THE USE BONE GRAFTS AND SUBSTITUTES IN THE TREATMENT OF DISTAL RADIUS FRACTURES

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Introduction
The interest in developing biomaterials to augment fracture healing continues to grow. This trend is in part fueled by the high market value of these products, but also associated with an increased incidence of fractures related to aging and osteoporosis. New products coming to the market promise early return to function with minimal morbidity; however, indications to use these products, particularly in the treatment of distal radius fractures, remain unclear.

An ideal bone graft material stimulates bone healing and provides structural stability while being biocompatible, bio-resorbable, easy to use and cost-effective. Commercially available products offer various combinations of those features, but not all. Moreover, it is important to understand that different anatomic locations have varying levels of bone forming activity and stability. Therefore, a single study validating the use of a bone graft material in one location may not predict its performance in another anatomic site. In distal radius fractures, the risk of nonunion is minimal. Consequently, bone graft substitutes are primarily used to provide structural stability and perhaps, early return to function. Structural stability is directly affected by the method of fixation, with each fixation technique providing a different level of structural support. Although minimally invasive methods of fixation (pins and external fixation) could effectively be supplemented with bone graft substitutes for added stability, advances in plate design and technology, such as locking plates, makes bone graft substitutes perhaps not as essential. This article will review the biology of bone grafts and the clinical evidence in the use of bone graft substitutes for the treatment of distal radius fractures.
Bone graft properties

There are 4 essential elements for bone healing: (1) osteogenic cells (e.g. osteoblasts or progenitor cells); (2) osteoinductive signals provided by growth factors; (3) an osteoconductive matrix; and (4) adequate blood and nutrient supply (1). Bone graft materials are described on the basis of osteogenicity (presence of bone forming cells), osteoconductivity (ability to function as a scaffold) and osteoinductivity (ability to stimulate bone formation). Following trauma, the resultant fracture hematoma provides a source of hematopoietic cells that produce secreting growth factors (eg. BMP, TGF-β, IGF-II, PDGF) that stimulate osteoblasts and differentiation of progenitor cells (2). This results in metaplasia of mesenchymal cells to produce collagen and proteoglycans, cartilage matrix and differentiate into osteoblasts. Every step of this process is regulated by a number of signaling pathways.

Types of Bone grafts

Based on their biological and physical properties, bone grafts can be divided into three main categories (3) (Table 1):

- **Autograft**
  
  Autogenous bone grafts are considered the standard material because they offer complete histocompatibility and provide the best osteoconductive, osteogenic, and osteoinductive properties (2-4). Autografts usually contain osteogenic cells (viable up to 2 hours in normal saline), and bone matrix proteins. They offer structural support (if harvested with its cortical part) and get incorporated into surrounding bone through creeping substitution (4). They also suffer from resorption, limited availability and viability. The most common source of these grafts is the iliac crest, but they can also be obtained in limited amounts from the tibial crest and olecranon. The iliac crest has frequently been used in the treatment of distal radius fractures (5-13), and for corrective osteotomies (14-17). Although the outcomes based on radiographic parameters and wrist function are satisfactory, iliac crest bone graft harvesting is associated with a number of complications, including donor site pain, hematoma, neuroma formation, chronic unexplained thigh pain, and local infection (18-22). Depending on the series and the amount of bone harvested, the prevalence of one or more of these complications are reported to range from 9% to 49% in various series (23-33). In addition, the procedure itself adds an average of 30 minutes to the operative time. Although iliac crest bone grafting was initially thought to be cost-effective, the direct and indirect costs (postoperative rehabilitation, cost of pain management and time off work) were found to be substantially high (34-37). Due to the high morbidity, increased operative time, and cost, surgeons are seeking alternative materials that can substitute for autogenous bone grafts.

- **Allograft**
  
  Allograft bone is osteoconductive and osteoinductive, but lacks the osteogenic properties of the autograft. Its major advantages include availability in various shapes and sizes and no donor site morbidity. However, it only partially retains the structural strength of the autograft. Although a few studies have shown disease transmission through allografts, recent advances in processing have likely made that a historical and theoretical concern (38-41).

