



## ■ INSTRUCTIONAL REVIEW: TRAUMA

# Bone graft substitutes currently available in orthopaedic practice

## THE EVIDENCE FOR THEIR USE

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**We reviewed 59 bone graft substitutes marketed by 17 companies currently available for implantation in the United Kingdom, with the aim of assessing the peer-reviewed literature to facilitate informed decision-making regarding their use in clinical practice. After critical analysis of the literature, only 22 products (37%) had any clinical data. Norian SRS (Synthes), Vitoss (Orthovita), Cortoss (Orthovita) and Alpha-BSM (Etex) had Level I evidence. We question the need for so many different products, especially with limited published clinical evidence for their efficacy, and conclude that there is a considerable need for further prospective randomised trials to facilitate informed decision-making with regard to the use of current and future bone graft substitutes in clinical practice.**

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Over the last decade there has been a substantial increase in the number of new bone graft substitutes available to the orthopaedic surgeon to assist with bone healing. Despite this, autologous graft is still considered to be the best, providing the three core elements required for bone growth (osteoconduction, osteoinduction and osteogenesis).<sup>1</sup>

Osteoconduction is the provision of a physical structure with a surface whose biocompatibility supports the migration of cells, such as mesenchymal lineage cells, onto it. Osteoinduction is the ability of the graft to allow the recruitment of host mesenchymal stem cells. It is widely accepted that autogenous bone is osteoinductive, owing at least in part to intrinsic bone matrix proteins such as those of the transforming growth factor (TGF)- $\beta$  superfamily, which includes the bone morphogenetic proteins (BMP). Osteogenesis is the synthesis of new bone from cells within the graft that can survive in a host environment; the viability of cells in non-vascularised autografts is not known.<sup>1-3</sup>

A fundamental disadvantage of autograft is donor site morbidity. Harvesting, commonly from the iliac crest, is considered a safe procedure, but can result in chronic pain, superficial infection, haematoma, and lesions to the lateral femoral cutaneous nerve leading to paraesthesiae and disturbances of gait.<sup>4-6</sup> Extremely rare complications include pelvic fracture, peritonitis and arterial injury.<sup>7,8</sup> The morbidity associated with the harvesting and the finite supply of this tissue has resulted in a search for synthetic materials as an alternative.

Allograft bone has been widely used and is an attractive alternative as it avoids donor site morbidity. Osteo-arthritic femoral heads removed at total hip replacement are the predominant source of allograft bone in the United Kingdom,<sup>9</sup> and remain the mainstay of grafts used in revision arthroplasty surgery. However, allograft material has the potential to transmit infectious diseases and can cause an immuno-rejection reaction.<sup>2</sup> Excluding tissue after serological testing for human immunodeficiency virus (HIV-1 and HIV-2), hepatitis B and C, syphilis and human T-cell lymphotropic virus (HTLV-1 and HTLV2) has reduced the rate of transmission of these pathogens via allograft bone.<sup>1,2,10</sup> Other laboratory methods used to reduce the transmission of disease include the processing of allograft material. Allograft bone is available in frozen and freeze-dried forms. Storing allograft at  $-80^{\circ}\text{C}$  minimises the degradation of graft and also reduces its immunogenicity.<sup>1</sup> Freeze-dried allograft also resists degradation when vacuum packed at room temperature.<sup>1</sup> Both frozen and freeze-dried forms of allograft retain their osteoconductive characteristics, although freeze-drying reduces the mechanical and osteoinductive properties of the graft. Allograft sterilisation using ethylene oxide, gamma-irradiation or thermal heat treatment can be performed to further improve its safety. All three processes, however, reduce the mechanical integrity and the osteoinductive capabilities of the graft.<sup>2</sup> Current methods of allograft sterilisation are ineffective against

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**Table I.** Levels of evidence for primary research questions<sup>12</sup>

| Level     | Description   |
|-----------|---|
| Level I   | 1. Randomised controlled trial (RCT) <ol style="list-style-type: none"> <li>a. Significant difference</li> <li>b. No significant difference but narrow confidence intervals</li> </ol> 2. Systematic review* of Level I randomised controlled trials (studies were homogeneous) |
| Level II  | 1. Prospective cohort study <sup>†</sup><br>2. Poor-quality randomised controlled trial (RCT) (e.g. < 80% follow-up)<br>3. Systematic review* <ol style="list-style-type: none"> <li>a. Level-II studies</li> <li>b. Non-homogeneous Level I studies</li> </ol>                 |
| Level III | 1. Case-control study <sup>‡</sup><br>2. Retrospective cohort study <sup>§</sup><br>3. Systematic review* of Level III studies  |
| Level IV  | Case series (no, or historical, control group)  |
| Level V   | Expert opinion  |

\* a study of results from two or more previous studies

† patients were compared with a control group of patients treated at the same time and same institution

‡ patients with a particular outcome ('cases' with, for example, a failed total arthroplasty) were compared with those who did not have the outcome ('controls' with, for example, a total hip arthroplasty that did not fail)

§ the study was initiated after treatment was performed

prion proteins, including variant Creutzfeldt–Jakob disease, raising the possibility of iatrogenic transmission via the allograft.<sup>10</sup> However, Grafton (Osteotech Ltd, Christchurch, United Kingdom) is one demineralised bone matrix that claims to be prion free. The manufacturers state that prion proteins are only associated with neural tissue and as the procurement of bone in Grafton originates solely from long bones, the final demineralised protein is prion free, eliminating the transmission of prion-related disease.<sup>11</sup>

Many bone graft substitutes are currently commercially available in the United Kingdom, but peer-reviewed clinical evidence of their efficacy is limited. The aim of this review was to highlight the main properties of the range of bone graft substitutes, give the levels of evidence for their use, and indicate the trauma and elective procedures in which they have been used.

## Materials and Methods

In order to complement our literature review, a total of 17 manufacturers of bone graft substitutes were contacted and asked to provide product details, unit costs and supporting peer-reviewed clinical literature of their efficacy. Our review of the literature included papers that detailed the use of a bone graft substitute in an orthopaedic situation. We excluded papers in neuro- and maxillofacial surgery and those not published in English. The ISI Web of Knowledge, PubMed, EMBASE (from 1980 to 2012) and Cochrane databases were searched in December 2012 using the criteria 'registered or trademarked product name', the boolean search term 'AND', plus the word 'bone'. Conference abstracts, *in vitro* and animal studies were excluded. Full-text peer-reviewed papers were obtained and graded according to the 'levels of evidence' introduced by Wright, Swiontkowski and Heckman<sup>12</sup>

(Table I). Level I evidence is a prospective randomised controlled trial (RCT) with definitive results to support the use of the bone graft substitute in a clinical setting, whereas single case reports were assigned as Level V evidence. All authors reviewed each paper and assigned a level of evidence independently. If there was disagreement on the level assigned to a paper, this was discussed and resolved. All papers with a level of evidence of I, II or III were included and referenced, as well as selected Level IV studies when they included case series of > 15 patients. All Level V studies were excluded. Osteoinductive growth factors such as the BMPs were excluded because they are a clearly defined pharmaceutical product.

