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The role of orthobiologics in foot and ankle surgery: allogenic bone grafts and bone graft substitutes

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- Orthobiologics are biological substances that are used therapeutically for their positive effects on healing skeletal and soft-tissue injuries. The array of orthobiological products currently available to the foot and ankle surgeon is wide, and includes bone allografts, bone substitutes, growth factors, and chondral scaffolds. Nonetheless, despite the surge in interest and usage of orthobiologics, there remains a relative paucity of research addressing their specific applications in foot and ankle surgery. In this review, we attempt to provide an overview of the literature on commonly available allogenic bone grafts and bone substitutes.
- There is Level II, III and IV evidence addressing allogenic bone grafts in primary arthrodesis and osteotomy procedures in foot and ankle surgery, which compares favourably with autogenic bone grafts in terms of fusion rates and clinical outcomes (often with fewer complications), and supports a Grade B recommendation for its use.
- Pertaining to bone substitutes, the multiplicity of products, coupled with a lack of large prospective clinical trials, makes firm recommendations difficult. Level II and IV studies of calcium phosphate and calcium sulphate products in displaced intra-articular calcaneal fractures have found favourable results in addressing bone voids, maintaining reduction and promoting union, meriting a Grade B recommendation. Evidence for TCP is limited to level IV studies reporting similarly good outcomes in intra-articular calcaneal fractures, warranting a Grade C recommendation. The use of demineralised bone matrix products in hindfoot and ankle fusions has been described in Level II and III studies, with favourable results in achieving fusion and good clinical outcomes, supporting a Grade B recommendation for these indications.
- Overall, despite the general lack of high-level evidence in foot and ankle surgery, allogenic bone grafts and bone substitutes continue to hold front-line roles in treating the bone defects encountered in trauma, tumour, and deformity correction surgery. However, more investigation is required before firm recommendations can be made.

Keywords: orthobiologics; allogenic bone grafts; bone graft substitutes

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Introduction

Orthobiologics are biological substances that are used therapeutically for their positive effects on healing skeletal and soft-tissue injuries. The use of such biological agents in the field of orthopaedic surgery has been drawing increasing attention over the past decade, particularly as adjuncts in promoting the healing of bone, cartilage, ligament and tendon injuries. The principal benefits of using orthobiologics are twofold – first, to reduce the need for surgery in treating musculoskeletal injuries; and secondly, to augment the effectiveness of existing orthopaedic implants and surgical techniques.

The array of orthobiological products currently available to the foot and ankle surgeon is wide, and includes bone allografts, bone substitutes, growth factors, and chondral scaffolds. Nonetheless, despite the surge in interest and usage of orthobiologics, there remains a relative paucity of research pertaining to their specific applications in foot and ankle surgery. In this review, we will attempt to provide an overview of the current literature on the allogenic bone grafts and bone substitutes commonly used by the foot and ankle surgeon.

Bone allografts

The successful surgical management of fractures is predicated by the Arbeitsgemeinschaft für Osteosynthesefragen concepts of fracture reduction and stable fixation. In the setting of fracture comminution, there is a further need to address the resultant bone loss and to provide a favourable biological environment for fracture union. To achieve these goals, autologous bone grafts

have traditionally been indispensable in filling bone voids. The inherent osteogenic, osteo-inductive and osteo-conductive properties are an immense advantage that has rendered autogenic bone grafts the acknowledged benchmark in the management of bone defects.

In foot and ankle surgery, these principles of fracture management have been extended to the techniques used in osteotomy and arthrodesis procedures, where autogenic bone grafts have achieved a similar level of importance when restoring volume, length, height and structural stability in alignment correction.[1-4]

However, there remain a number of disadvantages that arise from using autogenous bone grafts. Donor site morbidity is a significant problem, which includes haematoma formation, infection, chronic pain, neurological deficits, iatrogenic fractures, and issues with cosmesis.[5-9] Furthermore, the amount of donor site bone graft available for harvesting is limited, which is a particular concern when addressing large bone defects. The use of bone allografts and the development of bone graft substitutes was driven by the need to mitigate these problems.

