



## Bone Substitutes in Management of Benign Bone Tumors, Review of Literature

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Article History	Abstract
Received: 06 June 2023 Revised: 05 Sept 2023 Accepted: 18 Nov 2023	<i>Intralesional excision or curettage is commonly used to treat benign and low-grade malignant bone tumors. The resulting defect can be treated with a variety of materials, such as autologous bone grafts, allografts, or synthetic materials like polymethylmethacrylate or composite alternatives. Because it is osteogenic, osteoinductive, and osteoconductive, autologous cancellous bone is often considered the gold standard of transplant material. However, issues including transplant size limitations, wound-related complications, and prolonged donor site pain have limited its usage in clinical practice. Concerns about immunogenicity and infection have also hampered the use of demineralized freeze-dried allografts and xenografts. As a result, synthetic materials have sparked substantial interest in orthopedics, and a variety of bone graft alternatives are now commercially accessible.</i>
CC License CC-BY-NC-SA 4.0	<b>Keywords:</b> Calcium Phosphate, Benign Tumors, Bone Autograph, Substitutes

### 1. Introduction

Benign bone tumors and tumor-like lesions are a broad collection of conditions of the bone that are far more common than malignant tumors among all skeletal cancers. Anyone of any age can be impacted, and any bone may be affected. They are rarely symptomatic and are commonly discovered by chance during an incidental radiography check [1]. Biopsies are required for symptomatic bone tumors that develop quickly or are radioactively ambiguous. Following histological examination, the necessary therapy is commenced. The therapy of choice is intralesional curettage, which and void repair. Several bone defect correction options have been described, including cancellous bone autograft as the most common. This method has numerous advantageous grafting features [1,2]. Yet there are several limitations to natural bone transplanting, such as donor area mortality, a lack of grafts that are adequate in size and shape, and further extraction operations. The incidences of complications have been reported to be 20%. Allografts, too, have a high complication rate [3]. Many synthetic bone substitute materials have been created to address the drawbacks of autografts and allografts. In contrast to bone harvesting operations, synthetic ceramic materials lower the chance of complications following surgery caused by

the harvesting technique, removing the requirement for a secondary surgical area and the risks related to a low transplant output. The optimal synthetic bone replacement should be made of a highly osteoconductive material with a high degree of porosity [1,4]. Surgical curettage is the most commonly used surgical treatment for benign bone tumors and is shown to be a suitable strategy with minimal relapse, even for the management of low-grade chondrosarcomas (CS). Yet, the handling of following bone deficiency remains highly contentious, with therapeutic options ranging from no treatment to the use of various filler substances. While excellent clinical results have been demonstrated in lesions without grafting, the danger of residual fracture remains a worry since natural bone healing might not be effective for all bone defects larger than a specific size [5,6]. For several years, cancellation allograft bone was the graft material preferred for bone deficiency rebuilding. However, even though curettage and bone grafting are frequently employed in the management of included defects in orthopedic tumor surgery in general, little information on clinical outcomes and incidences of complications has been released in the past few years [5]. Bone replacements have been divided into two main groups: biological replacements for bones and synthetic bone substitutes [7]. Bone is an intricately designed complicated organ. The inner matrix, cancellous bone, is a porous network of trabecular structures red marrow, and vasculature that serves as the location of hematopoiesis while additionally offering rigidity, mobility, and reducing bone weight. Cortical bone, the outer matrix, is a thick region with vascular canals that can endure a high mechanical strain and resist bending and torsional stresses. The periosteum, or outermost layer of bone, is a thin vascular membrane that contains osteoblasts and progenitor cells and is capable of generating new bone. The matrix of extracellular cells serves as a scaffold for bone deposition, reinforces the construct, and contains signalling components important for bone formation, development, reconstruction, and degradation [8]



**Figure 1** Upper row: (a) Preoperative X-ray of a GCT in a 29-year-old female's proximal tibia. (b) An immediate postoperative X-ray indicates that the lesion has been filled with bone graft. (c) A year after surgery, an X-ray shows graft integration with minor radiolucent regions beneath the lateral subchondral plate and the tibial eminence (MNC grade 2). (d) Five years after surgery, the defect looks to be entirely cured (MNC grade 1). Lower row: (e) A 15-year-old girl's preoperative X-ray of FD in the proximal ulna. (f) An immediate postoperative X-ray indicates that the defect has been filled. (g) A year after surgery, an X-ray shows complete graft integration (MNC grade 1) and the start of cortical consolidation. (h) Two years after surgery, an X-ray shows evidence of increasing graft insertion and restructuring GCT stands for giant cell tumor, and FD stands for fibrous dysplasia. MNC: Neer's Classification Modified.

