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Edison Explains

Bone grafts

What are bone grafts and bone graft substitutes and how do they help treat bone defects and voids?

What are bone voids and grafts?

A bone void is a cavity in bone that results from a failure of the bone's self-healing process. Healthy bone tissue can be lost or damaged as a result of trauma, infection, tumours and complications from joint replacements. A bone graft is a material used to fill a bone defect or void.

What causes bone voids?

Trauma is a common cause of bone voids. When a traumatic defect is too large or bone fragments are too far apart, the void will not heal correctly.

Osteomyelitis is a difficult-to-treat bacterial infection of the bone tissue that can lead to bone voids. It is often a complication of an underlying condition, such as a bone fixation procedure after trauma, especially if an open fracture is present. If not managed during the acute phase, osteomyelitis can become chronic and lead to bone destruction.

Osteomyelitis is also a common symptom of the chronic foot wounds caused by diabetes, which become contaminated and colonised by bacteria. Diabetic foot ulcers commonly lead to repeated infection and chronic osteomyelitis, frequently resulting in multiple partial amputations.

Bone voids can also occur due to revision arthroplasty. Revision arthroplasty can be subdivided into aseptic loosening and periprosthetic joint infections. Both are potential complications of joint replacement procedures.

How do surgeons manage bone voids?

A bone void may be treated by a surgeon using a bone graft, bone graft substitute or bone void filler.

For example, after removing a patient's infected hip implant, the surgeon will clear away the infected bone tissue, which will leave some voids.

The surgeon will likely replace the implant and fill in the gaps with a graft or filler.

Osteoconductive material serves as a scaffold for bone growth, while osteoinductive and osteogenic substances help create new bone. If treated properly, bone can regenerate completely due to constant bone remodelling – a balance maintained by bone-producing cells (osteoblasts) and osteoclasts, which break down and resorb bone tissue.

What types of bone graft are available?

Autograft is the gold standard for bone grafts and the most commonly used procedure. The intervention involves grafting the patient's bone, taken from the iliac crest at the hip.

Autograft is osteoconductive, osteoinductive and osteogenic, the three properties needed to achieve bone remodelling. Although autograft works well, it provides a limited amount of bone for filling cavities and requires a separate surgical intervention, which carries the risk of blood loss, infection and pain.

Another solution is allograft. Here, bone is taken from deceased or living donors. Allograft is osteoconductive, but there is little evidence that osteoinduction and osteogenicity are present in the bone after the processing required to store it in a bone bank. Allograft is also at a disadvantage compared to autograft due to extensive infrastructure requirements and the potential for disease transmission.

Donor allograft can be further processed to create demineralised bone matrix (DBM), a type of allograft that retains much of the bone's protein content while reducing its mineral content.

The original idea was that the protein content, including growth factors, would act as potent osteogenic/osteoinductive agents. Although there is some evidence supporting DBM's properties compared to allograft, this type of graft is soft so lacks mechanical strength. DBM is

Edison's Insight

'There are over 60 companies active in the orthobiologics market and many of the key players have their own range of products to complement their surgical hardware products. Investors may find more attractive opportunities on the more innovative end of the orthobiologics market, where some companies have managed to create differentiated products. For example, antibiotic-eluting bone graft substitutes add clinical value and can command premium pricing.'
Jonas Peciulis, Edison healthcare analyst

therefore unable to act as a mechanical support for damaged bone.

Synthetic bone graft substitutes are manufactured but still have some of the same beneficial properties as materials from biological sources.

What are synthetic bone graft substitutes made from?

Ceramic materials are the most common choice and are based on types of calcium sulphate or calcium phosphate, or a combination of the two.

Calcium sulphate was the first material used in synthetic bone graft substitutes. The main drawback of calcium sulphate grafts was quick resorption over six to eight weeks and a lack of support for bone growth. The addition of calcium phosphate substantially improved resorption time and over the last two decades, different combinations of these materials have been explored in various forms.

Other materials used less frequently for synthetic bone graft substitution include bioglass, degradable and non-degradable polymers and other biomaterials.

Historically, the perceived downside of synthetic bone grafts was a lack of signalling cues present in naturally derived materials, making them osteoconductive only. However, they are an attractive option as they can be manufactured in unlimited amounts, given they do not require natural bone. In addition, a synthetic graft's mechanical and chemical properties can be tailored, so use is more predictable.

What companies are active in this space?

There are many companies that manufacture and sell synthetic bone graft substitutes and allograft products. According to Evaluate Pharma, there are 522 bone void filler brands marketed in the US, marketed by 67 companies. This compares to 311 in Europe, marketed by 50 companies.

Major medical device companies operate in this 'orthobiologics' market segment, offering their own bone graft substitutes or allograft products to complement hardware products such as total knee implants.

These include Baxter International, Exactech, Globus Medical, Johnson & Johnson, Medtronic, NuVasive, Smith & Nephew, Stryker and Zimmer Biomet.

To our knowledge, the best-selling bone graft substitute is Infuse, a recombinant bone morphogenic protein (Medtronic), which achieved $763m in sales in 2017.

How can bone graft substitutes help manage bone infection?

The risk of infection due to trauma and orthopaedic surgery is particularly concerning when dealing with bone damage. Around 30% of open fractures and 2–5% of surgically treated closed fractures become infected. The percentage is much smaller in joint replacement procedures (1–2%) but is still a major issue.

In the case of infection, antibiotics can be delivered systemically and/or locally. Although there are various materials used for delivering antibiotics locally, in situations where bone grafting is needed, their combination in a bone graft substitute is a natural solution.

Osteoset-T (Wright Medical) was the first synthetic bone graft substitute to include anti-infectives, using calcium sulphate with the antibiotic tobramycin, and was CE marked by European regulators in the late 1990s. Unfortunately, calcium sulphate alone is not an ideal synthetic bone substitute. It is minimally osteoconductive, quickly resorbed and not injectable.

Bonesupport has developed a bone void filler, CERAMENT G/V, which contains an antibiotic (either gentamycin or vancomycin). The company's patented CERAMENT synthetic bone graft consists of powder and a liquid component; the powder is a 60% calcium sulphate to 40% hydroxyapatite mix.

Top-line data from a recent Phase III study showed CERAMENT was non-inferior to autograft in treating tibia plateau fracture defects.

Other antibiotic bone graft substitutes that are resorbable include STIMULAN (Biocomposites), HERAFILL G (Heraeus), and PerOssal (aap Implantate).