Allografts obviate the inherent donor site problems of autogenous bone grafts, but are beset by issues with graft rejection, slower graft incorporation, and the possibility of disease transmission, particularly in areas where the blood supply is comparatively tenuous.[10,11] Nonetheless, in well-vascularised bone sites, the calcaneus being a prime example, there seems to be no significant difference when comparing incorporation and complication rates of allografts *versus* autogenous grafts.[12,13]

The types of allograft available can be classified according to bone structure (cortical, cancellous, cortico-cancellous); cortical and cortico-cancellous allografts are more rigid and are conventionally used to provide structural support, while cancellous allografts are often used to address bone defects where no physical support is needed. Allografts can be processed by different methods (fresh, fresh-frozen, freeze-dried, de-mineralised); increasingly vigorous processing reduces the risk of disease transmission and infection, but also simultaneously weakens the structural properties of the graft, and diminishes osteogenic and osteo-inductive potential. Hence, fresh-frozen grafts are commonly used in situations where structural stability is deemed important, while freeze-dried and de-mineralised grafts are cost-effective at well-vascularised sites where host osteoprogenitor cells and growth factors are readily available. The latter are also useful when combined with autogenous bone as graft expanders. Furthermore, it is thought that de-mineralised bone graft may retain a useful modicum of osteo-inductive potential, in addition to its osteo-conductive properties.[14]

In foot and ankle surgery, there are a good number of clinical studies documenting the efficacy and safety of allograft usage in primary arthrodesis and osteotomies. However, the majority are case series or small non-randomised studies. Interpretation is further compounded by the heterogeneity in the clinical and radiological definitions of successful graft incorporation and union. Additionally, the studies vary in the surgical sites and procedures being investigated, although lateral column lengthening and calcaneal procedures are the most common. Furthermore, there is heterogeneity in the types of allografts used in the various studies. Lastly, the sample sizes are generally small and under-powered to assess complication rates.

With these limitations in mind, the literature is fairly consistent in demonstrating allograft incorporation rates of between 90% to 100% in lateral column lengthening and other calcaneal procedures.[15-17] None of these case series (Level IV) showed clinically significant complication rates. Retrospective cross-sectional studies comparing allografts with autografts in the paediatric population showed no statistical or clinically significant differences in union rates and complication rates.[18-20] The good clinical results suggest that autogenic bone grafts may not be required in the paediatric group, particularly in calcaneal procedures where vascularity is good. Likewise, retrospective reviews (Level III) in the adult population found no significant differences in graft incorporation and complication rates when comparing allografts with autogenic bone grafts.[12,21]

Dolan et al[13] conducted a randomised controlled trial (Level II) comparing autogenous iliac crest bone graft with freeze-dried tri-cortical allografts in adults undergoing lateral column lengthening. There were 15 procedures using autografts and 18 procedures in which allografts were used. The primary endpoint of the study was graft incorporation, defined by radiological bridging across both ends of the graft. Their results showed no significant difference in graft incorporation rates (100% in both groups) and time to graft incorporation. The authors noted that two patients in the autograft group had persistent donor site hip pain even after three months.

A systematic review (Level II) conducted by Müller et al[22] in 2013 compared autografts with allografts in hindfoot arthrodesis and osteotomy procedures. They analysed ten studies involving 928 hindfoot procedures, and found equivalent rates of incorporation of allografts compared with autografts. However, the authors cautioned that the analysed studies were of poor quality owing to small sample sizes and the presence of confounding variables.

In summary, there is a limited amount of consistent evidence (Level II, III and IV) showing equivalence between autogenic and allogenic bone grafts in terms of union rates, time to graft incorporation, and complication rates in both the paediatric and adult populations, warranting a Grade B recommendation for the use of allografts as an alternative to autografts. However, it should be noted that the literature is mainly focused on primary surgeries,

typically involving well-vascularised sites. Whether these results can be extrapolated to the setting of revision surgery in regions of relatively tenuous blood supply remains to be resolved.

Bone graft substitutes

A bone graft substitute is a synthetic or biological substance that can be implanted for the treatment of bone defects as an alternative to autogenic and allogenic bone. The ideal bone substitute should have osteo-conductive and osteo-inductive properties, exhibit good biocompatibility without inciting any adverse inflammatory response, be easily handled and moulded to fill bone defects within an appropriate working time, and should be visible on radiological imaging for *in vivo* monitoring.