The main hindrance to bone recovery with existing therapy techniques is inadequate vascularization and graft material integration. Inadequate vascularization leads to cellular necrosis inside the inner areas of the implantation material and regenerative bone failure. The "gold standard" autograft, allograft, synthetic bone graft alternatives, vascularized fibular graft, induced membrane method, and distraction

osteogenesis remain current therapy options for critical-size bone lesions. Bone tissue engineering (BTE) remains a promising therapy option for extensive segmental bone abnormalities [9].

Bone substitutes are a key aspect of the diamond idea, which comprises the conditions for bone regeneration and defect therapy. The four components of the diamond concept are bone-forming cells, scaffolding, growth elements, and mechanical strength [10].

### **Bone substitutes derived from biological products**

**Demineralized bone matrix:** Demineralized bone matrix (DBM) is acid-treated bone that eliminates the mineral matrix while leaving the organic matrix and growth hormones like bone morphogenetic protein (BMP), insulin growth factor (IGF), transforming growth factor (TGF), or fibroblast growth factor (FGF) intact. DBM has been clinically employed since the early 1980s [11], following the work of Urist and colleagues [12], and is now used in 50% of allografts performed in the United States [13], even though proof for or against its efficacy is still lacking. Because the antigenic surface structure of the bone is lost during the acid removal of minerals, DBM exhibits no immune rejections.

**Platelet-rich plasma:** an autologous solution of platelets obtained by twice centrifugation from whole blood. The high platelet levels in PRP are high in numerous important growth factors. These variables involve, but are not limited to, PDGF, TGF-beta, and VEGF. Platelets are taken from the injured person's blood and activated with calcium chloride before being put in the place of injury. Despite animal studies showing that PRP increases cellular proliferation, chondrogenesis, and callus strength when applied to a fracture site, there is insufficient data to justify its frequent usage in human fracture repair [13].

**Bone morphogenetic proteins BMPs:** are osteo inductive growth factors that are members of the transforming growth factor (TGF-) superfamily They are created by osteoblasts and play an important role in the skeletogenic process, allowing for ectopic bone growth. BMPs are involved in the migration of osteoprogenitor cells to bone-forming areas [7].

**Hydroxyapatite** Given its nanostructure and mineral and biological composition comparable to bone, has been claimed to be a highly beneficial bone-like nanocomposite HAp/col composites with a high capacity for absorption, osteo conductivity, and bone regeneration. According to the stated process for HAp/col substitution by newly generated bone, HAp/col composites promote the migration of macrophages and are resorbed by osteoclast-like cells via phagocytosis, whilst newly formed bone is produced by osteoblasts. This method is comparable to bone remodeling, which involves osteoclasts absorbing calcified bone and osteoblasts forming bone matrix [14].

**Corals** contain interconnecting porosity and a structure that is comparable to cortical and spongy bones, and the FDA approved their usage as a bone substitute in 1992[15]. Coral-based alternatives are primarily calcium carbonate, which can be commercially converted into HA or left in its natural state for improved dissolution by natural bone. Coralline HA can be utilized to transport growth factors such as BMP, TGF-, or FGF. It can be obtained in many forms such as grains or blocks. Despite its sluggish resorption, it has no negative consequences such as inflammatory responses. Coralline HA is osteoconductive, has a high bone-bonding ability, reduces donor area morbidity, and is unlikely to induce disease transfer or deep infection hazards [7].

### **Synthetic bone substitutes**

**Calcium sulphate:** is a low-cost, commonly available synthetic bone replacement. It is available in a variety of forms, including hard pellet [Osteoset (Wright Medical Technology), JAX (Smith & Nephew), and Chalcedon (Synthes)] and injectable viscous fluids that harden in vivo (MIIG, Wright Medical Technology). The primary benefit of using liquid grafts is that they allow for the percutaneous filling of bone gaps. Calcium sulfate grafts are the most quickly absorbed synthetic bone replacement. Resorption normally takes 1 to 3 months, which is faster than true deposition of bone. The full medical impact of such misaligned mechanisms is still unknown [16].