  Allogenic bone is available in the form of demineralized bone matrix, morselized and cancellous chips, corticocancellous and cortical grafts, and osteochondral and whole-bone segments. Despite its low cost, there are only a few studies to date that have tested the performance of this graft on the treatment of distal radius fractures. Herrera et al treated 17 patients with an average age of 70 using cancellous bone chips and external fixation. This study did not include a control group and the authors reported complete incorporation of the
graft in 8 weeks with no loss of reduction (42). Rajan et al compared the performance of allograft bone chips with iliac crest bone graft in a randomized study of 90 patients with large metaphyseal defects. The overall functional outcome between the two groups showed no statistically significant difference. The iliac crest group had higher rates of donor site morbidity, longer operative and anesthesia times, and higher cost of treatment. They concluded that allograft was a reliable alternative to iliac crest bone grafting in the treatment of distal radius fractures (43). Ozer et al conducted a non-randomized study on corrective osteotomies of the distal radius. Twenty-eight patients in two groups had corrective osteotomy and application of volar locking plate with and without allograft bone chips. In all patients, the thicker volar cortical contact was maintained or restored during the surgical procedure, which provided additional stability to the distal radius construct. Osteotomies in both groups healed uneventfully without significant difference in the functional outcome. The authors concluded that if the volar cortical contact was maintained with the volar locking plate, the use of the bone graft substitute did not have a negative effect on functional outcomes (44). Based on these limited number of studies, allograft seems to be a reliable alternative to autogenous bone grafts.

Substitutes

- **Biological Substitutes**
  - **Coral:** Corals have skeletons similar to cortical and cancellous bone. A hydrothermal exchange method converts the coral calcium phosphate to crystalline hydroxyapatite, which has a structure similar to human trabecular bone with a pore diameter of 200 and 500 μm. Despite its natural appearance, the product does not easily undergo osteoclastic resorption, and remains visible on radiographs for a long time. Although it has been used in different areas of the body, only in one study was this product tested in the treatment of distal radius fractures (45). Wolfe et al used coral hydroxyapatite bone graft along with external fixation and K-wires to treat distal radius fractures in 21 consecutive patients. Although the study did not have a control group, authors reported comparable results to historical cohorts treated with autografts, but with significant cost savings by using the hydroxyapatite. They concluded that coral was a safe and effective option as a bone graft substitute.

- **Demineralized bone matrix:** Demineralized bone matrix (DBM), also known as allograft bone matrix, is an osteoinductive and osteoconductive material that provides no structural support to the articular surface (46-50). DBM also revascularizes quickly and acts as a suitable matrix for bone marrow cells. It does not induce an immunogenic reaction because the antigenic surface structure of bone is destroyed during demineralization (51). Consequently, its osteoinductive capacity can be affected by storage, processing, and sterilization methods and can vary from donor to donor and from batch to batch. It is commonly used in structurally stable bone defects to stimulate bone healing and is used in conjunction with autologous bone marrow. There are no clinical studies published to date to test the performance of this product in the treatment of distal radius fractures. Because nonunion is rarely a concern for distal radius fractures, indication to use a non-structural bone graft substitute is limited.

- **Synthetic Substitutes**
  - **Factor-Based Substitutes (TGF-β, PDGF, FGF, BMP):** The family of transforming growth factor-beta-like molecules and the related family of bone morphogenic proteins (BMPs) 2 through 10 have been shown to induce primitive mesenchymal stem cells to differentiate into chondrocytes and osteoblasts (52). Among those, rhBMP-7, also called osteogenic protein-1 (OP-1) is an osteoinductive growth factor and is the only one used to treat distal radius fractures (53). In a randomized study including 30 patients with distal...
radius malunions, Ekrol et al compared rhBMP-7 and iliac crest bone grafting following corrective osteotomies. Bony fixation was achieved either through non-bridging external fixation or the pi-plate. The authors concluded that rh-BMP7 does not confer the same stability as the iliac crest bone graft when used in conjunction with non-bridging external fixation, resulting in delayed union and osteolysis. Although healing has occurred when used with the pi-plate, overall healing at the osteotomy site was at a slower rate for the rh-BMP7 group than the iliac crest bone graft group (53).

