Successfully managing bone defects remains a considerable challenge in orthopaedic practice. From tibial nonunions to acetabular defects to spinal tumours, the difficulty of achieving a stable, functional skeleton affects many of our patients. Donor site morbidity and the limited volumes of autologous bone graft have led to the development of bone graft substitutes. The goal of this review is to outline the biological principles of these substitutes as a guide to understanding their utility in clinical practice.

**Bone grafting biology**

Several processes are involved in the successful reconstitution of a bone defect: osteogenesis, osteoconduction and osteoinduction.

Osteogenesis is the formation of new bone by cells derived from precursors such as mesenchymal stem cells or pre-osteoblasts that are in the grafting material. In appropriate host conditions, these precursors proliferate and differentiate and then generate new bone.

Osteoconduction is the provision of a scaffold over which new bone formation can be propagated. This facilitates the development of new bone, and also integration with the host skeleton. The effectiveness of an osteoconductive material is dependent on a number of factors such as porosity and surface roughness.

Osteoinduction is the proliferation and differentiation of bone-producing cells from precursors such as mesenchymal stem cells in the surrounding host tissues. This is stimulated by a number of molecules such as inflammatory cytokines and bone morphogenetic proteins that can be contained in the grafting material.

**The ideal bone graft material**

The most effective grafting material would provide signaling molecules, osteoprogenitor cells and a supporting scaffold to support osteoinduction, osteogenesis and osteoconduction. An ideal material would also be readily available in a range of quantities at low cost, and have minimal toxicity and morbidity associated with its use. No bone graft material currently available meets all of these requirements.

**Classification of bone graft substitutes**

1. **Allograft-based substitutes**

   Allograft provides an osteoconductive framework, and can also exhibit osteoinductive properties if the signaling molecules that lie within the matrix are preserved. Structural allograft has a long history of successful implantation, although problems with union to host bone are still present.

   Demineralised bone matrix (DBM) is prepared from allograft subjected to acid to remove the mineral component, and is composed of 90% Type 1 collagen and 10% non-collagenous proteins. It is both osteoconductive and osteoinductive, although the osteoinductive property of DBM varies from donor to donor and with different preparation and storage conditions. It has been shown to be effective in a number of clinical situations such as bone defects, fractures and arthrodesis.

2. **Factor-based bone graft substitutes**

   The signaling molecules involved in osteoinduction have been extensively investigated. Bone morphogenetic proteins (BMPs) are part of the TGF-β super-family, and some (BMP-7 and BMP-2) are now produced and sold commercially.

   Platelets are a rich source of signaling molecules such as PDGF, TGF-, VEGF and EGF. Commercially available products isolate the patient’s platelets and allow them to be transplanted into grafting sites, in order to supplement the levels of growth factors.

3. **Cell-based substitutes**

   Bone marrow aspirates have been used, but are an inefficient method of obtaining osteoprogenitor cells, and most of what is obtained is red blood cells. Devices to concentrate the cells have not been proven effective.

   Modern culture techniques allow mesenchymal stem cells to be isolated from a bone marrow aspirate and cultured in vitro, expanding the number of cells and discarding the non-bone cell precursor cells such as haematopoietic cells. In the presence of dexamethasone, ascorbic acid and β-glycerophosphate, mesenchymal stem cells will differentiate into osteoblasts in culture. This application is not yet widely available for clinical purposes, but is the focus of much research.

4. **Ceramic-based bone graft substitutes**

   The primary inorganic component of bone is hydroxyapatite, and calcium phosphate-based ceramics attempt to mimic this material. They include hydroxyapatite itself, β-TCP, and bioactive glass. They have been used since the 1980s. Ceramics have no osteogenic or osteoinductive properties and must provide only minimal structural strength. Osteoid is laid down directly on the ceramic, and then remodeled into bone. Injectable forms are available commercially.
5. Polymer-based bone graft substitutes
Polymers represent a broad group of bone graft substitutes with varying properties. They can be natural or synthetic, degradable and non-degradable. By and large they are not osteoinductive, but can be osteoconductive. Some provide a degree of mechanical support.

6. Miscellaneous
Substitutes such as Coral are difficult to classify. Coral calcium phosphate can be converted to coralline hydroxyapatite. This has a similar structure and pore size to human bone, and has also been used as a carrier for bone growth factors.

Summary
The search for alternatives to autologous bone graft has led to the development of many substitutes with varying degrees of success. No bone graft material currently meets the criteria of the ideal bone graft. Cell-based therapies are currently the most promising research area.

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References