Soluble Calcium Salts in Bioresorbable Bone Grafts

Joseph D. Gresser, Kai-Uwe Lewandrowski, Debra J. Trantolo, Donald L. Wise, and Yung-Yueh Hsu

1. Introduction

Bone is the second most implanted material in the body, after blood. There are over 450,000 bone graft (BG) procedures annually in the United States (2.2 million worldwide), with a market potential of $400–600 million. Autografts and allografts are used in current BG procedures to repair defects caused by surgery, tumors, trauma, implant revisions, and infections, and also for joint fusion. However, drawbacks, such as the need for a second surgery to retrieve the graft (autograft), or the risk of viral infection, contamination, and long-term complications (allografts), make bioresorbable BG substitutes viable alternatives to autografts and allografts. Only 10% of these procedures use synthetic materials, because the currently approved synthetic grafts are considered to be inferior to the use of autograft or allograft. Significant problems include lack of resorbability, inclusion of animal- or marine-derived components, and poor handling characteristics.

Therefore, development of bioresorbable BG substitutes seems eminently worthwhile. They could serve immediately as an osteoconductive path to bone reconstruction. Ultimately, one could incorporate an osteoinductive growth factor, such as a bone morphogenic protein (BMP) to accelerate healing. The developmental goals of a biodegradable for void filling should address degradation (1), porosity (2), in situ curing properties, and the ultimate flexibility in formulation, to permit use in reconstructive situations calling for varying rates of degradation and bony recovery.

Currently approved synthetic products have significant disadvantages. The authors have developed a BG substitute that does not contain biological material, either collagen or protein, and does not stay in the bone after the healing process has occurred. This bioresorbable BG substitute is made from the unsaturated polyester, poly(propylene glycol-co-fumaric acid) (PPF), which can be crosslinked in the presence of soluble and insoluble calcium (Ca) filler salts, and grouted directly in the void created by removal of a cyst or infected bone, or from trauma. The graft material could provide an osteoconductive pathway by which bone will grow in faster. Several clinical indications would benefit from such a bioresorbable osteoconductive BG substitute.

2. Clinical Indications for Bioresorbable BG Substitutes

Immediate applicability may be for reconstruction of defects caused by surgical debridement of infections, previous surgery, tumor removal, trauma, and implant revisions, and for joint fusion.
the pelvic veins to the lumbar veins, and, under conditions of increased abdominal pressure, retrograde flow through the paravertebral venous plexus of Batson. The complications of vertebral OM include extension of the infection to the adjacent disk space, and extension to retropharyngeal, mediastinal, peritoneal, and meningeal sites, depending on the vertebrae involved. In general, the clinical course of OM will depend on the characteristics of the causative organism, the route of the infection, and the age of the patient.

With continuation of the bone infection, chronic inflammatory cells (lymphocytes, histiocytes, plasma cells), proliferating fibroblasts, and reactive new bone formation contribute to the microscopic picture of chronic OM. Reactive new bone formation occurs. The elevated periosteum is stimulated to form new bone, which surrounds the underlying infected and inflamed bone with a bony envelope, termed an “involucrum.” If chronic OM is undiagnosed or inadequately treated, the avascular dead tissue, pus, and bacteria may remain isolated within an area of bone fibrosis and sclerosis, and give rise to recurrent episodes of acute OM. The treatment of these chronic bone infections usually requires, in addition to antimicrobial therapy, surgical intervention to drain abscesses and remove necrotic tissue. Reconstruction of the surgical defect can be accomplished with the authors’ bioreabsorbable BG substitute filler. In fact, it may prove to be particularly suitable for this application, because it is bioreabsorbable.

2.1. Surgical Debridement of Osteolysis

In osteomyelitis (OM), pathogenic microorganisms can invade bone by hematogenous spread, direct extension from a contiguous site of infection, and direct introduction. Acute hematogenous OM occurs predominantly in children, and before the age of epiphysial closure. It typically originates in the metaphysis of long bones in the region of most rapid growth and greatest vascularity (Fig. 1). The bloodborne bacteria are carried to the marrow space by way of the nutrient artery. The initial site of infection within a particular bone is determined by the vascular anatomy as related to the epiphysial growth plate. Hematogenous OM in adults rarely involves the long bones, but usually occurs in the vertebrae, which are generally highly vascular. The hematogenous spread of infection can occur by way of the nutrient branches of the spinal artery or by flow from the pelvic veins to the lumbar veins, and, under conditions of increased abdominal pressure, retrograde flow through the paravertebral venous plexus of Batson. The complications of vertebral OM include extension of the infection to the adjacent disk space, and extension to retropharyngeal, mediastinal, peritoneal, and meningeal sites, depending on the vertebrae involved. In general, the clinical course of OM will depend on the characteristics of the causative organism, the route of the infection, and the age of the patient.

With continuation of the bone infection, chronic inflammatory cells (lymphocytes, histiocytes, plasma cells), proliferating fibroblasts, and reactive new bone formation contribute to the microscopic picture of chronic OM. Reactive new bone formation occurs. The elevated periosteum is stimulated to form new bone, which surrounds the underlying infected and inflamed bone with a bony envelope, termed an “involucrum.” If chronic OM is undiagnosed or inadequately treated, the avascular dead tissue, pus, and bacteria may remain isolated within an area of bone fibrosis and sclerosis, and give rise to recurrent episodes of acute OM. The treatment of these chronic bone infections usually requires, in addition to antimicrobial therapy, surgical intervention to drain abscesses and remove necrotic tissue. Reconstruction of the surgical defect can be accomplished with the authors’ bioreabsorbable BG substitute filler. In fact, it may prove to be particularly suitable for this application, because it is bioreabsorbable.

2.2. Treatment of Solitary Lucent Bone Lesions

Another potential application of a bioreabsorbable BG substitute is in the reconstruction of defects created during the surgical treatment of solitary lucent bone lesions. The differential diagnosis includes fibrous dysplasia, osteoblastoma, giant cell tumor, metastasis/myeloma, aneurysmal bone cyst, chondroblastoma/chondromyxoid fibroma, hyperparathyroidism (brown tumors)/hemangioma, nonossifying fibroma, eosinophilic granuloma/enchondroma, and solitary bone cyst (Fig. 2). Most expansile, lucent lesions are located in the medullary space of the bone and tend to occur in a “favorite” part of the bone.

Fig. 1. (A) AP and (B) lateral radiographs of the right knee. (C) axial cut and (D) sagittal MRIs (T1-weighted) of the right knee, showing osteomyelitis in the proximal tibial plateau.