Synthetic bone graft substitutes

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REVIEW ARTICLE

SYNTHETIC BONE GRAFT SUBSTITUTES

WILLIAM R. MOORE,* STEPHEN E. GRAVES† AND GREGORY I. BAIN‡

**Department of Orthopaedic Surgery, Modbury Public Hospital, Modbury, †Department of Orthopaedics, Repatriation General Hospital and Flinders Medical Centre, Bedford Park and ‡Department of Orthopaedics and Trauma, Royal Adelaide Hospital, Adelaide, South Australia, Australia*

Replacement of extensive local bone loss is a significant clinical challenge. There are a variety of techniques available to the surgeon to manage this problem, each with their own advantages and disadvantages. It is well known that there is morbidity associated with harvesting of autogenous bone graft and limitations in the quantity of bone available. Alternatively allografts have been reported to have a significant incidence of postoperative infection and fracture as well as the potential risk of disease transmission. During the past 30 years a variety of synthetic bone graft substitutes has been developed with the aim to minimize these complications. The benefits of synthetic grafts include availability, sterility and reduced morbidity. The present article examines the relevance of synthetic bone graft substitutes, their mechanical properties and clinical application.

Key words: allograft, autograft, bone graft substitute, future.

INTRODUCTION

There are four characteristics that an ideal bone graft material should exhibit which include: (i) osteointegration, the ability to chemically bond to the surface of bone without an intervening layer of fibrous tissue;[1] (ii) osteoconduction, the ability to support the growth of bone over its surface;[1] (iii) osteoinduction, the ability to induce differentiation of pluripotential stem cells from surrounding tissue to an osteoblastic phenotype;[2] and (iv) osteogenesis, the formation of new bone by osteoblastic cells present within the graft material.[2]

Only autogenous bone graft satisfies all of these requirements. Allograft is osteointegrative and osteoconductive and may exhibit osteoinductive potential, but it is not osteogenic because it contains no live cellular component. Synthetic bone graft substitutes currently possess only osteointegrative and osteoconductive properties.

Autograft

Autogenous cancellous bone graft is the most effective bone graft material possessing all four characteristics. Few mature osteoblasts survive the transplantation[2] but adequate numbers of precursor cells do.[3] It is from these precursor cells that the osteogenic potential is derived. Limitations include the increased operative time, limited availability and significant morbidity related to blood loss, wound complications, local sensory loss and, most importantly, chronic pain.[4] Donor site pain persisting for more than 3 months has been reported in up to 15% of patients having an iliac graft harvested. The amount of pain seems to be proportional to the extent of dissection required to obtain the graft.[5]

Correspondence: G. I. Bain, Department of Orthopaedics and Trauma, Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia. Email: greg@gregbain.com.au

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Allograft

Allograft as an alternative offers the same characteristics as autograft with the exclusion of osteogenic cells. It does possess osteoinductive properties but these may not be recognized unless the graft is utilized in either a morsellized or demineralized form. Complications associated with allograft include fracture, non-union and infection.[6] Allograft fracture rates of up to 19% have been reported. Allograft union is difficult to assess and discrepancy has been found between clinical, radiological and histological union. Radiological non-union can be expected in up to 17% of cases. Bacterial infection is more common with increased size of graft and may be seen in more than 10% of massive allografts. Viral transmission (hepatitis B, C, HIV) is a potential risk that is historically and serologically screened for. Despite the exceedingly low risk, transmission of HIV 1 from seronegative cadaveric donors has occurred.[7] The advantages of allograft include availability and avoidance of morbidity associated with harvesting autogenous graft. Allografts are of particular importance when there are large bone defects, which require structural support, or when inadequate autogenous graft volume is available.

SYNTHETIC BONE GRAFT

A variety of artificial materials has been used over the centuries to fill bone defects.[8] Synthetic bone grafts at most possess only two of the four characteristics of an ideal bone graft material (osteointegration, osteoconduction). Ideally synthetic bone graft substitutes should be biocompatible, show minimal fibrotic reaction, undergo remodelling and support new bone formation. From a mechanical point of view synthetic bone graft substitutes should have a similar strength to that of the cortical/cancellous bone being replaced. This needs to be matched with a similar modulus of elasticity to that of bone in an attempt to prevent stress shielding as well as maintaining adequate toughness to prevent fatigue fracture under cyclic loading. Synthetic materials that demonstrate some of these properties are composed of either calcium, silicon or aluminium.

