton (Field and Rushton, 2005; Field *et al*., 2006) developed the Cambridge Cup to replace the horseshoe of articular cartilage in the acetabulum in patients under going what would normally be a hemiarthoplasty, that is replacement of the femoral head only, after femoral neck fractures, in elderly, low activity, osteoporotic patients. In these patients a large femoral head articulates with the articular cartilage and with time the cartilage can wear through, however many of these patients are not well enough in themselves to be suitable for a total hip replacement. The Cambridge cup consists of 3mm of UHMWPE supported by a 1.5mm thick layer carbon fibre reinforced polybutylenetere-phthalate (PBT) or in a later design polyetheretherketone (PEEK). Implant fixation was either a 60µm thick of plasma sprayed HA coating or PMMA bone cement supplemented with some composite fixation pins (Figure 3.9). The concept of this design is that the implant stiffness is similar to that of the articular cartilage and subchondral bone plate structure that it is replacing. Compared to other studies using composite materials this was a much older age group of patients from 70 to 100 years with a mean age of 81.8 years, however this age range did mean that post mortem studies have been performed. They found that despite the relatively thin layer of UHMWPE there was no significant wear, which they attributed to the flexibility of the device. The PMMA implanted prostheses migrated more than those relying on the HA coating for fixation, which would normally be considered an indictor of increased long term risk of implant loosening (Ryd, 1985). Dual Energy X-ray Absorptiometry (DEXA) of the bone surrounding and supporting the implant showed that the bone density dropped in the first 6 to 12 months, but then returned to post operative levels. Brooks *et al*. (2010) performed post-mortem histological analysis of 12 of these cups, retrieved 2 to 84 months post implanation, from an initial group of 50 women. These post mortem studies showed more bone contact with the HA coated implants, even

Figure 3.9 Cambridge Cup showing the outer polybutyleneterephthalate (PBT) carbon fibre composite shell with the inner UHMWPE bearing and holes for the insertion of fixation pegs (From Field and Rushton, 2005).

after resorption of the HA coating, than the non-coated implants where fibrous encapsulation was seen. They further note that the flexible component produced by the combination of the PE lining and the composite backing did not reduce stability of the implant or lead to excessive wear.

The treatment of bony defects has been considered by various groups. The requirement is to provide a scaffold in contact over which osteoblasts can travel and deposit new bone, thus working on the principle of osteoconduction, with the scaffold eventually removed by osteoclasts. Many clinicians use hydroxyapatite or other calcium phosphates as granules or as porous blocks and these will not be considered here. A few groups have investigated composite implant materials, an example is Sotome *et al*. (2016) who compared HA/collagen (Refit®) with β-tricalcium phosphate (β-TCP, Osferion®) to fill medium, but above the critical size defects (less than 30cm$^3$) in two groups each of 63 patients, with patients allocated by a computer program to produce equivalent groups. Follow-up was using radiographs at various times between 2 and 24 weeks, each radiograph was assessed by three orthopaedic surgeons, however, due to the differences in the radiographic density of the two implants, they could not be blinded. Each defect was scored between 0 and 2 for both the marginal zone to describe the degree of integration where 0 was a complete radiolucent line and 2 was no line visible, while bone regeneration was 0 for no bone regeneration and 2 was complete replacement by new bone, thus "highly effective" was a total of 4 dropping down to "ineffective" for 0 or 1 total. They comment that once wetted the HA/collagen composite was "elastic". By 18 weeks statistically more of the HA/collagen treated patients were classed as having highly effective healing than those with the β-TCP implants.