## Results

A total of 59 bone graft substitutes marketed by 17 different companies were identified on sale in the United Kingdom, but only 22 (37%) from 12 manufacturers met our inclusion criteria for published peer-reviewed clinical literature. A total of 96 clinical papers for these products were found. Figure 1 outlines the methodological process used to locate them. The levels of evidence are summarised in Tables II to VIII.<sup>13-102</sup> We wrote to all 17 companies to verify our literature search but only six replied. The available information regarding the porosity, biomechanical strength, size, price and rates of resorption of each substitute is shown in Tables II to VIII. Some companies supplied unit costs for each product, which should be viewed as approximations as prices are subject to change. All the grafts are osteoconductive and act as a scaffold to maintain space during bone healing and ingrowth, and the demineralised bone matrices in particular have some additional osteoinductivity. Recommended indications for the clinical use of each product are also listed in Tables II to VIII.

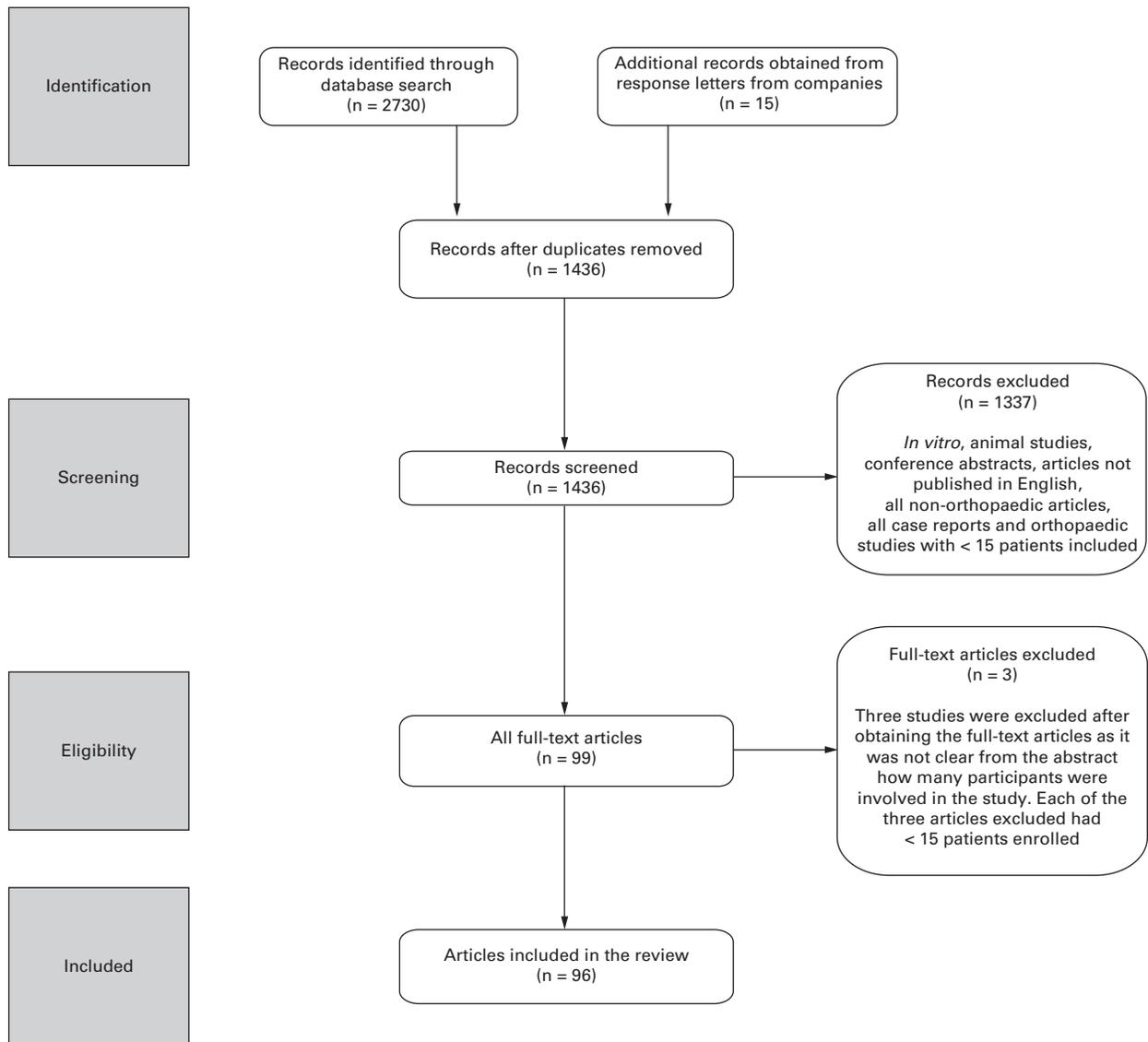


Fig. 1

Flow diagram of the systematic review process.

Not all RCTs were awarded Level I evidence, as many had poor methodology. After critical appraisal of the literature only five papers from four products, Alpha-BSM (DePuy, Leeds, United Kingdom), Cortoss (Orthovita, St Albans, United Kingdom), Norian SRS (Synthes, Welwyn Garden City, United Kingdom) and Vitoss (Orthovita), were considered to have Level I published data equal to or superior to autograft.<sup>13-17</sup>

**Types of bone graft substitute. Demineralised bone matrix (DBM).** DBM is generally prepared into a putty or paste by removing calcium phosphate by acid extraction, and is thus composed of collagen, non-collagenous proteins and glycoproteins, including osteoinductive BMPs, which can promote the formation of bone. DBMs have limited porosity

and mechanical strength; they can be safely used as a bone graft extender in spinal and trauma surgery, with good clinical results.<sup>47,50,53,55</sup>

**Calcium phosphate and hydroxyapatite.** Calcium phosphate cement is a white powder that consists of a combination of tricalcium phosphate (TCP), calcium carbonate and monocalcium phosphate. When mixed with water it forms a paste that can be shaped to any bone defect. It hardens quickly at physiological pH and the reaction is isothermic, thereby eliminating any risk of thermal damage to the surrounding bone. The hardening reaction forms a hydroxyapatite or apatite-like material that has a compressive strength equal to or greater than that of cancellous bone after 48 hours. The differing combinations of the three calcium materials affect the

**Table II.** Bone graft substitutes with levels of evidence. Manufacturers: Apatech (Elstree, United Kingdom) and Biocomposites (Keele, United Kingdom)

| Manufacturer/<br>Product name | Material*                              | Delivery       | Cost   | Morphology                       | Properties† | Recommended use  | Level of evidence‡ |
|-------------------------------|--|----------------|--|----------------------------------|-------------|--|--------------------|
| <b>APATECH</b>                |  |                |  |                                  |             |  |                    |
| Apapore <sup>18</sup>         | HA                                     | Granules       | NA <sup>§</sup>  | 25% interconnected microporosity | OC          | Low load (e.g. small voids, autograft extender)  | n = 1 (III)        |
| Actifuse <sup>19-21</sup>     | Calcium phosphate +silicon             | Granules       | NA   | 80% porosity                     | OI + OC     | Low load (e.g. small voids and spinal fusion)  | n = 3 (IV)         |
| ActifuseABX                   | Calcium phosphate +silicon             | Putty          | NA   | Contains 96% scaffold            | OI + OC     | Low load (e.g. small voids and spinal fusion)  |                    |
| <b>BIOCOMPOSITES</b>          |  |                |  |                                  |             |  |                    |
| Stimulan                      | Calcium sulphate                       | Pellets, paste | Pellets: 5 ml, 3 mm £100; 10 ml, 4.8 mm £120; 20 ml, 4.8 mm £200. Paste: 5 ml £235; 10 ml £375 | Resorbable                       | OC          | Low load (e.g. small voids, spine, trauma with fixation, can be used in presence of infection as fully resorbed) |                    |
| GeneX <sup>22</sup>           | Calcium phosphate and calcium sulphate | Paste, putty   | 5 ml, £298; 10 ml £525   | Resorbable                       | OC          | Scaphoid nonunions, trauma and bone void filler  | n = 1 (IV)         |
| Allogran-N <sup>23</sup>      | HA                                     | Granules       | 35 ml £210   | Non-resorbable                   | OC          | High load (e.g. impaction grafting as autograft extender); revision hip arthroplasty                             | n = 1 (III)        |
| Allogran-R                    | HA                                     | Granules       | 35 ml £210   | Resorbable                       | OC          | Void filler, spines, delayed union, can be used in presence of infection   |                    |