Bioactive glasses

Two families of silicon-based compounds have the ability to bond directly to bone. These are the bioactive glasses and the glass ionomers. Bioactive glasses are hard, solid (non-porous), materials that were first described in the 1970s. They consist of sodium oxide, calcium oxide, phosphorus pentoxide and silicon dioxide. Silicon dioxide (also known as silicate) forms the main component. By varying the proportions of sodium oxide, calcium oxide and silicon dioxide, forms can be produced that are soluble *in vivo* (solubility being proportional to the sodium oxide content) right through to those that are essentially non-resorbable.[9]

Bioactive glasses possess both osteointegrative and osteoconductive properties. A mechanically strong bond between bioactive glass and bone forms as a result of a silica-rich gel layer that forms on the surface of the bioactive glass when exposed to physiologic aqueous solutions. Within this gel Ca^{2+} and PO_4^{2-} ions combine to form crystals of hydroxyapatite (HA) similar to that of bone, hence a strong chemical bond.[9,10] When used as a preformed implant they have significantly greater mechanical strength when compared to calcium phosphate preparations such as ceramic HA.[1] Bioactive glass blocks resist drilling and shaping, however, and they may fracture in the process. As a consequence they are difficult to fix to the skeleton. They have been successfully used as a bone graft expander and alone in maxillofacial surgery.[11,12] Their use in granular form in unloaded areas as a void filler does not exhibit any benefit over other preformed hard materials, with the exception that they may be reabsorbed more readily than particulate HA therefore allowing earlier restoration of the bone defect.[13] Other successful uses include ossicular replacement and coating metal implants to enhance their osteointegration.[1,14]

A variation of the bioactive glasses is the bioactive ceramics. Bioactive ceramics generally have higher strengths and improved mechanical properties over bioactive glass but both still have low fracture toughness in relation to cortical bone (Table 1). That is, they are relatively brittle and prone to fracture with cyclic loading. Bioactive ceramics have been successfully used for vertebral prostheses in the treatment of tumours and burst fractures[15] and as orbital implants (Table 2).[16]

To improve the fracture toughness of bioactive glasses and bioactive ceramics two methods have been trialled. Incorporation of stainless steel fibres into bioglass increased bending strength (from 42 MPa to 340 MPa), and incorporation of ceramic particles (zirconia) into apatite–wollastonite (A/W) glass ceramic increased bending strength (from 680 MPa to 703 MPa) and toughness (from 2.0 to 4.0).[17] Despite the increase in strength and toughness these materials have a modulus of elasticity that is much higher than that of cortical bone.

Of recent interest are the bioactive glass composites, which have more elastic characteristics than the rest of the bioactive glass family. The most favourable yet is a combination of bioactive glass with a polysulfone polymer.[15] This most closely resembles cortical bone and is dependent on a combination of bioactivity, strength, fracture toughness and modulus of elasticity (Table 1). Bioactivity is a measure of the rate at which osteointegration occurs. Bioactive glass composites are currently being trialled for vertebral body prosthesis.[18]

Glass ionomers

Glass ionomer cements were first introduced in 1971 for dental use where a cement was required to bind tooth enamel in a moist environment. Ionomeric cement consists of calcium/aluminium/fluorosilicate glass powder (0.001–0.1 mm diameter) which is mixed with polycarboxylic acid. This results in an exothermic reaction ($\leq 56°C$)[19] with CO_2 evolution to produce a porous cement paste. The paste sets hard in approximately 5 min after which it is water insoluble. Prior to this it must be protected from wound fluids which will dissolve it. After 24 h it has a compressive strength (180–220 MPa) and modulus of elasticity comparable to cortical bone.[20,21] It is biocompatible and osteointegrates in a manner similar to bioactive glasses. Its porous structure aids osteoconduction and subsequent bone ingrowth. It is non-reabsorbable and therefore is not replaced by bone. Its use outside of dentistry has included ear, nose and throat (ENT) surgery, where it has successfully been used in auditory ossicular reconstructions as well as in sinus operations. It has also been used to seal imperfections in the skull and in maxillofacial reconstructive surgery,[1,22] but its use in contact with neural tissue or cerebrospinal fluid (CSF) is contraindicated because the release of aluminium ions and polyacid in its unset form is neurotoxic.[23] In maxillofacial reconstructive surgery an ionomeric implant is fashioned to suit the patient and cured outside the body; at the time of operation it is cemented in place with ionomeric paste. Glass ionomer has been considered as a replacement for polymethyl methacrylate (PMMA) bone cement, which has the potential disadvantage of a significant exothermic reaction during polymerization.[24] The amount of heat produced (78–120°C) depends on the quantity and pre-mix temperature of the cement.[19] Glass ionomers such as PMMA may also have antibiotics and high molecular weight proteins added to them for slow release. Glass ionomers, however, release proteins more efficiently than PMMA and are less likely to damage heat-labile proteins (Table 2).[25]

