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Bone graft substitutes and bone morphogenetic proteins for osteoporotic fractures: what is the evidence?

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K E Y W O R D S

bone graft bone graft substitute bone morphogenetic protein BMP calcium phosphate calcium sulfate fracture osteoporosis osteoporotic fracture

ABSTRACT

Despite improvements in implants and surgical techniques, osteoporotic fractures remain challenging to treat. Among other major risk factors, decreased expression of morphogenetic proteins has been identified for impaired fracture healing in osteoporosis. Bone grafts or bone graft substitutes are often used for stabilizing the implant and for providing a scaffold for ingrowth of new bone. Both synthetic and naturally occurring biomaterials are available. Products generally contain hydroxyapatite, tricalcium phosphate, dicalcium phosphate, calcium phosphate cement, calcium sulfate (plaster of Paris), or combinations of the above. Products have been used for the treatment of osteoporotic fractures of the proximal humerus, distal radius, vertebra, hip, and tibia plateau. Although there is generally consensus that screw augmentation increased the biomechanical properties and implant stability, the results of using these products for void filling are not unequivocal. In osteoporotic patients, Bone Morphogenetic Proteins (BMPs) have the potential impact to improve fracture healing by augmenting the impaired molecular and cellular mechanisms. However, the clinical evidence on the use of BMPs in patients with osteoporotic fractures is poor as there are no published clinical trials, case series or case studies. Even pre-clinical literature on in vitro and in vivo data is weak as most articles focus on the beneficial role for BMPs for restoration of the underlying pathophysiological factors of osteoporosis but do not look at the specific effects on osteoporotic fracture healing. Limited data on animal experiments suggest stimulation of fracture healing in ovariectomized rats by the use of BMPs. In conclusion, there is only limited data on the clinical relevance and optimal indications for the use of bone graft substitute materials and BMPs on the treatment of osteoporotic fractures despite the clinical benefits of these materials in other clinical indications. Given the general compromised outcome in osteoporotic fractures and limited alternatives for enhancement of fracture healing, clinicians and researchers should focus on this important topic and provide more data in this field in order to enable a sound clinical use of these materials in osteoporotic fractures.

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Introduction

Despite improvements in the treatment of osteoporosis, osteoporotic fractures remain challenging to treat. Osteoporotic fractures have an impaired ability to heal [1,2], and often require more time to heal [3–6]. Since osteoporotic bone is less likely to heal on its own and the degree of comminution is generally high, patients often require surgery to repair the fracture. Poor bone quality, however, may complicate implant fixation. Modern angle-stable plate-screw systems and minimally invasive operative techniques have improved the stability of fixation in osteoporotic bone, but success is still not guaranteed. Due to the high porosity and low mechanical strength of osteoporotic cancellous bone, implants are often augmented with bone void fillers in order to

* Corresponding author at: Department of Trauma Surgery University Hospital Giessen-Marburg, Campus Giesen, Rudolf-Buchheim-Str. 7, 35392 Giessen, Germany. improve outcome. Furthermore, decreased expression of bone morphogenetic proteins (BMPs) in osteoporosis combined with the essential general role of BMPs in fracture healing made BMPs attractive for improvement of impaired molecular and cellular mechanisms in osteoporotic fracture patients [7].

Bone grafts can be used to stabilize the implants and provide a scaffold for ingrowth of new bone. BMPS have the potential of de novo new bone formation due to their osteoinductive capabilities [8].

So, these materials are suitable as bone grafts fill voids, provide support, and may enhance the biological repair of the fracture or the fracture defect. This paper is aimed at providing an overview of available evidence for the use of bone graft substitutes and BMPs for the treatment of osteoporotic fractures.

Bone graft substitute materials

The limitations of autografts and allografts led to the development of bone graft substitutes. Both synthetic and

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naturally occurring products are available. Each has its specific composition, which determines its biological and biomechanical behavior [9–11]. As such, each product will have its unique clinical indication(s).

Bone graft substitute materials provide an osteoconductive matrix, but do not contain osteogenic cells or osteoinductive growth factors. Sufficient porosity, especially the presence of interconnected pores determine the ability of bone graft materials to foster ingrowth and osteointegration. Pore sizes of at least 100 μ m are sufficient for osteoid formation and osseous ingrowth [12]. The presence of interconnecting pores may be more critical for osseous ingrowth than the pore size per se [13,14]. Most bone graft substitute materials used for treating osteoporotic fractures contain calcium sulfate or calcium phosphate.

Calcium sulfate is a self-setting, biologically inert, moldable, and osteoinductive material that provides a scaffold for osteoblasts. It rapidly dissolves (without cellular influence) in 6–8 weeks. This may be advantageous in some cases, but if it dissolves too quickly, the augmenting effect may be lost too early, causing implant loosening.

Calcium phosphate materials include synthetic tricalcium phosphate, beta tricalcium phosphate, and coralline hydroxyapatite. The osteoconductive matrix allows osteogenic cells to create new bone under the influence of host osteoinductive factors. Calcium phosphate materials degrade at a slower rate than calcium sulfate materials, with hydroxyapatite being relatively inert. Calcium phosphate materials are available as block, granules, or cement. Blocks and granules are highly porous. They provide less initial biomechanical strength, but strength will increase upon ingrowth of new bone. Calcium phosphate cement is injected as a paste and hardens in vivo. They can be injected or molded into small bone defects and provide structural support with low porosity but good initial compressive strength.