Interest in bone graft substitutes arose due to the disadvantages inherent in allogenic bone grafts, such as complications associated with the host reaction to foreign antigens and the risk of disease transmission.[23-26] The other advantages of bone substitutes further relate to their theoretically unlimited supply, ease of processing and sterilisation, and convenient storage. Nonetheless, the inevitable limitation of using synthetic materials is the deficiency in osteogenic, and oftentimes osteo-inductive, properties. The key clinical utility of these materials therefore lies in their 3D porous structure that provides an osteo-conductive scaffold, which enhances the adhesion and proliferation of osteoprogenitor cells, and correspondingly promotes the ongrowth or ingrowth of new bone.[27,28] To this end, sufficient porosity of the material is required, with a pore size of at least 100 μm and the presence of an interconnecting porous structure being necessary for osseous ingrowth.[29-31] Bone graft substitutes currently available to surgeons are typically bio-absorbable ceramics, and include calcium sulphate (CS), calcium phosphate (CP), and tricalcium phosphate (TCP) products (Table 1).

Table 1. Examples of synthetic bone substitutes in clinical usage

Tricalcium phosphate / Hydroxyapatite	Bonesave (Stryker) Calcibon (Biomet) Chronos (Synthes) Mastergraft (Medtronic)
Calcium phosphate (CP)	Actifuse (Apatech) Alpha-BSM (Etex) Bonesource (Stryker) Calcibon (Biomet) Norian SRS (Synthes)
Calcium sulphate (CS)	Osteoset (Wright) Stimulan (Biocomposites)
CS + CP composite	Cerament (Bonesupport) Genex (Biocomposites) Prodense (Wright)
Demineralised bone matrix	DBX (Synthes) Grafton (Osteotech) Opteform (Exatech) Optium DBM (DePuy) Orthoblast (Isotis)

Calcium sulphate

CS is one of the oldest bone substitutes, and is available in both pellet and powder forms, the latter of which can be mixed into a paste for shaping or administration by injection. Historically, it was first used to address bone defects in patients with tuberculosis; subsequently, it was noted that CS could be resorbed and replaced by new bone.[32] In addition to its osteo-conductive properties, another proposed mechanism of action relates to the generation of a locally acidic environment as CS is resorbed, which demineralises the adjacent bone and leads to the release of bone morphogenetic proteins, stimulating bone formation.[33] However, CS is typically rapidly resorbed in approximately six weeks,[34,35] which has been associated clinically with the development of serous discharge.[36] Furthermore, the rapid rate of resorption may outpace the rate of new bone formation, and there is limited utility of CS as a mechanical buttress.

The safety and efficacy of CS in treating long bone defects arising from trauma, infection and tumours is well documented in the literature,[36-38] with the option of incorporating antibiotics for treating osteomyelitis being a particularly useful feature.[39] However, there are few studies that directly address the application of CS in foot and ankle surgery, and caution must be exercised in extrapolating the favourable results from studies involving other anatomical sites.

Notably, Chen et al[40] conducted a prospective randomised trial (Level II) in 90 patients with displaced intra-articular calcaneal fractures, comparing percutaneous fixation augmented with CS cement *versus* conventional open reduction internal fixation (ORIF), and found that the percutaneous fixation group had earlier weight-bearing, reduced stiffness, and better patient satisfaction. Chen et al[41] also reported on a case series (Level IV) of five patients with calcaneal bone cysts presenting with pathological fractures who were treated with percutaneous fixation and CS augmentation, all of whom went on to have satisfactory fracture healing with no soft-tissue complications or cyst recurrence.