\* HA, hydroxyapatite

† OC, osteoconductive; OI, osteoinductive

‡ n, number of peer-reviewed papers describing clinical use of the registered or trade-marked product; Level of evidence denoted I to IV (see Table I)

§ NA, data not available

compressive and tensile strength of the cement. The compressive strengths of these materials are high, ranging from 10 to 100 MPa, whereas the tensile strengths are much weaker at 1 to 10 MPa.<sup>1,2,10</sup> There is a broad range of applications for this material, including filling of cranial burr holes and craniofacial reconstructive surgery (BoneSource; Stryker, Newbury, United Kingdom), and in orthopaedic surgery where load is shared with an implant (Norian SRS; Synthes). These materials are slow to remodel and can be considered permanent. Norian SRS has the most peer-reviewed literature with accompanying Level I evidence.<sup>13,59,61,66-84</sup>

Preformed granules and blocks of calcium phosphate are composed of tricalcium phosphate and/or hydroxyapatite. They are manufactured using a high-temperature sintering process to produce a material with a highly crystalline structure and interconnecting porosity similar to bone. A minimum pore size of 200 µm is considered optimal for bone ingrowth, whereas pore sizes > 400 µm greatly improve the formation of osteoid.<sup>103</sup> Pore interconnectivity is extremely important, as a closed pore structure severely impairs the penetration of ingrowing bone with its associated vasculature.

Hydroxyapatite can be produced from marine coral exoskeletons that are hydrothermally converted to

hydroxyapatite, the natural mineral composition of bone. The interconnected porous structure closely resembles the porosity of human cancellous bone. Little has been published about the use of pure hydroxyapatite bone graft substitutes, and clinical trials are required to assess their efficacy.

**Calcium sulphate.** Calcium sulphate is a biocompatible osteoconductive bone graft substitute that is resorbable and steadily substituted for new bone by 12 weeks.<sup>104</sup> Clinical indications include the filling of bone voids, the treatment of benign bone lesions, and the expansion of grafts often used in spinal fusion. Calcium sulphate products should not be used to fill metaphyseal defects resulting from intra-articular fractures or in load-bearing applications, as the fast resorption time may result in loss of strength before fracture healing, leading to bone collapse.<sup>105</sup>

**Bioactive glass.** Bioactive glasses are biocompatible products composed of silicate, calcium and phosphorus, and are both osteoinductive and osteoconductive.<sup>106</sup> By varying the proportions of silicon oxide, silicon dioxide and calcium oxide, different bioactive glass products, whose solubility varies from completely soluble to non-resorbable, can be manufactured. The porosity of the products provides a scaffold that allows new bone deposition after vascular

**Table III.** Bone graft substitutes with levels of evidence. Manufacturers: Biomet Europe (Bridgend, United Kingdom) and Etex (Cambridge, Massachusetts)

| Product name*              | Material†                 | Delivery                  | Cost   | Morphology   | Properties‡ | Recommended use§  | Level of evidence¶ |
|----------------------------|---------------------------|---------------------------|--|--|-------------|---|--------------------|
| <b>BIOMET EUROPE</b>       |                           |                           |  |  |             |   |                    |
| Calcibon <sup>24-26</sup>  | HA                        | Granules and cement       | Granules: 5 ml £212; 10 ml £355; 20 ml £615  | Compressive strength 35 to 55 MPa; Young's modulus 2500 to 3000 MPa. Resorption noted at 24 weeks. Porosity 30% to 40%. Pore size < 1 µm | OC          | Use with bone marrow aspirate, autograft or PRP in metaphyseal cancellous defects   | n = 3 (II, III)    |
| Endobon                    | HA                        | Block, cylinder, granules | Block: 12.5 ml £212; 20 ml £355. Cylinder: 10 ml £222; 15 ml £430. Granules: 5 ml £145; 10 ml £237; 15 ml £430; 50 ml £710 | Resorbable. 60% to 80% porosity. Pore size 390 to 1360 µm. Compressive strength 1 to 20 MPa. Young's Modulus 20 to 3100 MPa              | OC          | Tibial plateau, distal tibial, calcaneal, distal radial fractures and in bone tumour surgery                              |                    |
| Collapat II                | Collagen/HA               | Fleece                    | NA**   | Resorbable   | OC          | Aseptic enclosed metaphyseal bone defects. Haemostatic properties. Best mixed with blood, bone marrow or PRP              |                    |
| Bonus II DBM               | DBM                       | Paste                     | NA   | Non-load-bearing   | OI + OC     | Injectable. Use with bone marrow aspirate. Use in non-unions, revision arthroplasty, ankle fusion and tumour surgery      |                    |
| <b>ETEX</b>                |                           |                           |  |  |             |   |                    |
| Alpha-BSM <sup>14-16</sup> | Calcium phosphate         | Paste                     | NA   | Resorbable. Porosity 50% to 60%. Average pore size < 1 mm  | OC          | Orthopaedic trauma, tibial plateau fractures, displaced intra-articular calcaneal fractures. Early weight-bearing allowed | n = 2 (I)          |
| EquivaBone                 | DBM and calcium phosphate | Paste                     | NA   | Resorbable   | OI + OC     | Bone void filler in spinal and trauma surgery   |                    |
| CarriGen                   | Calcium phosphate         | Paste                     | NA   | Resorbable. 65% total porosity. Pore size 1 to 300 µm  | OC          | Bone void filler of the pelvis, extremities and spine, including posterolateral spine fusion                              |                    |
| Beta-BSM                   | Calcium phosphate         | Paste                     | NA   | Resorbable   | OC          | Orthopaedic trauma and bone void filler   |                    |
| Gamma-BSM                  | Calcium phosphate         | Paste                     | NA   | Resorbable   | OC          | Orthopaedic trauma and bone void filler   |                    |

\* DBM, demineralised bone matrix

† HA, hydroxyapatite

‡ OC, osteoconductive; OI, osteoinductive

§ PRP, platelet-rich plasma

¶ n, number of peer-reviewed papers describing clinical use of the registered or trade-marked product; Level of evidence denoted I to IV (see Table I)

\*\* NA, data not available

ingrowth and osteoblastic differentiation.<sup>106</sup> A strong bond formed by hydroxyapatite crystals is created between bone and the bioactive glass without an intervening connective tissue interface, which gives it good apposition to bone. After long-term implantation the bioactive glass is partially replaced by bone.<sup>107,108</sup> Cortoss (Orthovita) contains bioactive glass and has been successfully used in kyphoplasty and vertebroplasty as well as spinal fusion.<sup>43-45</sup>

**Collagen and collagen/HA.** Collagen is an osteoconductive material and when used alone provides minimal structural support as a bone graft substitute, which limits its use clinically. However, it can be used as a carrier for growth and bone differentiation factors, especially BMPs.<sup>106</sup> Collagen can be combined with other osteoconductive materials, such as hydroxyapatite or tricalcium phosphate, as well as osteoinductive bone marrow aspirate.<sup>109</sup> Vitoss (Orthovita) is one such product that combines type 1 collagen with