Treating osteochondral defects, that is defects affecting both the articular cartilage and the underlying bone, is seen as a treatment for patients with early localised osteoarthritis, rather than leaving until the problem is serious enough to require total joint replacement. This treatment has particularly concentrated on the knee and ankle problems. Mosiacplasty, that is implanting plugs of

cartilage and underlying subchondral and cancellous bone from the non-load bearing edges of a joint into the defect has been tried (Cognault *et al*., 2015), but has the usual limitations of autografts of a limited supply of donor tissue, thus various groups have tried to develop an artificial equivalent. FinCermica in Faenza, Italy have commercialised one implant, Maioregen®, based on the work of Tampieri *et al*. (2003). It is described as three layered implant where the outermost layer, to replace the cartilage, is of smooth surfaced type I collagen, the second layer replacing the tide-layer in the cartilage is 60% type I collagen and 40% hydroxyapatite and the deep, cancellous bone contacting, layer is 30% type I collagen and 70% hydroxyapatite (Kon *et al*., 2009). Although whether the collagen-hydroxyapatite contents are described by weight or volume is not defined, but based on the data from Tampieri *et al*. (2003) it is probably by weight. Given the nearly a factor of three difference in densities between these two phases this will make a substantial difference in the actual amounts of the two phases present. All layers are porous and the collagen-hydroxyapatite composite is described as nanostructured and the hydroxyapatite is non-stoichiometric, but self assembled into the collagen. Kon et al. (2009) report a single 46 year old patient with 4 individual defects in one knee treated. By a year post surgery he was back playing tennis with only minimal oedema present on MRI scans. The same group (Kon *et al*. 2014) report on 11 patients with a total of 13 defects in their tibial plateaux, up to 12.5cm$^2$ in area. The patients' knee scores increased at one year and remained at that level at 2 years, and of these patients eight considered that they had a marked improvement, two had moderate improvements and one considered that they were slightly worse at 2 years. The authors considered the results to be "promising" for an initial study. In contrast, Brix *et al*. (2016) using the same implants treated 8 patients between the ages of 15 and 51. While the clinical scores increased, MR imaging showed good integration at the cancellous bone level, but limited integration of the cartilage, a known problem with attempting to repair cartilage defects. More recently Christensen *et al*. (2016) using the same device in 10 patients followed for 3 years in a prospective study, two patients has their implants removed at 6 days and 3 months post surgery due to swelling of their knees, two more patients had long term swelling leaving 6 patients for MRI studies of their knees at 1 and 2.5 years post-operation and unlike other studies they performed CT (computed tomography). The CT analysis found limited subchondral bone ingrowth into the lowest layer of the device and limited cartilage repair between the implant and the native surrounding tissue. They did find significant and substantial improvements in the pain, sporting activity and Quality of Life score, but still stopped the study and suggest that the this implant "should be used with caution" despite the good results seen by other groups.

A similar concept osteochondral defect implant, commercially known as ChondroMimetic™, was produced by a combined Cambridge-MIT group (Lynn *et al*., 2010; Harley *et al*., 2010a; 2010b), but with only two layers. The outer, articular cartilage replacing, layer is a composite of type II collagen and glycosaminoglycan (GAG), while the inner cancellous bone contacting layer is produced by co-precipitation of collagen type I, glycosaminoglycans and calcium into phosphoric acid to produce a calcium phosphate reinforced collagen composite and then freeze drying to produce porosity. The calcium and phosphoric acid produced octocalcium phosphate, which was then hydrolytically transformed into HA. Cross linking was performed chemically using a solution of 1-ethyl-3-(3-dimethylaminopropyl) carboniimide and N-hydroxysuccinimde in water. The two layers were joined by pouring the type I collagen-GAG-HA composite into a

mould, followed the type II collagen-GAG composite and allowing the two materials to diffuse into each other for 30 minutes at room temperature, prior to freeze drying. Controlling the freezing rate and final temperature produced interconnected pores and allowed control of the pore size between 56µm and 1085µm. While the clinical results have been reported in a conference abstract, they have not as yet been published.

### 3.3.2 External applications

The principal applications of composites external to the body are in fracture fixation. Two major applications are in use; fibre reinforced composites as external casts and carbon fibre reinforced epoxy rings used in the Ilizarov External Fixator.