Calcium phosphate

Calcium phosphate (CP) products are commonly available as a bio-absorbable cement paste, with the most widely used products being Norian SRS (Norian Corp., Cupertino, California), Bone Source (Stryker Howmedica Osteonics, Mahwah, New Jersey), and chronOS (DePuy Synthes, Warsaw, Indiana). When applied as a cement, inorganic calcium phosphate salts harden *in vivo* by way of an isothermic reaction to form crystalline dahlite, a structure similar to the mineral phase of bone. Unlike CS, which is rapidly broken down *in vivo*, CP is gradually resorbed over a period of 26 to 86 weeks, and replaced with new bone.[42-44] It shows good biocompatibility, and

does not elicit any significant inflammation or foreign body response *in vivo*.[45] Furthermore, it has been shown that CP cement, when compared with cancellous bone, has a four- to tenfold greater strength in compression, and similar strength in tension.[46]

This synergistic combination of characteristics has made CP cement a particularly useful tool in addressing bone voids – with the concomitant benefits of providing interim structural support to the host bone, and improving the purchase of surgical fixation devices such as screws. Also, the mechanical strength afforded by the CP cement will further increase with the ingrowth of new bone. In the literature, these beneficial effects have been borne out by multiple randomised controlled trials. Notably, a meta-analysis (Level II) of 14 randomised controlled trials by Bajammal et al[47] found that patients treated with CP cement had a significantly lower rate of loss of fracture reduction when compared with those treated with autogenic bone grafts (relative risk reduction of 68%); the authors also found that there was less fracture site pain in the CP cement group than in the controls managed with no grafts at all.

In foot and ankle surgery, CP cement is especially advantageous when employed in the surgical fixation of displaced intra-articular calcaneal fractures, where the main difficulties lie in obtaining anatomical reduction of the weight-bearing posterior facet, addressing the bone voids that invariably follow the elevation of the posterior articular surface, and ultimately maintaining fracture reduction post-operatively. Of note, cancellous bone grafting of the bone defects has been demonstrably unsuccessful in preventing post-operative calcaneal collapse, often resulting in a loss of calcaneal height and articular surface reduction.[48] On the other hand, clinical studies have consistently shown better results with the use of CP cement.

Multiple published case series (Level IV) have demonstrated good outcomes following surgical fixation of calcaneal fractures with CP augmentation, with early post-operative weight-bearing and preservation of Bohler's angle being the notable findings.[49-53] CP was also found to exhibit good biocompatibility *in vivo*. In addition, a series of 11 patients with Sanders II and III calcaneal fractures treated by closed reduction and balloon-assisted augmentation with CP was reported by Biggi et al[54] more recently; the authors noted bony union by three months with an average Bohler's angle of approximately 23° at two years, and no significant complications.

A randomised controlled trial (Level II) performed by Johal et al[55] involving 52 displaced intra-articular calcaneal fractures compared ORIF augmented by injected CP (alpha-BSM) *versus* ORIF alone, with the primary outcome measure being the maintenance of Bohler's angle on radiographic evaluation after one year. The authors found that CP augmentation was significantly better, with a Bohler's angle loss of 6.2° *versus* 10.4° after a year ($p = 0.03$). There was also no significant difference in complication rates with alpha-BSM use.

Tricalcium phosphate

Tricalcium phosphate (TCP) ($Ca_3(PO4)_2$) is a resorbable ceramic material that can exist in two crystalline forms – polygonal alpha-TCP and spherical beta-TCP. Beta-TCP is the form that is commonly used in orthopaedic surgery as it has a finer micro-architecture with porosity resembling cancellous bone, allowing more rapid resorption.[56] TCP is usually available as granules or in blocks, and has similar strength to cancellous bone under both compressive and tensile stresses.[57] TCP typically undergoes integration by six to 18 months,[58] and demonstrates good biocompatibility, generating minimal inflammatory or foreign body giant-cell reactions.[59] Coralline hydroxyapatite is formed by treating marine coral with ammonium phosphate, and has similar structure and physical properties to TCP.

The physical properties of TCP make it a natural choice in dealing with bone defects that require additional structural support; TCP blocks are often used to fill and stabilise uncontained bone defects. In addition, TCP granules are often mixed with autogenic grafts as a bone graft expander to increase the volume of material available to fill large defects. Nonetheless, the literature on the usage of TCP in foot and ankle surgery is scarce, and is limited mainly to retrospective case series.