- Ceramic-Based Substitutes: These are inorganic materials hardened by heat and subsequent cooling. Calcium Hydroxyapatite (CaHA) is a biocompatible ceramic that is a highly crystalline form of calcium phosphate. Its composition of calcium-to-phosphate atomic ratio is 1.67, which makes it very similar to the mineralized phase of bone. The mineralized phase of bone is widely known for providing a rigid structure to support and protect the internal organs, but it is also responsible for the storage of ions such as calcium, magnesium, and sodium. This property makes it important in maintaining the proper concentrations of ions in the extracellular fluids. The unique similarity of CaHA to mineralized bone accounts for its osteoconductive potential and excellent biocompatibility (54-56). Sakano et al. tested CaHA on 25 patients with unstable distal radius fractures treated with external fixation (57). Despite a minor loss of radial height, they concluded that CaHA was a useful adjunct to external fixation and a reliable alternative for bone grafting. Later, Huber et al. reported the results of 22 distal radius fractures of AO types C2 and C3 fixated using a non-locking palmar plate and CaHA. All patients had an uneventful healing with no loss of reduction (58). In a recent study of comminuted distal radius fractures fixated with volar locked plating in elderly patients, Goto et al reported increased ulnar variance in the group without bone graft compared to the group supplemented with CaHA (59). They concluded that a locking plate system would benefit from this bone substitute especially in comminuted intra-articular fractures of the distal radius.

Tricalcium Phosphate (TCP) is also a bioabsorbable and biocompatible material with a chemical composition and crystalline structure similar to that of the mineral phase of bone. Its rate of biodegradation is higher when compared with hydroxyapatite (60). An inflammatory reaction and the resultant osteolysis around the graft material become visible on radiographs (61-63). Scheer and Adolfsson reported on 17 patients who underwent corrective osteotomies of the distal radius fixated with 2 different kinds of plates (dorsal and volar locking) and supplemented with TCP. Although they noted a slight loss of height at the final follow-up along with osteolysis around the graft in 10 out of 14 patients, they recommended TCP as an alternative to iliac crest bone grafting (62). In a recent study on 39 patients with angular malunions of the distal radius, patients were randomized into two groups, those augmented with TCP and those without TCP, and then both fixated with a dorsal plate following corrective osteotomies (63). The authors reported no advantage in using TCP as a bone substitute with regards to functional and radiographic outcome.

Finally, calcium phosphate (CaP) is the second most commonly tested material after autograft in the treatment of distal radius fractures (64-69). Calcium phosphate cement offers the advantage of being freely moldable and adaptable to bone defects, as well as having chemical and physical characteristics similar to the mineral phase of bone. Calcium and phosphate are mixed with a buffer solution to form an injectable material. Sanchez-Sotelo and Munuera prospectively compared casting of acute fractures with and without CaP on 110 patients more than 50 years of age. They concluded that the CaP group showed better range of motion, grip strength, and reduction of pain with significantly lower rate of malunion (64). Two randomized prospective studies by Cassidy et al. (65) and Kopylov et al. (66) compared external fixation without bone graft and casting with calcium phosphate showed improved grip strength and range of motion in the calcium phosphate groups at the
6- to 8-week interval. However, both studies reported no differences beyond 3 months (65,66). Calcium phosphate was found to accelerate rehabilitation. Other studies on the use of calcium phosphate in the treatment of distal radius fractures are uncontrolled case series to show it is a safe material and that it provides additional support at the fracture site (67,68). One consistent issue was extra-osseous distribution of the material, which in some series resulted in up to 70% of the subjects experiencing loss of reduction if no other method of fixation was used.