Table 1. Mechanical properties

	Cancellous bone	Cortical bone	HA	Bioglass	A/W glass ceramic	Bioglass PS modified
Bioactivity (A)	13	13	3	13	6	13
Fracture toughness K1c (B)	0.1	6.0	1.0	0.6	2.0	1.2
Elastic modulus GPa (C)	1	15	85	35	118	5
Tensile strength MPa (D)	3	151	80	42	215	103
Quality index = (A × B × D)/C	4	500	3	9	20	303

HA, hydroxyapatite; A/W, apatite–wollastonite; PS, polysulfone.

Table 2. Summary

Substance	Bioactive glass	Glass ionomer	Aluminium oxide	Calcium sulfate
Form	Granules, blocks, rods	Powder	Granules, blocks	Powder, pellets
Reabsorption	Non-resorbable to resorbable	Non-resorbable	Non-resorbable	Dissolves in 5–7 weeks
Incorporation of antibiotics, bone-promoting substances	Not possible	Yes	Not possible	Yes
Mechanical properties	Stronger than HA implants	Compressive strength and elasticity comparable to cortical bone	Stronger than HA implants, does not osteointegrate	No structural properties *in vivo*
Uses	Bone graft expander Vertebral body prosthesis Ossicular replacement Orbital implants Coating metal implants	Dental Maxillofacial Ossicular replacement	Bone graft expander Wedge, osteotomy Ossicular replacement Prosthetic joint linings	Void filler Bone graft expander Osteomyelitis
Product name	NovaBone (Fig. 1a)	Fugi IX gp (Fig. 1b)	Alumina ceramic (Fig. 1c)	Osteoset (Fig. 1d)
Comparative costing	6+ for 10 mm^3 granules	1+ for 10 mm^3 powder	—	5+ for 10 mm^3 pellets
Manufacturer	US Biomaterials	GC Corporation	Orthomed SA	Wright Med. Tech. Inc.

HA, hydroxyapatite.