A retrospective review (Level IV) of 43 patients with post-traumatic nonunion and bone defects afflicting the long bones and calcaneus, and who were treated with ORIF and TCP augmentation, showed that 90% of the fractures and 85% of the nonunions had united by the last outpatient follow-up at 12 months.[60] The authors concluded that TCP was useful as a substitute for cancellous bone graft. Another retrospective case series (Level IV) of 74 cases of intra-articular calcaneal fractures treated with ORIF and augmentation with TCP showed that the Bohler angle improved by 23° post-operatively, and decreased by a mean of only 4° after one year. Similarly, favourable results were noted with regards to the Gissane angle, as well as calcaneal height and width.[61] Finally, Labbe et al,[62] in their series (Level IV) of six patients with displaced intra-articular calcaneal fractures reduced by balloon kyphoplasty and stabilised by TCP injection, found that stabilisation and maintenance of articular surface reduction was good, allowing early full-weight-bearing ambulation (median 52.5 days) and favourable American Orthopedic Foot and Ankle Society scores (median score of 87), with little by way of complications.

Composite grafts

As we have seen, the use of monophasic bone graft substitutes has been associated with generally positive results in

the literature, but has been hampered by limitations such as an increased incidence of serous discharge and wound complications (CS), early resorption and loss of mechanical strength (CS), as well as slow or incomplete integration into host bone (CP and TCP). This has led to an increasing interest in manufacturing products that combine the properties of these graft substitutes, in the hope of *in vivo* synergism.

The combination of rapidly-resorbed CS with the relatively-inert CP creates a biphasic ceramic composite graft that promotes angiogenic invasion and graft integration as the CS is resorbed, while still maintaining an adequate mechanical scaffold to provide structural support.[63] Commonly available products in this class include Cerament (Bonesupport, Lund, Sweden) and Pro-Dense (Wright Medical Technology Inc., Memphis, Tennessee). The use of these biphasic composite grafts in treating bone voids in tumour, trauma and spine surgery has been described in a number of case series, with good clinical and radiological outcomes, and no clinically significant increase in complication rates.[64-67]

In addition, it has been demonstrated in biomechanical studies that biphasic CS-CP grafts are useful in increasing screw purchase and pull-out strength by 100% to 200%, particularly in the setting of bone loss or osteoporosis.[68-70] In addition, it has numerous advantages over polymethylmethacrylate bone cement when employed in this role. CS-CP cements harden by an isothermic reaction, with little resultant risk of thermal necrosis in adjacent tissues. The good biocompatibility of these products is another significant benefit, as biological resorbability and osteo-conduction allow for the eventual integration and replacement by host bone.[69]

Pertaining to foot and ankle surgery, a novel off-label use of Cerament has been described in a series (Level IV) by Karr,[71] in which vancomycin-impregnated Cerament beads were implanted successfully in the management of patients with diabetic foot osteomyelitis. The isothermic and bioresorbable characterisitics of Cerament were advantageous in allowing for the incorporation of heat-unstable antibiotics, and also in negating the requirement for subsequent surgery to remove the beads.

Another approach to enhancing the biological efficacy of composite grafts has been to combine the osteo-conductive scaffold provided by CP ceramics with the osteo-inductive properties of recombinant human bone morphogenetic proteins (rhBMPs). An animal study in primates showed that percutaneous injection of a rhBMP-2 / CP composite matrix resulted in faster healing of a fibular osteotomy.[72] Similarly, favourable results were obtained in a recent rat study assessing the efficacy of a rhBMP-2 / CP composite in treating standardised bone defects.[73] However, clinical data in humans is currently lacking and requires further in-depth investigation.

To address the lack of osteogenesis in bone substitutes, some investigators have attempted to combine bone marrow aspirate (BMA) with these products. The clinical data on this approach is scanty, with a high degree of heterogeneity. A systematic review by Khashan et al[74] attempted to compare the efficacy of BMA in combination with bone substitutes *versus* iliac crest autograft in the setting of spinal fusion. Only four level II and III studies were found, and the authors found that the results of these studies were inconsistent, concluding that there was insufficient evidence to support the use of BMA combined with bone substitutes.