**Table IV.** Bone graft substitutes with levels of evidence. Manufacturers: DePuy (Leeds, United Kingdom), Exactech (Redditch, United Kingdom) and Isotis Orthobiologics (Irvine, California)

| Manufacturer/<br>Product name* | Material†                               | Delivery            | Cost                                 | Morphology  | Properties‡ | Recommended use§   | Level of<br>evidence¶ |
|--------------------------------|---|---------------------|--------------------------------------|---|-------------|--|-----------------------|
| <b>DEPUY</b>                   |   |                     |                                      |   |             |  |                       |
| Healos <sup>27-31</sup>        | Collagen - HA                           | Sponge,<br>matrix   | NA**                                 | Resorbable<br>mineralised porous<br>collagen matrix                     | OC          | Mix with bone<br>marrow. Used in<br>spinal surgery   | n = 5 (III, IV)       |
| Conduit TCP                    | Beta TCP                                | Granules            | NA                                   | Resorbable. Pore size<br>from 1 to 600 µm.<br>70% porosity              | OC          | Enclosed meta-<br>physeal defects and<br>mixed with blood,<br>bone marrow or PRP                                   |                       |
| Optium DBM                     | DBM                                     | Gel/putty           | NA                                   | DBM particle size 125<br>to 850 µm. Calcium<br>content < 8%             | OI + OC     | Spinal fusion, bone<br>voids, tumours,<br>spine, pelvis, ankle<br>and calcaneal<br>fractures. Non-load-<br>bearing |                       |
| <b>EXACTECH</b>                |   |                     |                                      |   |             |  |                       |
| Optecure                       | DBM                                     | Putty               | NA                                   | 81% concentration<br>of DBM by weight.<br>Non-load-bearing              | OI + OC     | Mix with blood or<br>autograft   |                       |
| Opteform                       | DBM                                     | Paste               | 2 ml £395; 5 ml £595;<br>10 ml £995  | Non-water-soluble.<br>Non-load-bearing                                  | OI + OC     | Multiple uses given<br>on website but not<br>load bearing  |                       |
| OpteMx                         | HA and TCP                              | Granules,<br>sticks | 2 ml £170                            | 70% porous.<br>Resorbable   | OC          | Bone voids, tumours,<br>spine  |                       |
| <b>ISOTIS ORTHOBIOLOGICS</b>   |   |                     |                                      |   |             |  |                       |
| Accell Connexus <sup>32</sup>  | DBM                                     | Putty in syringe    | 1 ml £205; 5 ml £619;<br>10 ml £1033 | Non-load-bearing  | OI + OC     | Spinal fusion, bone<br>voids, revision hip<br>and knee surgery   | n = 1 (III)           |
| Accell 100                     | DBM                                     | Putty in syringe    | 1 ml £299; 5 ml £898;<br>10 ml £1589 | Non-load-bearing  | OI + OC     | Spinal fusion, bone<br>voids.  |                       |
| Dynagraft II                   | DBM                                     | Putty/gel           | NA                                   | Non-load-bearing,<br>void filling                                       | OI + OC     | Bone graft extender<br>for extremity, pelvis<br>or spine   |                       |
| Integra Accell<br>Evo3         | DBM                                     | Putty/gel           | NA                                   | Non-load-bearing,<br>void filling                                       | OI + OC     | Bone graft extender<br>for extremity, pelvis<br>or spine   |                       |
| Integra Mozaik                 | Beta TCP and<br>bone marrow<br>aspirate | Putty/strip         | NA                                   | 80% Beta TCP and<br>20% purified<br>collagen                            | OC          |  |                       |
| Orthoblast <sup>33-35</sup>    | DBM                                     | Putty, paste        | Putty: 5 ml £465; 10 ml<br>£650      | 50% macroporous,<br>50% microporous,<br>non-load-bearing                | OI + OC     | Contained defects,<br>ankle/foot fusions,<br>nonunions   | n = 3 (III)           |
| OsSatura BCP                   | 20% Beta TCP<br>and 80% HA              | Granules            | 1 ml £100; 10 ml £320                | Rapidly resorbable.<br>50% interconnected<br>porosity                   | OC          | Mix with blood<br>products. Contained<br>defects. Load<br>sharing.   |                       |
| OsSaturaTCP                    | Beta TCP                                | Granules            | 5 ml £145; 15 ml £228;<br>30 ml £495 | Pure TCP, resorbable<br>OsSatura BCP; 70%<br>interconnected<br>porosity | OC          | Mix with blood<br>products. Contained<br>defects. Load<br>sharing.   |                       |

\* TCP, tricalcium phosphate; DBM, demineralised bone matrix

† HA, hydroxyapatite

‡ OC, osteoconductive; OI, osteoinductive

§ PRP, platelet-rich plasma

¶ n, number of peer-reviewed papers describing clinical use of the registered or trade-marked product; Level of evidence denoted I to IV (see Table I)

\*\*NA, data not available

tricalcium phosphate. It has been successfully used in spinal fusion and elective knee surgery.<sup>15,37-40</sup>

**Substituted hydroxyapatites: silicon and magnesium hydroxyapatites.** Recent developments in bone graft substitutes include the formation of substituted silicon and magnesium hydroxyapatites. Silicon plays an important role in bone metabolism, and silicon deficiency can result in abnormal bone

formation secondary to the decreased deposition of extracellular matrix (collagen) and hydroxyapatite. Actifuse (Apatech, Elstree, United Kingdom) is 80% porous calcium phosphate in which some phosphate ions ( $PO_4^-$ ) are replaced with silicate ions ( $SiO_4^-$ ). This stimulates osteoprogenitor and mesenchymal stem cells, leading to new bone formation. Silicon substituted bone graft substitutes may be used to fill bone voids, and in

**Table V.** Bone graft substitutes with levels of evidence. Manufacturers: JRI Orthopaedics (London, United Kingdom), Mathys Orthopaedics Ltd (Alton, United Kingdom) and Medtronic (Watford, United Kingdom)

| Manufacturer/<br>Product name  | Material*  | Delivery                        | Cost   | Morphology                                       | Properties† | Recommended use   | Level of<br>evidence‡ |
|--------------------------------|--|---------------------------------|--|--|-------------|---|-----------------------|
| <b>JRI ORTHOPAEDICS</b>        |  |                                 |  |  |             |   |                       |
| Repos                          | 60% HA,<br>40% Beta TCP                            | Granules, blocks                | NA§  | Non-load-bearing.<br>80% porosity                | OC          | Bone void filler or auto-graft extender. Mix with blood products  |                       |
| RegenOss                       | Collagen-HA  | Patch strips                    | NA   | Resorbable over<br>6 to 12 months                | OC          | Long bone fractures, Revision hip arthroplasty to fill acetabular defects and spinal fusion                       |                       |
| ENGIpore                       | HA   | Chips blocks,<br>wedge cylinder | NA   | 90% porosity.<br>Resorbed over<br>6 to 18 months | OC          | Trauma, revision arthroplasty surgery, spinal surgery and bone void filler  |                       |
| SINTlife <sup>36</sup>         | Mg-HA  | Granules,<br>paste/putty        | NA   | Porosity from<br>600 to 900 µm                   | OC          | Bone void filler in trauma and spinal surgery. High tibial osteotomy for patients with osteoarthritis of the knee | n = 1 (II)            |
| <b>MATHYS ORTHOPAEDICS Ltd</b> |  |                                 |  |  |             |   |                       |
| CycLOS                         | Beta TCP and<br>fermented<br>sodium<br>hyaluronate | Putty, granules                 | NA   | Resorbable                                       | OC          | Bone void filler.<br>Non-load-bearing<br>applications   |                       |
| <b>MEDTRONIC</b>               |  |                                 |  |  |             |   |                       |
| Mastergraft                    | 15% HA,<br>85% Beta TCP                            | Granules                        | NA   | Resorbable                                       | OC          | Bone void filler in<br>trauma and spinal<br>surgery   |                       |
| BCP Granules                   | 35% HA, 65%<br>Beta TCP                            | Granules                        | NA   | NA   | OC          | Bone void filler in<br>trauma and spinal<br>surgery   |                       |
| Nanostim                       | 100% HA  | Granules                        | 1 ml £105;<br>2 ml £150;<br>5 ml £345;<br>10 ml £645 | NA   | OI + OC     | Spinal surgery and<br>fusion  |                       |