**Calcium phosphate:** Calcium phosphate synthetic replacements are a type of calcium salt compound calcium phosphate compounds used in bone grafting. Notably, hydroxyapatite is a naturally occurring mineral that accounts for over 50% of bone weight. There are few pure, single-compound calcium phosphate cements available; most commercially available compositions contain various percentages of mixed calcium salts. For example, Norian (Synthes) is a popular bone substitute with the mineral composition of tricalcium phosphate (85%), CaCO<sub>3</sub> (12%), and monocalcium phosphate dehydrate (3%) [17].

**3-  $\beta$ -tri-calcium phosphate ceramics** is a calcium phosphate chemical that is also known as whitlockite. When compared to  $\alpha$ -Tri-calcium-phosphate, this form is more extensively employed because of its chemical stability, high mechanical strength, and superior bio-sorption. In this study,  $\alpha$ -tri-calcium phosphate was produced by precipitating calcium oxide and phosphoric acid reactions. Precipitation at 50 °C while sintering at 600, 700, 800, 900, and 1000 °C over 1-5 hours. Green mussel shell contains 60-70% calcium carbonate (CaCO<sub>3</sub>), which is subsequently calcined at 1000 °C to produce calcium oxide (CaO). The results reveal that the  $\alpha$ -tricalcium phosphate optimum was 72% at a sintering temperature of 1000 °C for 5 hours. The generated  $\alpha$ -tri-calcium phosphate crystal structure is a rhombohedral crystal with a Ca / P ratio mole of 2.72 [18].

**5- Biphasic calcium phosphates (HA and  $\beta$ -TCP ceramics)** In vivo and in vitro, BCP bioceramic material produced from butterfish bones showed good biocompatibility and osteogenesis potential. The biological material comes from a variety of sources and is produced straightforwardly. The material features a nanostructure and a high porosity. It is also composed of two phases. It also has some osteoconductivity and osteoinductivity. As a result, it has a promising future development as a bone replacement graft [19]. This association highlights the benefits of its two components (osteoconductivity biocompatibility safe and nonallergenic use, and bone formation stimulation). The main advantage of employing biphasic ceramics (HA and  $\beta$ -TCP mixture) is their dissolution. The combination of  $\beta$ -TCP and HA allows for a greater rate of growing bones than HA alone, while also providing better mechanical properties than  $\beta$ -TCP alone. A few studies mention the use of composite calcium sulfate replacements linked with  $\beta$ -TCP, which would result in relatively few problems. When treated to long bones, the average time to recover to full weight bearing and unrestricted activities of daily living is 7.3 weeks, compared to 14 weeks when HA or  $\beta$ -TCP is used [7].

Despite their varying mineral compositions, share several features that make them an appealing option for many surgeons: slow decomposition, better compressing strength, and a special capacity for osteointegration, or the ability for growing host bone to interdigitate with a rough crystalline graft interface. Norian, like many calcium phosphate cements, promises compressive strength "4-10 times greater than cancellous bone" [20].

Experimental evaluation of the treatment of benign bone tumors and tumor-like lesions with CERAMENT as a bone substitute. An examination of the treatment and diagnosis pathways, as well as the symptoms experienced by patients with tumors and tumor-like lesions There are various therapeutic options available, including curettage and bone grafting. CERAMENT is a new bioresorbable bone substitute that is used in grafting. And the results were The most typical kind of lesion (36.8%) was a single-member bone cyst. Pain was the most often reported complaint (28.9%). Half of all instances were detected by chance on X-rays ordered for another reason. Pathological fractures complicated nearly a quarter of the cases (23.7%). The amended Neer score distribution was as follows: I have a score of 52.6%. II SCORE- 15.8% SCORE III – 10.6% SCORE IV = 2.6%. Procedure problems were reported in 18.4% of patients. 10.5% of patients experienced significant discharge from the operated site, and 7.9% had surgical wound infection. There was one case of relapse this study concluded CERAMENT is a bone substitute that can be used to treat benign bone tumors and tumor-like abnormalities. It is simple to apply and well-accepted by patients. The issue is the high rate of complications, primarily serous leaking from the site [20].