Demineralised bone matrix

Demineralised bone matrix (DBM) is produced by processing bone allograft to remove its inorganic mineral content while preserving the organic collagen matrix –this process is thought to retain osteo-inductive factors such as bone morphogenetic proteins (BMPs), while the removal of inorganic minerals exposes BMPs for release into the bone defect. As such, DBM is thought to offer the twin benefits of providing an osteo-conductive scaffold while concurrently preserving a degree of osteo-inductive potential, and consequently is the source of considerable clinical interest. However, one of the difficulties in analysing clinical studies of DBM lies in the significant variation in osteo-inductive properties that exist between different manufacturers, and even between different product batches from the same manufacturer.[75] This reflects the different processing techniques used commercially, in particular pertaining to the sterilisation phase, which typically involves gamma irradiation or ethylene oxide, and which are processes that negatively affect the osteo-inductive properties of the product.[76] Another confounding factor could well be the heterogeneity in growth factor content from different donor bone sources used in DBM production. DBM is available commercially in a variety of preparations, including gel, powder, granules, and chips.

Despite the generally encouraging results in trauma and spine surgery, DBM has had mixed reviews in the foot and ankle literature. Michelson and Curl[77] published a prospective comparative study (Level II) of 55 patients who underwent hindfoot fusion (11 with subtalar and 44 with triple arthrodesis) and who were offered either autogenic iliac crest bone graft (ICBG) or DBM. They found that DBM did as well as ICBG autograft when comparing fusion rates (seven out of eight patients had successful subtalar fusions and all 29 patients had successful triple fusions with DBM) and time to fusion (three to four months in both groups), while avoiding the increased blood loss, cost, and post-operative pain seen in the ICBG group. Notably, the authors also found that cost in the DBM group was actually significantly cheaper when factoring in the cost of ICBG harvesting. In addition,

Table 2. American Academy of Orthopaedic Surgeons (AAOS) levels of evidence and grades of recommendation

Levels of Evidence	Grades of Recommendation
Level I: High quality randomised controlled trial (RCT) Systematic review of Level I RCTs	**Grade A:** Supported by good evidence (Level I studies with consistent finding) for or against recommending intervention
Level II: Lesser quality RCT Prospective comparative study Systematic review of Level II studies	**Grade B:** Supported by fair evidence (Level II or Level III studies with consistent findings) for or against recommending intervention
Level III: Case control study Retrospective comparative study Systematic review of Level III studies	**Grade C:** Conflicting or poor quality evidence (Level IV or Level V studies) not allowing a recommendation for or against intervention
Level IV: Case series	**Grade I:** Insufficient evidence to make a recommendation
Level V: Expert opinion	

Adapted from the AAOS[83]

Thordarson and Kuehn[78] presented a retrospective series (Level III) of 63 patients undergoing complex hindfoot or ankle arthrodesis procedures who had two different DBM products applied to the fusion site – 37 had Grafton (Osteotech, Eatontown, New Jersey) putty and 26 received Orthoblast (Isotis, Irvine, California). The former group achieved a fusion success rate of 86%, while the fusion rate was 92% in the latter group, and the authors concluded that the union rate was comparable with historical controls, with no difference in efficacy between the two products.

On the other hand, Collman et al[79] reported on a series (Level IV) of 39 patients undergoing arthroscopic ankle fusion who had platelet-rich plasma or DBM used as a bone graft expander. They found that neither substance seemed to increase fusion rates; instead, it was noted that ten of the patients developed minor complications. Crosby et al[80] (Level IV) studied 42 patients undergoing arthroscopic ankle arthrodesis using a combination of DBM and iliac crest bone marrow (ICBM), and described radiological and clinical union rates of 74% and 93% respectively after a mean of 5.5 months. The authors noted that although 85% of patients were satisfied with the outcomes, there was a relatively high complication rate of 55% (pain, nonunion, fractures, pin site infections and hardware problems), and they ultimately recommended against the use of the DBM / ICBM slurry.

Apart from its role in augmenting joint fusion, DBM has also seen application in the management of talar dome osteochondral lesions (OLT) with cystic degeneration, with promising results in a case series by Galli et al[81] (Level IV). The authors reported on their results of subchondral defect reconstruction using DBM in a cohort of 12 patients with medial cystic full-thickness OLTs who had previously failed microfracture chondroplasty. At two years, they found that pain and disability had significantly reduced ($p < 0.001$), with no additional complications seen.