\* HA, hydroxyapatite; TCP, tricalcium phosphate

† OC, osteoconductive; OI, osteoinductive

‡ n, number of peer-reviewed papers describing clinical use of the registered or trade-marked product; Level of evidence denoted I to IV (see Table I)

§ NA, data not available

spinal fusion when supplemented by appropriate fixation.<sup>18,19</sup> Actifuse has currently not been cleared for use in vertebroplasty.

It has recently been shown that magnesium ions enable the hydroxyapatite crystal cell structure to become unstable and more biologically active, thereby promoting rapid cell-mediated material resorption, new bone formation and remodelling. The inclusion of magnesium in the hydroxyapatite improves its interaction with water, further stimulating osteogenesis.<sup>36</sup> SINTlife (JRI Orthopaedics, London, United Kingdom) is a magnesium-substituted hydroxyapatite that is resorbed over a period of six to 18 months, allowing time for the formation and maturation of new bone. Clinical indications are as a bone-void filler in trauma, knee and spinal surgery. A recent small RCT showed promising results using SINTlife in the treatment of medial compartment osteoarthritis of the knee treated with a high tibial osteotomy supplemented with internal fixation, when it was compared with the use of lyophilised bone chips.<sup>36</sup>

There is some evidence for the use of bone graft substitutes in tibial plateau fractures, distal radial fractures, calcaneal fractures and spinal surgery.

**Indications for use of bone graft substitute. Tibial plateau fractures.** Buttress plating and elevation of a depressed articular surface leaves a contained metaphyseal void that should heal but this runs the risk that the subchondral surface will collapse. Autologous bone graft is commonly packed into the defect but it lacks the mechanical stability to allow early weight-bearing. Alternative substitutes that can be used are the calcium cements, which can be injected into the void and offer improved stability and strength, allowing early weight-bearing. Jubel et al<sup>69</sup> performed a prospective study looking at the use of injectable Norian SRS cement in 21 tibial plateau fractures to supplement internal fixation. The mean follow-up was 30 months. Full weight-bearing was achieved after a mean of 3.7 weeks, with clinical and radiographic results comparable to those following the use of autologous graft. They

**Table VI.** Bone graft substitutes with levels of evidence. Manufacturers: Orthovita (St Albans, United Kingdom), Ossacur AG (Oberstenfeld, Germany) and Osteotech (Christchurch, United Kingdom)

| Manufacturer/<br>Product name  | Material*                           | Delivery                    | Cost                         | Morphology  | Properties† | Recommended use  | Level of evidence‡        |
|--------------------------------|-------------------------------------|-----------------------------|------------------------------|---|-------------|--|---------------------------|
| <b>ORTHOVITA</b>               |                                     |                             |                              |   |             |  |                           |
| Vitoss <sup>15,37-42</sup>     | Beta TCP,<br>20% Type 1<br>Collagen | Foam                        | NA <sup>§</sup>              | 90% porosity. Pore size from 1 to 900 µm. Resorbable  | OI + OC     | Spinal and trauma surgery  | n = 7<br>(I, II, III, IV) |
| Cortoss <sup>17,43-45</sup>    | Bioactive glass cement              | Paste                       | NA                           | Non-resorbable. Lower setting temperature than polymethyl-methacrylate (PMMA), less thermal necrosis. Pore size 150 µm. Compressive strength 91 to 179 MPa. Young's modulus 6400 MPa. Tensile strength 52 MPa | OC          | Kyphoplasty vertebroplasty. Trauma surgery, bone void filler                           | n = 4<br>(I, II, III, IV) |
| <b>OSSACUR AG</b>              |                                     |                             |                              |   |             |  |                           |
| Colloss                        | Collagen lyophilisate               | Fleece                      | NA                           | Resorbable after a few weeks  | OC          | No primary stability   |                           |
| Targobone E                    | Colloss and Teicoplanin             | Fleece with antibiotic      | NA                           | Resorbable after a few weeks  | OC          | No primary stability, marketed for use in infection                                    |                           |
| <b>OSTEOTECH</b>               |                                     |                             |                              |   |             |  |                           |
| Grafton <sup>33,35,46-56</sup> | DBM                                 | Matrix, paste, putty, gel   | Putty: 5 ml £365; 10 ml £595 | Non-load-bearing  | OI + OC     | Multiple uses. Spinal fusion, void filler, trauma, arthrodesis                         | n = 15<br>(II, III, IV)   |
| Plexure                        | DBM and Polylactide-co-glycolide    | Granules, wedge, blocksheet | NA                           | Resorbable  | OI + OC     | Void filler, oncology bone surgery, tibial plateau fractures, and arthroplasty surgery |                           |

\* TCP, tricalcium phosphate; DBM, demineralised bone matrix

† OC, osteoconductive; OI, osteoinductive

‡ n, number of peer-reviewed papers describing clinical use of the registered or trade-marked product; Level of evidence denoted I to IV (see Table I)

§ NA, data not available

concluded that the high compressive strength of the calcium cement allowed early weight-bearing with no risk of loss of fracture reduction. Similar results were reported by Lobenhoffer et al<sup>73</sup> using Norian SRS cement.

Dickson et al<sup>60</sup> used BoneSource (Stryker), a calcium phosphate cement, in metaphyseal fractures, including those of the tibial plateau, with a successful outcome in 83% of cases. A recent multicentre RCT by Russell and Leighton<sup>16</sup> compared Alpha-BSM (Etex Ltd, Cambridge, Massachusetts), a calcium phosphate, and open reduction and internal fixation (ORIF) to ORIF and autologous bone graft in Schatzker I to IV<sup>110</sup> tibial plateau fractures. A total of 120 closed unstable tibial plateau fractures were enrolled in this prospective trial involving 12 centres in the United States. The range of movement of the knee was higher in the Alpha-BSM group than in the autograft group at six and 12 months, and radiologically there was a significantly higher rate of articular subsidence in the autograft group than in the Alpha-BSM group after one year. There were no major complications and the authors

supported the use of Alpha-BSM in the management of tibial plateau fractures.<sup>16</sup>

**Distal radial fractures.** A Cochrane review on the use of cements in distal radial fractures conducted by Handoll and Watts<sup>61</sup> showed that anatomical outcome was improved when using cement compared with plaster cast treatment alone, although there was no statistically significant difference in functional outcome, there were some concerns regarding extraosseous deposition of the cement. Cassidy et al<sup>13</sup> performed a randomised trial involving 323 patients with distal radial fractures, treating them either with closed reduction and percutaneous injection of Norian SRS cement, closed reduction alone, or external fixation. Significant clinical differences were seen at six to eight weeks' follow-up, with better grip strength, range of movement, reduced swelling and social function when using the Norian SRS compared to the control group ( $p < 0.05$ ). However, at 12 months there were no clinical differences between the groups. Zimmerman et al<sup>82</sup>