Use of bone graft substitutes for treatment of osteoporotic fractures

Calcium sulfate and calcium phosphate cement have clear benefits when used for screw augmentation, as described in detail elsewhere [15]. Clinical applications described include osteoporotic fractures of the proximal humerus, distal radius, vertebra, hip, and tibia plateau.

Both calcium sulphate and phosphate cements show promising results in the treatment of proximal humeral fractures. Minimally invasive plate fixation (internal locking system (PHILOS) augmented with calcium sulfate cement (MIIG X3; Wright Medical Technology, Arlington, TN, USA) resulted in fewer complications, less reduction loss, and better joint function than plating alone [16]. MIIG 115 also resulted in fewer failed reductions when injected in the medial metaphyseal junction [17]. Reduction failed in 7.1% (1 of 14) grafted patients versus 13.3% (4 of 30) non-grafted patients. Functional outcome was good in both groups. Unfortunately, treatment allocation was not randomized. Augmentation of severely impacted valgus fractures with Norian, an injectable hydroxyapatite cement, resulted in good functional outcome [18]. Augmentation was used after open reduction with screws or buttress plate fixation. All fractures united within the first year, and no patient showed loss of reductions or osteonecrosis of the humeral head.

Clinical benefit of bone graft substitute material use in osteoporotic distal humerus fractures is undecided, as studies show contradicting results. A biomechanical study showed that cement augmentation increased the biomechanical properties in volar plating. This included significant increase in cycles and load to failure, and construct stiffness at loads >325 N as well as less fracture gap movement and screw cutting distance at the holes of the ulnar column [19]. Augmentation with calcium phosphate cement also maintained fixation of unstable distal radius fractures [20]. Garcés-Zarzalejo et al., on the other hand, stated that bone grafts and bone graft substitutes are not mandatory for the treatment of unstable distal radius fractures with locking compression plates [21]. All 60 fractures in their study (treated without graft), healed uneventfully with no significant loss of reduction. A randomized study also showed that augmentation of metaphyseal defects with calcium phosphate bone cement after volar locking plate fixation offered no benefit over plate fixation alone [22].

Two studies showed increased screw hold in spine after augmentation [23,24]. Bone graft substitutes for the treatment of osteoporotic vertebral fractures have been used for kyphoplasty and vertebroplasty. Although pain and the disability scores decreased after balloon kyphoplasty with injectable calcium phosphate cement (Callos), the augmentation properties also decreased within six months, including progression of vertebral height loss and increase in kyphotic angle [25]. Epidural leakage of the paste into the spinal canal was observed in 48.4% (15 of 26) cases. Vertebroplasty using calcium phosphate cement resulted in immediate pain relief and prevented the vertebral body from late collapse and pseudoarthrosis [26]. All 86 patients (99 vertebroplasties) had complete bone union within six months after surgery. Vertebroplasty using bisphosphonateloaded calcium phosphate cement gave good results in sheep [27]. Pedicle screw fixation combined with transpedicular bone grafting with demineralized bone matrix (OsteoSet, Wright Medical Technology, TN, USA) restored and maintained vertebral height successfully, and patients reported less pain at three months follow-up than pre-surgery [28].

Two studies reported that cement augmentation can increase the rotational stability and screw pull-out force in osteoporotic femoral heads [29,30]. Augmentation with calcium phosphate cement enhanced the fixation stability of femoral neck and trochanteric fractures [31]. A meta-analysis, however, found no convincing evidence for the use of any orthobiologic bone cement in the augmentation of fractures of the hip [32].

Current evidence does not unequivocally support the need to use bone graft substitutes in the treatment of osteoporotic tibia plateau fractures. A meta-analysis showed that for tibia plateau augmentation, hydroxyapatite granules, tricalcium phosphate, demineralized bone matrix, allografts, and autografts all resulted in uneventful healing in >90% of cases [33]. The rapid degradation of calcium sulfate may be a disadvantage, as 11% of cases treated with calcium sulfate showed subsidence [34]. Injectable calcium phosphate cements allow to support a reduced joint surface using a noninvasive procedure. Cement extrusion into a joint cavity should be prevented as these cements will not dissolve [35].

Preclinical studies of the role of BMPs in osteoporosis and in osteoporotic fractures

After the key discovery of the osteoinductive potential of BMPs to form ectopic bone reported by M. Urist in 1965 [8], more than 40 different BMPs have been described in the meantime. M. Urist himself called osteoporosis a "bone-morphogenetic auto-immune disorder" [36] and certain important interactions between BMPs in the pathomechanism of osteoporosis could be identified. Genetic polypmorphisms in BMP-2 were found to be responsible for familial osteoporosis [37,38]. The link between BMP-2 and osteoporosis is mainly the role of BMP-2 in the achievement of peak bone mass rather than osteolytic activity during bone loss. Both decreased anabolic activity and reduced gene expression of BMP-2 have been reported in aged rats and

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