Plaster of Paris has many disadvantages being fairly radiopaque, mechanically brittle, of fairly high density and not being water resistant. Various orthopaedic companies have developed a wide woven fibre mesh impregnated with a settable polymer as a plaster of Paris replacement. The requirements are low radiopacity to allow the process of fracture healing to be followed radiographically without the need to remove the cast, higher failure properties, water resistance and lower density. The polymer setting initially was by heat, however the more recent formulations are light settable. After a few initial problems with the heat setting formulations in the developed world plaster of Paris casts have been almost completely replaced with composite materials.

The Ilizarov external fixator was developed by Gavriil Ilizarov in Siberia in the 1950s, however it was only the 1980s that this external fixator became known in the West (Ilizarov, 1988). The fixator is used for fracture fixation, in limb lengthening and limb straightening. It consists of a series of thin wires, 1.5 or 1.8mm in diameter, that pass through the bone above and below the fracture or osteotomy, these wires are then tensioned onto a series of rings that are connected to form a scaffolding system around the injured limb. For limb correction, the rings are gradually moved using the connectors that cross the osteotomy site to move the bones to their required anatomy. Initially the entire fixator was fabricated of stainless steel, which made a heavy system with large amounts of radiopaque metal, potentially making imaging the fracture difficult. However, random chopped carbon fibre in epoxy resin and knitted Kevlar-29 in epoxy rings for the Ilizarov have been developed (Baidya *et al*., 2001 a & b). These rings were extensively tested both as individual structures and as parts of external fixators. They found that the composite rings were less stiff than the steel rings, but had sufficient stiffness and strength to be used clinically, while the reduced weight and radiopacity has benefits to both patients and surgeons.

## 3.4 Advantages in the use of composites for hard tissue applications

Composites can be produced that have similar stiffness to the natural tissues they are replacing. This modulus matching can lead to better biological responses in the form of reducing stress shielding below the devices or stress concentrations at the ends of the implant. Furthermore many of these newer composites contain one or more calcium phosphates, which are released from the implant providing a supply of calcium and phosphate ions, or other biologically active moieties, that can be incorporated into the bone and accelerating the healing process. Composites implants can be tailored in the operating theatre to fit the patient, unlike most metal implants, which can only be bent but not cut, or all ceramic implants, which are difficult to cut and cannot be bent. However, the methods of shaping composites intraoperatively are different from those used with metal implants requiring heat or cutting rather than plastic deformation of the metal.

### 3.5 Disadvantages in the use of composites for hard tissue applications

As yet most of the composites which have been implanted have been limited to lower load bearing applications due to their poor strength and fracture toughness. Some of the less successful applications have been where the metal implant design has been exactly reproduced in a composite rather than start with the implant requirements and use the properties of the composite to drive the design, that is design based on the properties of the composite to be used.

### 3.6 Future trends

Composites have been used in patients since the 1970s. However the early composites were carbon containing and produced only acceptable biological responses. The newer variations of composites are bioactive producing beneficial or active biological responses. One of the major developments has been the selection of either non-degradable or degradable polymers as the basis of composites depending on the clinical application. In joint replacement and similar applications non-degradable implants are required, while for fracture fixation, and even more so for tissue engineering scaffolds, degradable scaffolds will allow the patient to be treated and then forget that they ever had an artificial material implanted. It seems likely that the implant material and design will be based on the best combination for the specific clinical problem rather than treating the clinical problem with an available implant.

It is interesting to note that there have only been a limited number of composites which have progressed through to published clinical trials, however considering how long it takes to progress from development of a new material to clinical use we should expect an increasing number of composites, such as those discussed elsewhere in this book, to enter clinical use in the next five to ten years. With time our understanding of the advantages and disadvantages of the clinical use of composites is increasing which should accelerate the introduction of further more advanced composites be they bioactive materials or Smart materials.

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