**Table VII.** Bone graft substitutes with levels of evidence. Manufacturers: Stryker (Newbury, United Kingdom), Synthes (Welwyn Garden City, United Kingdom) and Textile Hi-Tec (Saint Pons de Thomières, France)

| Manufacturer/<br>Product name        | Material*                  | Delivery         | Cost   | Morphology <sup>†</sup>   | Properties <sup>‡</sup> | Recommended use   | Level of evidence <sup>§</sup> |
|--------------------------------------|----------------------------|------------------|--|---|-------------------------|---|--------------------------------|
| <b>STRYKER</b>                       |                            |                  |  |   |                         |   |                                |
| Bonesave <sup>57,58</sup>            | 20% HA, 80% TCP            | Granules         | NA <sup>¶</sup>  | 50% surface porosity ranging from 10 to 400 µm  | OC                      | Bone void filler. Revision hip surgery. Spinal fusion surgery   | n = 2 (III, IV)                |
| BoneSource <sup>59-62</sup>          | Calcium phosphate          | Cement           | NA   | Ca:P ratio 1.65:1.67 and equivalent to natural bone. Not load-bearing. 46% porosity. Pore size 2 to 50 µm. Compressive strength 6.3 to 34 MPa. Young's modulus 2500 to 3000 MPa | OC                      | Void filler used in tibial plateau fractures and proximal femoral voids in revision hip surgery with distal stem fixation. Humerus fractures and bone void filler in tumour resection surgery | n = 4 (II)                     |
| Hydroset                             | HA                         | Cement           | NA   | NA  | OC                      | Injectable. Not load-bearing  |                                |
| <b>SYNTHES</b>                       |                            |                  |  |   |                         |   |                                |
| DBX                                  | DBM                        | Putty            | 0.5 ml £86; 1 ml £128; 2.5 ml £268; 5 ml £386; 10 ml £594  | Non-load-bearing applications   | OI + OC                 | Void filler in long bones and pelvis  |                                |
| ChronOS <sup>63-65</sup>             | Beta TCP                   | Granules, blocks | 1 ml £89; 10 ml £296   | Resorbable at 6 to 18 months. 60% to 70% porosity. Pore size 100 to 400 µm. Non-load-bearing applications   | OC                      | Void filler in areas where cancellous bone is required rather than cortical bone. Trauma, spinal and reconstruction surgery.  | n = 3 (II, IV)                 |
| Norian SRS <sup>13,59,61,66-84</sup> | Calcium phosphate          | Cement           | 5 ml £372; 10 ml £592  | Resorbable. Remodelling by 76 weeks. Early weight-bearing. 50% porosity. Compressive strength 14 to 27 MPa. Tensile strength 2.1 MPa  | OC                      | Distal radial, proximal and distal tibia, calcaneum, proximal and distal femur, proximal humerus and acetabulum fractures   | n = 22 (I, II, III, IV)        |
| <b>TEXTILE HI-TEC</b>                |                            |                  |  |   |                         |   |                                |
| Tri-Calcit                           | 70% HA, 30% TCP. Synthetic | Granules, blocks | Granules: 2 ml £70; 10 ml £91; 16 ml £134. Block: 5x5x20, 0.5 ml £86; 10x10x20, 2 ml £93; 20x20x40, 16 ml £134 | 70% macroporosity 550 µm. Microporosity (< 10 µm) absorbable  | OC                      | Bone void filler in trauma surgery  |                                |

\* HA, hydroxyapatite; TCP, tricalcium phosphate; DBM, demineralised bone matrix

† Ca, calcium; P, phosphate

‡ OC, osteoconductive; OI, osteoinductive

§ n, number of peer-reviewed papers describing clinical use of the registered or trade-marked product; Level of evidence denoted I to IV (see Table I)

¶ NA, data not available

compared Kirschner (K)-wire fixation alone with K-wire fixation and Norian SRS in unstable distal radial fractures in 52 osteoporotic women. At a follow-up of two years, patients treated with Norian SRS had better function with improved grip strength than those treated with K-wire fixation alone ( $p < 0.001$ ).

Jakubietz et al<sup>65</sup> performed an RCT in which 20 patients were randomised to be treated with a dorsal plate (Pi-Plate; Synthes) and ChronOS (Synthes) bone graft substitute and 19 were randomised to be treated with a dorsal plate alone. All patients were aged > 50 years and had a closed AO type C<sup>111</sup> distal radial fracture. The authors used ChronOS granules to fill the defects remaining after reduction of the

fracture and stabilisation with the Pi-Plate. Post-operative treatment regimes were identical for both groups. All fractures were united by 12 weeks and there was no statistical difference in radiological and clinical outcomes between the two groups. Most RCTs involving distal radial fractures and bone graft substitutes include different treatment regimes and multiple fracture patterns, ranging from AO type A2 to C3. Jakubietz et al<sup>65</sup> showed no benefit of ChronOS on AO type C fractures when used in conjunction with the dorsal Pi-Plate.

Norian SRS has also been used successfully in the treatment of malunited distal radial fractures when combined with a radial osteotomy. Abramo et al<sup>84</sup> reviewed 25 consecutive

**Table VIII.** Bone graft substitutes with levels of evidence. Manufacturer: Wright Medical Technology (Pulford, United Kingdom)

| Manufacturer/<br>Product name*   | Material                                     | Delivery                              | Cost   | Morphology†  | Properties‡ | Recommended use  | Level of evidence§  |
|----------------------------------|--|---------------------------------------|--|--|-------------|--|---------------------|
| Allomatrix <sup>85-89</sup>      | DBM with calcium sulphate carrier (Osteoset) | Paste, chips                          | Paste: 1 ml £240; 5 ml £350; 10 ml £510. Chips: 5 ml £585; 10 ml £725; 20 ml £890                                | Non-load-bearing   | OI + OC     | Bone void filler in trauma surgery. Lumbar spine surgery. Tumour resection surgery and long bone non-union. Non-load-bearing applications  | n = 5 (III, IV)     |
| Osteoset <sup>90-97</sup>        | Calcium sulphate                             | Pellets, beads                        | Pellets: 5 ml, 3 mm £210; 10 ml, 3 mm £325; 10 ml, 4.8 mm £160; 20 ml, 4.8 mm £250. Beads: 5 ml £250; 25 ml £385 | Resorbable. Compressive strength 0.6 to 0.9 MPa. Young's modulus 59 MPa                      | OC          | Spinal surgery, trauma, treatment of benign cysts and adult reconstruction   | n = 8 (II, III, IV) |
| Osteoset II DBM <sup>98,99</sup> | Calcium sulphate and DBM                     | Pellets                               | 5 ml, 3 mm £550; 10 ml, 3 mm £606; 10 ml, 4.8 mm £636; 20 ml, 4.8 mm £735  | 53% vol DBM. Contains BMP-2, BMP-4, IGF-1, TGF-β1. Resorbable. Rapid remodelling             | OC          | Spinal surgery, trauma, treatment of benign cysts and adult reconstruction. To treat avascular necrosis of the femoral head when combined with autograft   | n = 2 (III, IV)     |
| Cellplex TCP                     | TCP  | TCP granules and bone marrow aspirate | 7 ml + marrow chamber £525. 15 ml + marrow chamber £695  | Resorbable. Allows early load-bearing  | OC          | Trauma surgery, bone void filler   |                     |
| MIIG X3 <sup>100,101</sup>       | Calcium sulphate                             | Paste                                 | 5 ml £395; 15 ml £490  | Resorbable. Compressive strength 0.6 MPa   | OC          | Trauma surgery in tibial plateau fractures. Ideal for metaphyseal defects  | n = 2 (IV)          |
| Ignite                           | DBM, Calcium sulphate, bone marrow aspirate  | Paste                                 | 4 ml £420; 20 ml £1470   | Resorbable   | OI + OC     | Used in cases of suspected nonunion where no callus is seen at 6-8 weeks. Cases of delayed union with well fixed hardware. Use in fresh fractures where there is high risk of nonunion e. g. smokers or diabetics. Contraindicated in infected cases or when bone gap > 3 mm, and when there are signs of hardware loosening |                     |
| ProDense <sup>102</sup>          | Calcium phosphate (TCP) and calcium sulphate | Paste                                 | NA¶  | Resorbable. 40 MPa initial compressive strength. 75% calcium sulphate. 25% calcium phosphate | OC          | Calcaneal, tibial plateau, distal radius and proximal humerus fractures as bone void filler. Used in treatment of benign bone cysts and in osteotomy and decompression surgery   | n = 1 (IV)          |
| ProStim                          | ProDense+DBM                                 | Paste                                 | NA   | Resorbable. 40 MPa initial compressive strength. 75% calcium sulphate. 25% calcium phosphate | OI + OC     | Calcaneal, tibial plateau, distal radius and proximal humerus fractures as bone void filler. Used in treatment of benign bone cysts and in osteotomy and decompression surgery   |                     |

