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Bone Graft Substitutes in the Treatment of Distal Radius and Upper Limb Injuries

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Over the years, autologous and allogeneic bone grafts have been used to supplement techniques in internal and external fixation to treat fractures in the upper extremity. The development of a variety of bone graft substitutes has allowed the use of these materials when there are significant comorbidities in harvesting autograft or when the use of allograft is undesirable. With recent advances in the synthesis, testing, and employment of bone graft substitutes, these materials have been used in the treatment of upper extremity fractures to fill a bony defect, to correct skeletal deformity, to restore structural integrity, and to stimulate bone healing. In this chapter, we will identify the major types of graft substitutes available or in development and review their unique features and capabilities. The authors have no financial interest in any of these products; rather, the cases included in this review are included solely as examples of the various types of commercially available products. The indications and potential applications for graft substitutes in the distal radius and the upper limb will be discussed, as we contemplate the future direction in the research and development of new graft substitutes.
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Autologous and allogeneic bone grafts have long been used in orthopedic surgery to augment fixation in the treatment of challenging fractures and skeletal deformities. However, when autograft harvest presents significant comorbidities or when allograft use is undesirable, alternatives to conventional bone graft materials are needed. With recent advances in biochemistry and material science, bone graft substitutes promise to revolutionize the surgical treatment of fractures and challenging deformities.

An extensive variety of bone graft substitutes exists to fill bony gap, restore structural integrity, correct deformity, and stimulate bone healing. Currently, surgeons may choose graft substitutes ranging from synthetic agents to biological-based materials and from inorganic substances, such as calcium sulfate or silicate to physiological compounds, such as collagen and hydroxyapatite (HA). Increases in patient demands coupled with further advances in technology will lead to more routine use of these materials in the future (Fig. 1).

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With an expansion in the indication and incidence of bone graft substitute use, medical device companies are motivated to create innovative and effective products. However, much of the corporate-sponsored research has focused on gaining regulatory approval for wider indications in product application, and a noticeable absence of well-designed and controlled studies exists to compare the various agents in terms of their efficacy and safety. Furthermore, prohibitive expenses currently limit routine use of many biologically active agents.

In this chapter, we will identify the major types of bone graft substitutes available or in development and review their unique features and capabilities. The indications and potential indications for graft substitutes in the distal radius and the upper limb will be discussed. We will end by talking about some of the challenges facing the use of bone graft substitutes, as well as the future directions in research and development of graft substitutes and tissue engineering.

Bone Composition and Biology

In the 1960s, Urist demonstrated the remarkable ability of bone to induce the formation of itself (autoinduction).[1] Since then, bone has been found to be a physiological composite of mineral, protein, and cellular elements with unique proper-

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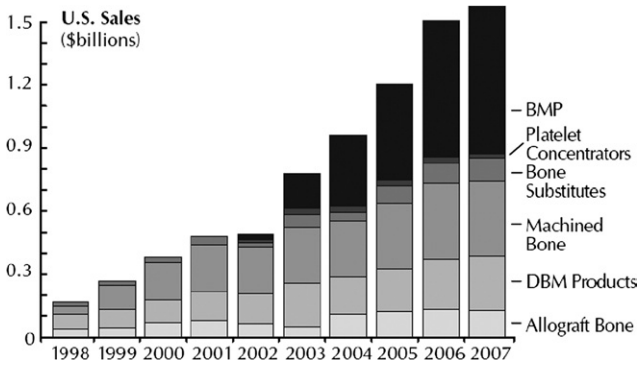

Figure 1 US sales of bone graft and bone substitutes, 1998-2007. *Source: Orthopedic Network News.*

ties. The structural mineral and protein matrix provides a scaffold for new bone formation (osteoconduction). Proteins, including growth factors and cytokines, stimulate and signal new bone growth (osteoinduction). New bone formation, that is, osteogenesis, requires the presence of osteoprogenitor cells in some milieu that favors osteoinduction and osteoconduction.

HA is the most abundant form of calcium phosphate in the mineral phase of bone (Fig. 2). Its weakly crystalline structure permits ionic exchange with carbon and the hydroxide ion and flux between different mineral precursors, such as calcium phosphate and tricalcium phosphate (TCP). This instability allows bone activity and tolerance of bone substitutes. HA deposits on a matrix of type I collagen in which cellular activity occurs to create the underlying latticework of mammalian bone.

Bone resorption refers to the disappearance of native bone or bone graft after initial implantation. Acute resorption can occur by chemical dissolution, by physical disruption, such as microfracture, or by phagocytosis as seen in a foreign body reaction. The slower process of bone remodeling may also account for resorption. True remodeling is a cellular activity of bone deposition and removal based on environmental and physiological stresses. Because different materials have varying resistance to dissolution and remodeling, the surgeon must consider these effects when choosing a substitute.

Confusing Nomenclature and Confounding Regulation

Biological graft materials have been used to fill bone voids, to augment fixation of fractures, and to stimulate bone growth. Clear indications for their use are often lacking, despite the substantial growth of the industry in the past few years. Limited clinical studies and scientific data, coupled with questionable advertising claims, produce a confusing landscape of bone substitutes and proteins. For example, the simple name of the product often changes from the time of development to the time of marketing, and is further altered when the manufacturer changes hands or is purchased by another company.

Even more confounding is how bone graft materials are categorized and regulated. Various agencies in the Food and Drug Administration (FDA) are charged with regulating bone products. The Center for Biologics Evaluation and Research of the FDA monitors the processing of human and animal bone and soft tissues, whereas biological cements are monitored by the Center for Devices and Radiological Health. The orthopedic panel of the Center for Devices and Radiological Health reviews and regulates growth factors as well as conventional internal fixation devices, but the Center for Drug Evaluation and Research reviews and regulates injectable proteins. Future genetically altered materials will be reviewed and regulated by the Center for Biologics Evaluation and Research.

The lack of a single government agency to regulate bone graft materials has led to confusion in their nomenclature, classification, and regulation. For example, the different arms of the FDA categorize these similar products at the same time as devices, drugs, or biological materials. Rather than treating these materials as related substances with shared properties, these products are regulated as separate entities, each with its separate codes and regulations.

Bone Grafting in Distal Radius Fractures

Trials of many bone-graft substitutes have focused on the treatment of distal radius fractures, as this classic osteoporotic fracture represents a common injury with a reliable mechanism and reproducible fracture pattern for study. This fracture typically presents with a displaced comminuted dorsal radial cortex, and variations, including involvement of the medial column, radiocarpal joint, radial styloid, and the distal radioulnar joint. Anatomic reduction in the articular surface with restoration of the radial height, radial inclination, and volar tilt is the central tenet to current treatment. Treatment modalities are selected depending on the fracture pattern and patient factors, and range from closed reduction and casting to various surgical techniques, including percutaneous pinning, open reduction internal fixation, and external fixation.

Autogenous bone grafting has played an important role in the treatment of complex fractures of the distal radius. In cases of severe fracture comminution or bone gaps, loss of bony integrity or alignment, and patients with poor bone stock secondary to advanced age or osteoporosis, the use of autogenous graft has supplemented fixation techniques and led to improved bone healing.[2] However, graft site morbidi-

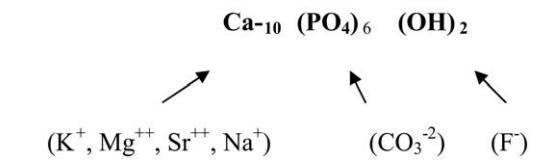

Figure 2 HA: the mineral backbone.