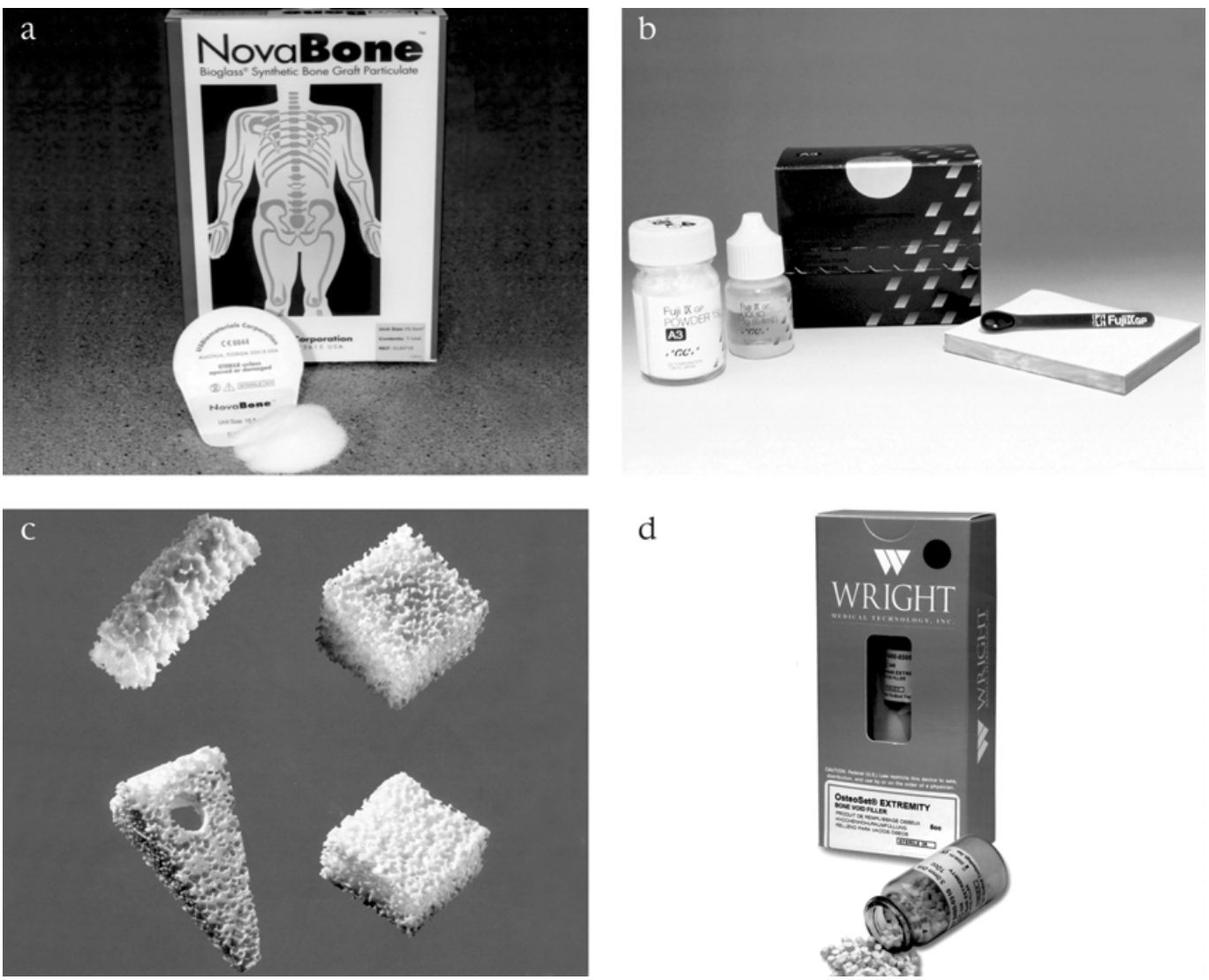

Fig. 1. (a) NovaBone; (b) Fugi IX gp (manufacturer endorses dental use only); (c) Alumina ceramic; (d) Osteoset.

Aluminium oxide

Alumina (Al_20_3) is a component of several bioactive materials but can serve as a bone graft substitute on its own. Alumina ceramics do not exchange ions between implant and bone, as is seen with bioactive glasses, and therefore do not osteointegrate. Instead a mechanical bond occurs as a result of stresses on the implant that bring it into intimate relationship with the surrounding bone.[26] Alumina ceramics are very hard and rigid and have a greater resistance to flexural fracturing as compared to ceramic HA. They have been used as a bone graft expander and for wedge osteotomies, but their application in orthopaedic surgery has been limited by their inability to osteointegrate. They have been successfully used in orbital implants, prosthetic joint linings and ossicular replacements (Table 2).[1]

Calcium sulfate

Calcium sulfate is actually plaster of Paris. It was first documented as being used for fracture treatment by the Arabs in the 10th century, who would surround the affected limb in a tub of plaster. In 1852 a Dutch army surgeon by the name of Mathysen incorporated plaster into a bandageable form (the form with which we are familiar today). In 1892 a German by the name of Dreesman successfully used plaster of Paris medicated with a 5% phenol solution to treat tuberculous osteomyelitis of long bones, the majority achieving successful healing.[27] Calcium sulfate is thought to act as an osteoconductive matrix for the ingrowth of blood vessels and associated fibrogenic and osteogenic cells. For this to occur it is critically important that the implanted calcium sulfate is adjacent to viable periosteum or endosteum.[28] Over a period of 5–7 weeks the calcium sulfate is reabsorbed by a process of dissolution.[29] Its rapid reabsorption may be used to advantage in the context of osteomyelitis where an antibiotic-impregnated form could be used in place of gentamicin beads, thus alleviating the need for a second operation. Currently a medical grade of calcium sulfate impregnated with tobramycin is commercially available (Osteoset; Wright Medical Technology, Arlington, TN, USA). Calcium sulfate in its set form has a compressive strength greater than cancellous bone and a tensile strength slightly less than cancellous bone (Table 3). Calcium sulfate, however, requires a dry environment to set and if it is re-exposed to moisture it tends to soften and fragment. For this reason it has no reliable mechanical properties *in vivo* and its application should be limited to a contained area. Hence the primary use of calcium sulfates should be as a bone void filler (Table 2).