- Implications on Current Practice

The use of bone grafts in the treatment of distal radius fractures seems to be determined by tradition, training and personal experience (70). This is mostly due to the lack of robust evidence. A recent Cochrane Database analysis of randomized clinical trials concluded that there was insufficient evidence regarding the functional outcome and safety in the use bone grafts and substitutes for the treatment of distal radius fractures (71). In the absence of sufficient level 1 evidence, one can only form his/her opinion based on the best evidence available. As summarized in this review, autogenous bone grafts come associated with significant morbidity and cost. Bone graft substitutes do not cause donor site morbidity, but can still be expensive and do not possess all of the features of an autogenous graft. In this case, perhaps, the first question that needs to be addressed is whether it is necessary to use bone grafts or substitute in every distal radius fracture with dorsal comminution? The quality of the bone, size of the bone defect, blood flow to the fracture site, and method of fixation/immobilization all affect the healing process and maintenance of reduction in distal radius fractures. Though it is not clear as to what constitutes a significant bone defect, in cases of open distal radius fractures with bone loss, or in corrective osteotomies requiring substantial lengthening, the use of iliac crest bone graft with cortical support is better justified. In case of a more common scenario when there is dorsal comminution without tricortical defect, if the fracture is amenable to be fixated with an angled locking plate and the thick volar cortex contact is restored, the use of a bone graft/substitute may not be necessary as long as the articular congruity is well-supported and maintained by the use of distal locking screws as it has been repeatedly shown in a number of previous reports (72-77). Other minimally invasive, and less rigid methods of fixation, such as external fixation, K-pin and cast immobilizations, however, may still need to be supported by a graft/substitute (64-66), which brings the second relevant question to be addressed. If the use of the bone graft or a substitute were deemed necessary, what is the ideal material? We advocate the use of iliac crest bone graft in cases of significant bone loss and nonunion. In all other conditions, the use of calcium phosphate and allograft bone chips, due to their ease of use, relatively low cost and potential to provide structural support seem to provide satisfactory healing and functional recovery and can be used as alternatives to autogenous bone grafting. However, no graft or substitute is ideal for all injuries. Indications and choice of graft substitute should be based on the needs of the individual patient until further comparative research clarifies the indications and most appropriate material for a given fracture and clinical situation.

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References


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Table 1

Table is modified from Laurencin's classification (1). OG: Osteogenic, OI: Osteoinductive, OC: Osteoconductive, SS: Structural Support.

<table>
<thead>
<tr>
<th>Bone Grafts and Substitutes</th>
<th>OG</th>
<th>OI</th>
<th>OC</th>
<th>SS</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autograft</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(*)</td>
<td>++++/++++ (†)</td>
</tr>
<tr>
<td>Allograft</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>(*)</td>
<td>/++</td>
</tr>
<tr>
<td>Biological</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Coral</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>++/+++</td>
</tr>
<tr>
<td>Collagen type 1</td>
<td>-</td>
<td>+</td>
<td>(+**)</td>
<td>-</td>
<td>(No studies on DRFx)</td>
</tr>
<tr>
<td>Demineralized bone matrix</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Synthetic</td>
<td></td>
<td></td>
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<tr>
<td>Factor-Based (TGF-β, PDGF, FGF, BMP)</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>++++/++++ (‡)</td>
</tr>
<tr>
<td>Cell-Based (Mesenchymal stem cells)</td>
<td>+</td>
<td>-</td>
<td>(+**)</td>
<td>-</td>
<td>(No studies on DRFx)</td>
</tr>
<tr>
<td>Ceramic-Based (Calcium HA, tricalcium phosphate, calcium phosphate cement)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Polymer-Based</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>(No studies on DRFx)</td>
</tr>
</tbody>
</table>

(*) If the graft includes cortical bone. HA: Hydroxyapatite.

(†) Including direct and indirect costs, data based on studies of spinal fusion and tibial nonunions.

(‡) Only Rh-BMP is tested on distal radius fractures.

(**) If used with a carrier.