Furthermore, Park et al[82] compared the outcomes of combining autogenous bone marrow with either DBM (percutaneous; ten cases) or freeze-dried allogenic bone chips (open surgery; 13 cases) in patients with unicameral bone cysts of the calcaneus. At a mean follow-up of 49.4 months, complete healing occurred in nine of the 13 cysts treated with bone chips and five of the ten cysts treated with DBM. There were no cases of infection or pathological fractures.

All told, the final chapter is far from having been written on the multitude of roles that DBM may play in foot and ankle surgery. The clinical literature seems promising and supports a Grade B recommendation for the use of DBM in ankle and hindfoot arthrodesis procedures. However, it should be noted that the data is largely retrospective with small samples, and typically involving short-term follow-up. In addition, the evidence for using DBM in treating talar OLTs and calcaneal bone voids is limited to Level IV case series, supporting a Grade C recommendation. Further investigation with prospective randomised controlled trials is required before a firmer recommendation can be made regarding its applications in arthrodesis and the management of bone defects in foot and ankle surgery. In addition, care must be taken not to extrapolate study results for any specific product to the entire family of DBM preparations, owing to the significant degree of inter-product variability in osteo-inductive potential.

Summary

As we have seen, the literature on allogenic bone grafts in primary arthrodesis and osteotomy procedures in foot and ankle surgery generally compares favourably with autogenic bone grafts in terms of fusion rates and clinic outcomes; often with fewer complications owing to the absence of donor site morbidity. Overall, the existing evidence merits a Grade B recommendation for

the use of allogenic bone grafts in these primary procedures (Table 2).[83]

When it comes to bone substitutes, the evidence is less clear, largely owing to the vast array of commercially available product types, and further compounded by the lack of well-conducted prospective clinical trials. Suffice it to say, the best clinical data in foot and ankle surgery comes from the realm of trauma, particularly in studies addressing bone voids in intra-articular calcaneal fractures. Level II and IV studies using both CS and CP in the surgical management of intra-articular calcaneal fractures have yielded good clinical results in maintaining articular reduction and fracture union, while producing minimal complications. As such, the available clinical data supports a Grade B recommendation for the use of CS and CP in treating displaced intra-articular calcaneal fractures. Pertaining to TCP, the data is limited to Level IV case series involving intra-articular calcaneal fractures, and only a Grade C recommendation is warranted.

More recently, the trend toward developing composite bone substitutes has shown some promise in *in vitro* and animal studies. In this regard, CS-CP biphasic ceramics and CP-rhBMP composites seem to have particular potential in achieving synergy by combining different biomaterial properties. Unfortunately, clinical studies in this area are currently lacking and a Grade I recommendation applies to composite bone substitutes as a group.

Lastly, DBM is a product that is appealing to the foot and ankle surgeon owing to its osteo-inductive and osteogenic properties. However, the evidence in the foot and ankle literature mainly comprises small prospective comparative studies and retrospective reviews of hindfoot and ankle fusions (Level II and III), supporting a Grade B recommendation for its use in these arthrodesis procedures. In addition, Level IV series have reported promising results when using DBM in the treatment of cystic talar OLTs and calcaneal bone cysts, supporting a Grade C recommendation for these indications. Nonetheless, significantly more clinical research will be required before firmer recommendations regarding DBM can be made.

Overall, despite the general lack of high-level evidence in the field of foot and ankle surgery, allogenic bone grafts and bone substitutes continue to hold front-line roles in addressing the bone defects encountered in trauma, tumours, and deformity-correction surgery. Furthermore, these products may play important supporting roles in delivering high-dose local antibiotics in orthopaedic infections, improving fixation strength in osteoporotic bone, and promoting bone healing and joint fusion.

To meet this multiplicity of clinical requirements, we must first identify the critère majeur for the successful development of an ideal graft material. Perhaps the answer lies within the four factors that have been promulgated by Giannoudis et al[84] as intrinsic to bone healing; osteogenicity, osteo-inductivity, osteo-conductivity and mechanical stability. Yet, in spite of advances in tissue and materials engineering, the ultimate goal of creating an orthobiological material that fully conforms to all four facets of this "diamond concept" remains an unrealised ideal.

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