Calcium phosphates

The calcium phosphate family of synthetic bone grafts has both osteointegrative and osteoconductive properties. Osteointegration results from the formation of a layer of HA shortly after implantation. The Ca^{2+} and PO_4^{2-} ions required to establish this layer are derived from the implant and surrounding bone. The pathways of both Ca^{2+} and PO_4^{2-} ions have been traced in serum and urine without any significant elevation in serum levels from which it can be concluded they are handled as part of the normal body ion pool. They have an excellent record of biocompatability with no reports of systemic toxicity or foreign body reactions.[30]

Beta tricalcium phosphate

Beta tricalcium phosphate (βTCP) was one of the earliest calcium phosphate compounds to be used as a bone graft substitute. In 1920 Albee and Morrison reported that the rate of bone union was increased when βTCP was injected into the gap of a segmental bone defect.[31] Beta tricalcium phosphate is available in porous or solid form as either granules or blocks. Structurally porous βTCP has a compressive strength and tensile strength similar to cancellous bone.[32] Like other calcium phosphate preparations it has been found to be brittle and weak under tension and shear, but resistant to compressive loads.[33] Typically it has been used in its granular porous form. Porous granules tend to migrate less than solid granules due to earlier fixation by fibrovascular ingrowth.[34] Beta tricalcium phosphate undergoes reabsorption via dissolution and fragmentation over a 6–18-month period. Unfortunately the replacement of βTCP by bone does not occur in an equitable way. That is, there is always less bone volume produced than the volume of βTCP reabsorbed.[35] For this reason the clinical use of βTCP has been as an adjunctive with other less reabsorbable bone graft substitutes or as an expander for autogenous bone graft (Table 4).

Synthetic hydroxyapatite

The next calcium phosphate preparation to become available was the synthetic HA in the 1970s. Hydroxyapatite $C_{10}(PO_4)_6(OH)_2$ forms the principal mineral component of bone. Synthetic HA comes in ceramic or non-ceramic form as porous or solid, blocks or granules. Ceramic refers to the fact that the HA crystals have been heated (sintered) at between 700 and 1300°C to form a highly crystalline structure. Ceramic HA preparations are resistant to reabsorption *in vivo*, which occurs at a rate of 1–2% per year.[1] Conversely non-ceramic HA is more readily reabsorbed *in vivo* and is also available in a self-setting cementable form. Synthetic HA have good compressive strengths but are weak in tension and shear. They are brittle and are fracture prone on shock loading (Tables 1,3). Synthetic HA in solid block form is difficult to shape, does not permit fibro-osseous ingrowth and has a much higher modulus of elasticity than bone. Synthetic HA has been successfully used to coat metal implants to enhance their osteointegration.[36–38] In porous granular form it has been used alone or with bone graft to fill voids (Table 4).[13]

Table 3. Mechanical properties

Strength MPa	Cancellous bone	Coralline HA	POP	Norian SRS	Porous HA	PMMA	Porous alumina ceramic	Bioglass	A/W glass ceramic	Bioglass PS modified	Glass ionomer	Cortical bone
Compressive	5.5	9.3	23	55	60	90	60	–	–	–	180	162
Tensile	3	2.8	4.1	2.1	2.5	6.9	15	42	215	103	–	151

HA, hydroxyapatite; POP, plaster of Paris; PMMA, polymethyl methacrylate; A/W, apatite–wollastonite; PS, polysulfone.

Table 4. Calcium phosphates summary

Substance	β tricalcium phosphate	HA	Coralline HA	Cementable
Form	Granules, blocks	Granules, blocks	Granules, blocks	Paste
Reabsorption	Dissolution in 6–18 months	1–2% per year	1–2% per year	Years
Incorporation of antibiotics, bone-promoting substances	Not possible	Not possible	Not possible	Yes
Mechanical properties	Porous form structurally similar to cancellous bone	Good compressive strength	Structurally similar to cancellous bone	Good compressive strength Weak in distraction
	Brittle	Brittle	Brittle	
Uses	Bone graft expander Void filler	Bone graft expander Void filler Prosthetic coatings	Bone graft expander Periodontal, maxillofacial Metaphyseal defects	Metaphyseal defects Craniomaxillofacial
Product name	Orthograft (Fig. 2a)	Calcitite (Fig. 2b)	ProOsteon (Fig. 2c)	Norian SRS (Fig. 2d)
Comparative costing	3+ for 10 mm^3 granules	7+ for 10 mm^3 granules	7+ for 10 mm^3 granules	15+ for 10 mm^3 paste
Manufacturer	Miter Inc.	Calcitek International	Interpore International	Norian Corporation

HA, hydroxyapatite.