\* DBM, demineralised bone matrix; TCP, tricalcium phosphate;

† BMP, bone morphogenetic protein; IGF, insulin-like growth factor; TGF, transforming growth factor

‡ OC, osteoconductive; OI, osteoinductive

§ n, number of peer-reviewed papers describing clinical use of the registered or trade-marked product; Level of evidence denoted I to IV (see Table I)

¶ NA, data not available

patients with a dorsally malunited distal radial fracture treated with a radial osteotomy and Norian SRS and found statistically significant improvements in movement, grip strength and

Disabilities of the Arm, Shoulder and Hand (DASH) scores.<sup>112</sup> In one case the cement had fragmented before bony union, with failure of fixation at two months.

**Calcaneal fractures and ankle fusion.** Schildhauer et al<sup>79</sup> reviewed 36 depression-type calcaneal fractures treated with Norian SRS and internal fixation. Full weight-bearing was achieved at three weeks, compared to the authors' previous practice of weight-bearing at 12 weeks after internal fixation alone. However, four patients (11%) developed a deep infection.<sup>79</sup>

Johal et al<sup>14</sup> conducted an RCT involving closed fractures of the calcaneum. A total of 24 fractures were treated by ORIF and Alpha-BSM, a calcium phosphate, and 28 by ORIF alone. Although there was a difference in the mean reduction of Bohler's angle in both groups one year post-operatively (6.2° in the ORIF and Alpha-BSM group *vs* 10.4° in the ORIF alone group;  $p = 0.05$ ), there was no difference in the Short-Form (SF)-36<sup>113</sup> and Oral Analog Scale (OAS) scores<sup>114,115</sup> between the two groups.

Thordarson and Kuehn<sup>34</sup> used demineralised bone matrix to stimulate fusion of the ankle or hindfoot. A total of 37 patients were treated with Grafton putty (Osteotech) and five (14%) developed a nonunion; 26 were treated with Orthoblast (Isotic Orthobiologics, Irvine, California) and two (8%) developed a nonunion. There were no statistical differences between the two groups. Rates of nonunion ranging from 5% to 30% continue to be reported for ankle or hindfoot fusions without bone graft substitutes.<sup>116,117</sup>

**Spinal surgery.** Autologous bone graft is often used to supplement healing in spinal surgery. A recent multicentre prospective study by Cammisa et al<sup>47</sup> included 120 patients in whom autograft bone was implanted on one side of the spine and a mixture of Grafton and iliac bone graft on the contralateral side. Fusion rates of 52% were seen on the Grafton/autograft side compared to 54% on the autograft side. Grafton may thus be useful in spinal fusion, as less graft needs to be harvested from the iliac crest to produce similar rates of fusion.

Balloon kyphoplasty has significantly improved the outcome after vertebral compression fractures. A recent RCT by Blatter et al<sup>66</sup> compared the use of Norian SRS with polymethylmethacrylate (PMMA) in balloon kyphoplasty. A total of 60 AO type A osteoporotic vertebral fractures were included, and Norian SRS or PMMA was injected into 30 randomised vertebrae each. The authors concluded that Norian SRS performed well in AO type A1.3 osteoporotic vertebral fractures; however, in more complex AO type 3 fractures, significant failure of this cement was seen. The authors and the manufacturers do not recommend the use of Norian SRS in the treatment of AO type 3 fractures by balloon kyphoplasty, favouring the use of PMMA for all osteoporotic vertebral fractures.

Lerner et al<sup>15</sup> conducted an RCT with a mean follow-up of four years comparing Vitoss (Orthovita), a Beta TCP, to autograft in the posterior instrumented correction of adolescent idiopathic scoliosis. Two groups of 20 patients received either iliac crest autograft or Vitoss to supplement fusion. In the Vitoss group all patients except one had radiological fusion at the final follow-up. Four patients in the autograft group had persistent donor site pain at four years.

There was no difference in the pain scores and the correction of the curves between the groups. A limitation of that study is that 17 patients underwent thoracoplasty, with the resected rib used as supplementary graft. Nine patients in the Vitoss group and eight in the autograft group had supplementary rib autograft, thereby introducing a systematic error into the study. However, the study supports use of Vitoss in posterior instrumented fusion in patients with adolescent idiopathic scoliosis.

Ploumis et al<sup>30</sup> performed a case-control study comparing Healos (a collagen-hydroxyapatite bone graft substitute; DePuy) with bone marrow aspirate and autograft ( $n = 12$ ) to cancellous allograft and autograft ( $n = 16$ ) in patients with degenerative lumbar scoliosis undergoing posterolateral fusion. Similar function and visual analogue pain scores were seen in both groups; however, the Healos, bone marrow aspirate and autograft group had a significantly slower rate of fusion than the allograft and autograft group (mean 10.9 months *vs* 8 months;  $p < 0.05$ ). The reduction in Cobb angle at two years was similar in both groups. The authors recommended the use of Healos when limited sources of autograft were available.

**Nonunion surgery.** Ziran et al<sup>85</sup> reviewed 41 patients with various nonunions treated with Allomatrix (DBM and calcium sulphate; Wright Medical Technology, Pulford, United Kingdom). A total of 20 patients (51%) developed post-operative drainage problems and 13 required debridement, and the nonunion persisted, with 11 developing deep infection. The authors did not recommend the use of Allomatrix in surgery for nonunion. Similar problems have arisen when Osteoset (Wright Medical Technology) has been used in nonunion surgery.<sup>93</sup>

Chu and Shih<sup>22</sup> recently described the treatment of 15 patients with nonunion of the scaphoid using percutaneous fixation supplemented with GeneX (calcium phosphate and sulphate; Biocomposites, Keele, United Kingdom). Union was confirmed in 14 patients (93%) at a mean of 15.3 weeks.