Biphasic ceramic bone substitute (BCBS) powders made of HA and calcium sulfate have an opportunity to be used in the less invasive treatment of benign and borderline bone tumors since they may be shaped and injected into tumor cavities after cysts have been treated. BCBSs have been utilized successfully in the restoration of bone defects following surgical treatment of benign bone tumors, as well as in the filling of low metaphyseal or compressed crack voids [21]. Although previous research indicated that BCBSs had a positive remodeling impact, follow-up data on bone graft resorption and consolidation following BCBS treatment are limited. Aside from a single case report, there is no follow-up data on magnetic resonance imaging (MRI) describing BCBS ingrowth BCBS expands the options for cavity filling in percutaneous and open therapies for bone cysts by demonstrating good bone remodeling properties in the perioperative term. However, percutaneous injection appeared to be related to early wound leaking and relapse. This data assists treating surgeons in identifying indications for minimally invasive therapy and improves understanding of the importance of surgical site checks. More research is needed to assess the rates of relapse and complications in open and minimally invasive bone lesion operations. The tested BCBS revealed acceptable surgical results in a small case series. Percutaneous injection appeared to be associated with initial wound leaking and recurrence. More research is needed to examine recurrence and bone graft resorption after open and percutaneous bone cyst operations, as

well as to better understand perioperative surgical wound inflammation, which appears to be self-limiting in the majority of instances [22].

To describe our experience with an injectable synthetic beta-tricalcium phosphate/calcium sulfate (GeneX; Biocomposites Ltd., Keele, UK) for the treatment of confined defects after curettage of benign bone tumors. The composite is created via a procedure known as zeta potential control, which results in a negative surface charge and is said to have both osteoconductive and osteoinductive properties. To yet, conflicting findings on GeneX's efficacy and tolerability have underlined the need for additional research. While GeneX has shown promise as a bone graft alternative in trauma treatments, this study may serve to guide its use in the setting of benign bone tumors. In our opinion, GeneX is a safe and successful filling agent when patients are handled using an MDT strategy and the surgical method includes precise curettage and containment of the bone defect [23].

The purpose of this retrospective study was to examine the efficacy of ABGS Cerasorb (Curasan-AG, Kleinostheim, Germany), a beta-tricalcium phosphate (beta-TCP), in terms of resorption profile, bone healing, and reconstructing after surgery, as well as to assess potential consequences. All patients had radiographic remission after curettage after a mean follow-up time of 14.6 months. Total resorption was reported in 16.3% of patients, whereas partial resorption was observed in the remaining 83.7%. Fractures occurred within 6 weeks following initial surgery in four patients, two of whom had tumors in the distal femur and two in the humeral diaphysis. In summary, based on our first findings, the -TCP Cerasorb appears to be a dependable bone graft substitute with minimal morbidity rates, and it is a viable option for autologous bone grafts or allografts. However, it exhibits a delayed resorption propensity [24].

Several researchers have recently proposed that these flaws do not require filling for combining, but the respective rate of problems for each approach is not well defined. As a result, we conducted a systematic review to answer: Is it possible that not filling bone voids after benign bone tumor curettage increases the risk of damage? Is the size of the bone defect a particular or valid indicator of breaking? Is there a difference in the mean functional outcome, recurrence, non-weight bearing time, additional perioperative problems, or bone fusion time between filling methods? However, the study showed that even in modest areas bone defects, not filling the bone cavity following benign bone tumor curettage may raise the breakage rate. Prophylactic fixation significantly lowers the fracture rate. Filling with cement shortens the period spent bearing weight. Even when the cavity is not filled, there are little distinctions in the methods utilized to fill it [25].

#### **4. Conclusion**

Despite major advancements in treatment regimens over the previous few decades, bone tumors remain a medical problem. Bone cancers necessitate immediate care and therapy. For these reasons, a special emphasis is being placed on enhancing traditional strategies through the use of alternative therapies, drug delivery via carrier systems rather than systemic delivery, and the development of multifunctional scaffolds for repairing bone defects caused by bone malignancies or tumor resection. The use of bone replacements in orthopedic surgery is becoming more common. Evidence-based medicine is becoming increasingly relevant as novel materials and implants enter the market. According to the findings of this perspective.

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