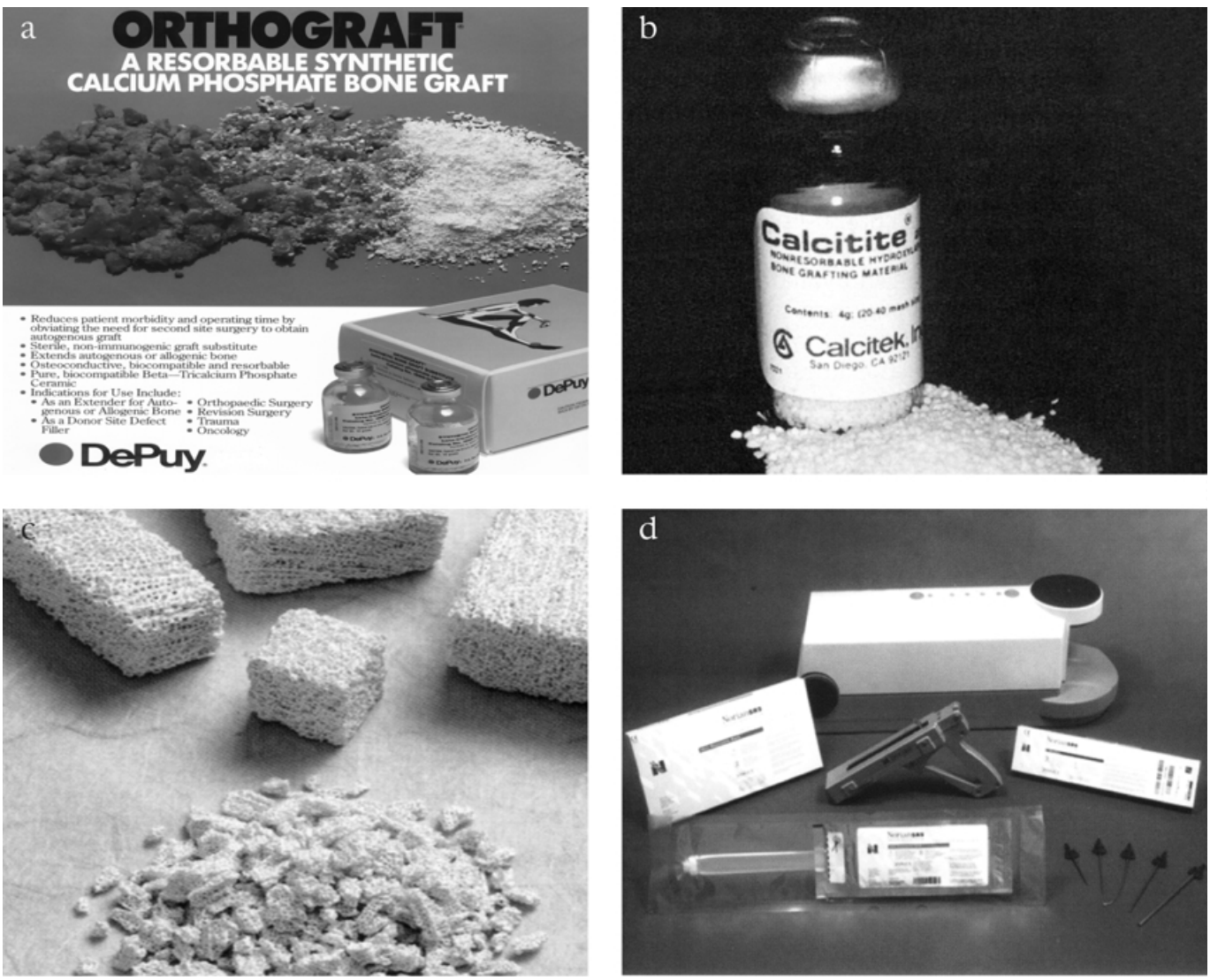

Fig. 2. (a) Orthograft; (b) Calcitite; (c) ProOsteon; (d) Norian SRS cement.