**Revision hip replacement.** Little has been published on the use of bone graft substitutes in revision hip surgery. Two case series using hydroxyapatites, Apapore 60 (Apatech Ltd) and Allogran-N (Biocomposites, United Kingdom), have shown some early clinical success. Aulakh et al<sup>23</sup> compared the use of a 50:50 mixture of allograft and Allogran-N with allograft alone in impaction bone grafting in revision hip arthroplasty. The survival rates for both groups at a mean of 13 years were similar (84% and 82%), supporting the use of Allogran-N in impaction bone grafting.

McNamara et al<sup>18</sup> reviewed 50 consecutive acetabular reconstructions using a 50:50 mixture of Apapore 60 and allograft bone. In all nine patients developed radiolucent lines in acetabular zones 1, 2 or 3<sup>118</sup> at one year, with no further progression. No patient had radiolucent lines involving all three zones and no patient required revision surgery. The authors were unclear about the significance of the early development of the radiolucent lines and these

patients remain under review. The study, however, supports the use of a mixture of Apapore 60 and allograft in complex acetabular surgery.

**Study quality.** Five RCTs were considered to be Level I evidence and the results showed that the substitutes were equal or superior to autograft.<sup>13-17</sup> Four were multicentre studies conducted in the United States,<sup>13,14,16,17</sup> and the study by Lerner et al<sup>15</sup> was performed at one centre in Germany. Both studies involving Alpha-BSM (DePuy) declared funding from industry, whereas the studies using Norian SRS (Synthes), Cortoss (Orthovita) and Vitoss (Orthovita) did not. Three studies reported the method of random sequence generation<sup>14,16,17</sup> but only three recorded the process of allocation concealment, two with the use of sealed envelopes<sup>15,16</sup> and the other using an independent worker pulling consecutive tabs.<sup>14</sup> Inclusion and exclusion criteria were reported in four studies.<sup>13,14,16,17</sup> Four studies had no differences in the baseline characteristics of the patients; however, the study by Cassidy et al<sup>13</sup> had a significant gender difference between the groups, which may have introduced bias. A sample-size calculation was conducted in three studies, as well as the reporting of a primary outcome measure.<sup>13,14,17</sup> No study had any post-randomisation exclusion criteria, which is a strength. The overall percentage of patients that completed the follow-up ranged from 75% to 95% in all studies and this was regarded as excellent. The two studies involving Alpha-BSM reported the use of blinded radiographers to score the post-operative radiographs. Alpha-BSM is a radiodense calcium phosphate material and therefore it would be impossible to blind the assessors when scoring the radiographs, which is a weakness.<sup>14,16</sup>

## Discussion

The reconstruction of large bony defects created during trauma or revision arthroplasty surgery is a major concern for orthopaedic surgeons. Over the last decade many new bone graft substitutes have become available. However, despite many *in vitro* and *in vivo* studies in animals, few clinical data are available to justify their use. Currently, many products are licensed for use in the axial skeleton without any published literature regarding their safety or long-term outcome. This is the largest review on bone graft substitutes, with 59 products from 17 manufacturers being considered. The summaries in Tables II to VIII will assist surgeons when choosing a product for a specific situation. Using three observers to assign each paper a level of evidence increases the validity of the study. However, it has limitations. First, the bone graft substitutes were searched using their product name in multiple databases, and some papers might have been missed if they did not specify which product had been used. Second, we only considered papers in English, and clearly papers are available for some products in other languages.

All 59 products have osteoconductive properties, with porosity, pore size and degradation potential being important factors when choosing which to use. Regeneration of

bone is facilitated by angiogenesis and porosity, with optimal pore sizes being between 200  $\mu\text{m}$  and 500  $\mu\text{m}$ .<sup>103</sup> Bioresorbability is facilitated by the microporosity of the graft, and pore sizes < 5  $\mu\text{m}$  are essential for degradation of the graft substitute.<sup>119,120</sup> The rate of resorption varies between the products and are dependent on their composition. Calcium phosphate cements are degraded by osteoclastic activity within two years.<sup>121</sup> Calcium sulphate cements are usually resorbed within two or three months, which limits their use as a bone graft substitute, and they are not suitable for cases where structural support is required. Sintered hydroxyapatite resists degradation and can remain in bone for more than ten years.<sup>121</sup>

All the bone graft substitutes are currently available in the United Kingdom, and their clinical indications are listed in Tables II to VIII. A large cortical void cannot be reconstructed using a bone graft substitute without additional structural support. Four substitutes have Level I data for orthopaedic surgery. Norian SRS has been used to treat fractures of the tibial plateau, calcaneum, distal radius and proximal femur with good results when supplemented by additional fixation.<sup>13,59-62,66,68-76,78-80</sup> Vitoss and Cortoss have been used as an alternative to PMMA in the treatment of vertebral fractures, with promising results.<sup>15,17,37-39,42,44,45</sup> Alpha-BSM has been used to treat tibial plateau fractures, with excellent results.<sup>14,16</sup> It is to be hoped that in future newer compounds will be incorporated into the grafts to make a composite material that is easier to mix and handle. Currently most grafts consist of a liquid and a powder that are mixed to create an injectable paste. Pre-mixed injectable bone substitutes are being made that are easier to use but have a slightly lower tensile strength. Recent work has looked at reinforcement of the graft by the addition of fibres to improve the elastic modulus and tensile strength.<sup>122</sup> The addition of chitosan, a linear polysaccharide, improves flexibility, tensile strength and elastic modulus, which allows the paste to be moulded into any shape without compromising its strength.<sup>122,123</sup> One area of continuing research is the incorporation of antibiotics into bone graft substitutes. Many experimental studies are being undertaken, and Rupprecht et al<sup>124</sup> reported good results in the treatment of mandibular nonunions treated with Targobone (Ossacur AG, Oberstenfeld, Germany), a bovine collagen compound that includes teicoplanin.

Cost is a major consideration: harvesting an iliac crest graft costs approximately £400 in our hospital, without taking into account the cost of the increased morbidity. An allograft femoral head weighing approximately 40 to 60 g costs £700. Where available, the cost of the product is given in Tables II to VIII; all are more expensive than allograft. They are, however, sterile, easily stored and immediately available for use.

Regulation of the use of bone graft substitutes is essential in order to prevent harm to patients. Before a substitute is licensed for clinical use, there should be a requirement that clinical data be published and reviewed by the regulatory

agencies. Thompson et al<sup>125</sup> have highlighted the shortcomings of the current system for approval of medical devices in the United Kingdom. The authors recommend that a public record is created every time a manufacturer approaches a notified body for approval of a new bone graft substitute or implant, and information on whether a product has previously been turned down by any other regulatory bodies should be made available. Although the European Commission is revising the regulation of medical devices, these changes are not expected to take effect until at least 2015. Currently, manufacturers are only required to submit information gathered from similar, equivalent products.<sup>126</sup> Thus a new bone graft substitute may be used worldwide, without evidence of its safety and performance. We recommend that all data for currently available bone graft substitutes should be published to allow surgeons and patients to make more informed decisions regarding their use.

In conclusion, little information is currently available about the safety and performance of new bone graft substitutes: only four products, Alpha-BSM (DePuy), Cortoss (Orthovita), Norian SRS (Synthes) and Vitoss (Orthovita) have Level I published data showing that their use gives the same as or better results than autograft. Further RCTs and clinical trials are essential to assess the clinical efficacy of these products in orthopaedic surgery. Surgeons using these products must be aware of the limited data that are available, and improved medical regulation of these products based on clinical evidence must be sought.

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