Coralline hydroxyapatite

Coralline HA marketed as ProOsteon (Interpore International, Irvine, CA, USA) was developed in 1971 with the aim to create a HA implant with a consistent pore size and improved interconnectivity. Synthetic HA relied on either the addition of hydrogen peroxide or naphthalene particles to the base material prior to compaction and sintering. Hydrogen peroxide would give evolution of bubbles, and naphthalene particles would sublime, leaving a pore-filled structure. Unfortunately with these methods it has been difficult to control pore size and pore interconnectivity, both of which are critical to the performance of a porous implant. Interconnectivity is essential because constrictions between pores or dead-end pockets limit vascular support to ingrowing tissue. Ischaemia of these cells may contribute to failure of the implant.[39–41] Klawitter and Hulbert pioneered studies that indicated that a minimum pore size of 45–100 μm is needed for bone ingrowth into porous ceramics. Pores of size 100–150 μm provide a more rapid ingrowth of fibrovascular tissue.[42] Coralline HA utilizes the genetically determined highly regular and permeable structure of marine coral (species porites and goniopora), which closely resembles that of cancellous bone. The replamineform process involves processing of the calcium carbonate coral to remove the bulk of its organic matter. It is then subject to both extreme pressure and heat in an aqueous phosphate solution. This converts the calcium carbonate coral skeleton entirely to calcium phosphate (HA) as well as sterilizing it at the same time.

Mechanically coralline HA is only slightly greater in compressive strength than cancellous bone (Table 3). Like the other HA preparations it is weak in tension, brittle and difficult to shape. Its main advantage is that its interporous structure allows complete ingrowth of fibro-osseous tissue. Fifty to eighty per cent of the void is filled within 3 months.[43] When fibro-osseous tissue ingrowth is complete the implant consists of approximately 17% bone, 43% soft tissue and 40% residual HA.[44] Studies on other ceramic bone graft substitutes have limited bone invasion to approximately 2 mm.[45] Coralline HA does not cause significant stress shielding[46] and allows remodelling according to Wolff's Law such that a gradient of more compact bone is found at the cortices and more trabecular bone is found near the metaphysis.[47] Coralline HA initially does not possess the strength of trabecular bone nor the plastic properties because it lacks a collagen matrix; but with completion of fibro-osseous ingrowth the coralline HA becomes stronger but is less stiff than cancellous bone.[48] This is a desirable property for metaphyseal defects because it gives structural support with good load distribution, thus decreasing the likelihood of stress concentration on the closely overlying articular cartilage[49]. Coralline HA has been successfully used in non-weightbearing applications such as maxillofacial, periodontal augmentation[46] and distal radial fractures.[50] Its use in weight-bearing metaphyseal defects (i.e. tibial plateau fractures) has also been successful, but due to its initial mechanical weakness it must be supported by internal fixation until completion of fibro-osseous ingrowth.[47] Other clinical uses include bone graft expansion in spinal fusions[51,52] and orbital restorations (Table 4).[53]

Calcium phosphate cements

Non-ceramic HA also comes in cementable forms that are mixed intraoperatively, moulded to shape and set *in vivo* to porous HA. Tetracalcium phosphate and dicalcium phosphate dihydrate marketed as Bone Source (Leibinger, Dallas, TX, USA) is one such composition which when mixed with water forms a dense paste. This sets via an isothermic reaction in 15 min, and as the cement hardens over 4 h it is converted to microporous HA. During this conversion period the implant must be kept free from accumulation of fluid because this will dissolve the implant and result in it setting in a particulate fashion. Following conversion to HA it is water insoluble and no longer at risk of dissolution. This material has been successfully used in sinus repair procedures and cranioplasty.[1,54]

Another HA cement with similar handling characteristics consists of monocalcium phosphate monohydrate, alpha tricalcium phosphate, calcium carbonate and sodium phosphate solution and is marketed as Norian SRS Cement (Norian Corp., Cupertino, CA, USA).[55] It comes as a set of powders in a blister pack which is mixed in an elaborate mixing machine to form a paste of toothpaste-like consistency. The paste is radiopaque and injected into the defect under fluoroscopic imaging to confirm entire filling of the fracture void. At body temperature it has a 2-min working time after which it should be left a further 8 min to set. Movement or manipulation after the 2-min working time results in disruption of the crystallization process with subsequent fragmentation and premature failure of the implant.

Both Bone Source and Norian SRS cement have similar mechanical properties, being good in compression but poor in distraction (Table 3). Both may undergo resorption and remodelling albeit over several years. Because the cementable calcium phosphates are isothermically setting there is the potential to add different molecules to enhance bioactivity. Factors promoting bone formation, bone cell attachment, angiogenesis and graft resorption should all come under consideration. Other substances such as antibiotics and chemotherapeutic agents may also be added without unduly affecting the strength of the cement. (Please note that Norian has not verified the effect of adding these substances.)

Norian SRS cement has the additional advantage that it will set in a wet environment without dissolution or fragmentation. Norian's recommended use is principally in cavitational metaphyseal defects subjected primarily to compressive loads. It has been successfully used in distal radial,[56] and calcaneal fractures.[57] Cadaveric studies have shown less settling of fracture fragments in distal radial fractures with Norian SRS cement as compared to K wires.[58] When compared to conservatively treated (plaster of Paris immobilized) distal radial fractures it offers earlier mobilization with a better clinical and radiological outcome. Its use in redisplaced distal radial fractures as compared to the use of external fixation again shows an improved clinical outcome at 7 weeks. Beyond 3 months, however, there was no difference in either group in the functional parameters measured.[59] The faster recovery of function is thought to be due to reduced time of immobilization which is possible due to the supportive role of Norian. This has implications with regards to the length of hospitalization and subsequent treatment as well as the ability of the patient to cope at home. A potential disadvantage of the paste-like nature of the cement is its extrusion into the soft tissues, which commonly occurs and is partly operator dependent.[56] Fortunately this remodels with time albeit slowly. For this reason caution must be exercised when treating intra-articular fractures so as to avoid extrusion of the cement into the joint. Other clinical uses include craniofacial repair[60] and as a sub-stitute for PMMA, which is sometimes used in augmenting fractured neck of femurs,[61] pedicle screws[62] and vertebral bodies (Table 4).[63]

THE FUTURE

In recent years there has been considerable improvement in understanding bone repair. This has significant implications for the future management of bone loss. The identification of osteoinductive proteins and other factors involved in the promotion of osteoblastic proliferation, differentiation and function has enhanced the potential for manipulating local repair in a beneficial manner.[64] The cascade of biological events leading to the initiation and maintenance of repair is a complex process. It involves the stimulation of an osteoblastic response and the development of a local environment capable of supporting that response. The restoration of an adequate blood supply and the ability to maintain stability and controlled loading during the repair process are also important in achieving a satisfactory outcome. In order to obtain optimum results it is likely that manipulation of this process will require a combination of strategies depending on the clinical situation. The most difficult is the management of large structural defects. These may occur following trauma, or resection for infection or tumour, but most commonly in association with failed joint replacement. It is likely that synthetic bone substitutes will play a significant role in the management of these defects in the future.

Currently most bone substitutes have little biological activity. They act as fillers and have osteointegrative and conductive properties. Ideally bone substitutes of the future will have structural integrity, provide a framework for host bone formation and act as delivery systems for factors important in regulating local bone response. To ensure effective activity as a delivery system it is likely that controlled resorption of the substitute will be required. This is necessary to ensure a timely and predictable release of factors incorporated within the substitute and the subsequent complete replacement of the substitute by host bone.

Ultimately bone formation occurs as a consequence of osteoblastic cellular activity. Recent advances in the purification and *in vitro* expansion of osteogenic precursors have added a new dimension to replacing bone defects.[65,66] A number of centres are now examining the potential of these cells to heal large defects either alone or in combination with biologically active factors. The use of autologous *in vitro* expanded precursors is capable of providing significant amounts of bone graft material. This, in combination with an appropriate bioactive bone substitute framework, has the potential to maximize repair of large bone defects.

CONCLUSION

Currently autogenous and allograft bone are the main sources for bone grafting procedures. Autogenous graft has by far the most osteogenic potential followed by allograft. Allograft bone is an important source when structural or large volumes of grafts are required. Concerns related to the use of both autograft and allograft has led to the search for alternatives. The synthetic bone graft substitutes as yet offer only a part solution to the management of localized bone loss. They possess some of the desired mechanical qualities of bone as well as osteointegrative/conductive properties but are largely reliant on viable periosteum/bone for their success. Ideally a synthetic bone graft substitute should mimic the native bone in both mechanical and osteogenic properties. The advent of composite synthetic bone graft substitutes and biologically active factors moves us ever closer to this goal.

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