

Arthrex Quickset™ Macroporous Calcium Phosphate Cement

Arthrex Research and Development

Introduction

Synthetic bone void fillers (BVF) are commonly used as adjuncts to modulate bone healing when the normal healing process is otherwise impaired. They have been in use for many years in the general orthopedic space, and are gaining traction in sports medicine and arthroscopic surgery. However, there are many types of BVFs with different compositions and handling characteristics. Here, the different types of BVFs will be identified, and the advantages of Arthrex Quickset, a new synthetic BVF, over other products on the market will be discussed.

What is a BVF?

BVFs are osteoconductive, as they provide a scaffold for new bone growth. The gold standard for bone grafting is autograft tissue directly from the patient^{1,2}. However, its retrieval can lead to additional pain and discomfort for the patient, and quantity of autograft is limited^{3,4}. Allograft tissue from a donor is also an option, but depending on the type utilized, this may lack adequate osteoconductive properties and/or mechanical strength. Alloplasts, or synthetic BVFs, are made using chemical processes. The material provides support for new bone formation, and the material eventually resorbs to leave only new bone. Alloplasts consist of polymers, ceramics, and composite materials. However, ceramics are the main alloplast, as that is the BVF that is the most similar to bone mineral. Table 1 contains a list of synthetic BVFs and their characteristics.

Calcium sulfate (CS) has been used for many years in dentistry and orthopedics to fill bone defects. The main issue with CS-based materials is the fast degradation *in vivo* via hydrolysis, which is faster than other ceramics that degrade via cell-mediated processes. This can lead to serous-wound drainage, which does not appear to resolve until the CS completely resorbs or has to be removed⁵.

The largest group of ceramic BVFs is calcium phosphate (CP), which includes tricalcium phosphate (TCP); hydroxyapatite (HA); biphasic calcium phosphate (BCP), a combination of TCP and HA; and calcium phosphate cement (CPC), which is a calcium orthophosphate powder mixed with a liquid component that becomes a hardened paste *in vivo*. These materials have their advantages and drawbacks, such as ease of use, available forms (powder, blocks, etc.), degradation time, and support for new bone formation⁶. HA and TCP have been used for many years, but BCP and CPC have recently gained much more attention clinically.

The last group of ceramic BVFs is bioactive glass. This group is made up of ceramics, usually CPs, that contain silicon and other modifiers commonly found in glass. Bioactive glass supports bone formation by controlled conversion to an HA-like material. If more silicon dioxide, or silica, is present in the glass, it becomes more difficult for the glass to convert to ceramic within the body. It is unknown if the unconverted silica can have any long-term negative effects in humans⁷. However, a study performed in a sheep spine model has shown that silica-containing BVFs can cause an inflammatory reaction⁸. In addition, it has been described that the ionic degradation products of the bioactive glass could potentially change the pH of the surrounding tissue^{7,9}, which could lead to impaired tissue formation. In cell culture, the silica particles from these types of ceramics become localized within vacuoles, or compartments, within the cells¹⁰. It can be postulated that the cells try to degrade these silica particles, but they are unable to do so. Therefore, the cells move the particles within these vacuoles, which are then stored within the cells.

Table 1

Synthetic BVF	Characteristics
Calcium sulfate (CS)	Very fast resorption time (4-12 weeks)
Tricalcium phosphate (TCP)	Faster resorption time than HA (6-18 months)
Hydroxyapatite (HA)	Mineral structure closest to bone; Slow resorption time: Can stay in body for many years
Biphasic calcium phosphate (BCP)	Combination of HA and TCP; 60 HA/40 TCP mixture most common; Faster resorption with more TCP; Slower resorption with more HA
Ceramic phosphate cement (CPC)	Calcium orthophosphate powders with liquid component; Injectable; Certain polymers contribute to wettability and macroporosity
Bioactive glass (BG)	Silicon is not metabolized by cells

Characteristics of Arthrex Quickset™

In any orthopedic application, the ideal BVF will degrade in a reasonable amount of time, support new bone formation, be easily injectable, and be usable in a fluid-based environment. CPCs, and more specifically, Arthrex Quickset, meet the above characteristics.

Composition:

The powder phase of Arthrex Quickset consists of three different calcium orthophosphate powders – α -TCP, anhydrous dicalcium phosphate (DCP), and calcium-deficient apatite (CDA). The powder phase also contains a biocompatible polysaccharide polymer. This polymer improves the viscosity, cohesiveness, and macroporosity of the Arthrex Quickset when combining the powders with the sodium phosphate liquid. After mixture of the powder and liquid phase, the process of crystallization begins, resulting in an injectable paste that hardens *in vivo* within 24 hours. The final product that is formed from the cement is CDA, which closely mimics the mineral phase of bone.

Competitors use similar calcium orthophosphate powders as their base material but such markers as the ratio of powders, liquid component, porosity-inducing material, and final product can vary. These items all play an important role in the characteristics of CPCs such as injectability, set time, strength, and porosity. Competitor CPCs are listed in Table 2.

Table 2

Product	Composition
Quickset (Arthrex/Graftys)	α -TCP; Anhydrous dicalcium phosphate (DCP); Calcium-deficient apatite (CDA); Hydroxypropyl-methylcellulose (HPMC); Sodium phosphate liquid
Norian SRS (Synthes)	α -TCP; Calcite; Monocalcium phosphate monohydrate (MCPM); Sodium phosphate liquid
Pro-Dense (Wright Medical)	Mixture of CS and CP; No information on liquid component
HydroSet (Stryker)	Dicalcium phosphate dihydrate (DCPD); Tetracalcium phosphate (TTCP); Trisodium citrate; Sodium phosphate and polyvinylpyrrolidone (PVP) liquid
Callos Inject (Acumed)	Calcium orthophosphate powder; Sodium silicate liquid

Preparation of Arthrex Quickset:

- Within a self-contained syringe, the sodium phosphate liquid is pushed into the calcium orthophosphate-polysaccharide polymer powder and mixed for two minutes. Mixing for a shorter or greater amount of time could compromise the crystallization process and cement properties.

- After mixing, it is recommended to inject the CPC into the defect within two minutes. Initial rigid fixation should be present before implanting the CPC. The cement should be left undisturbed after injection, so as not to compromise the crystallization process. Screws and other hardware can then be inserted across the cement throughout the rest of the procedure. Be aware that the cement is not intended for primary fixation. The cement should not be used as a fixation point for rigid fixation with screws and/or additional hardware.

- The initial setting time marks the time that it takes the cement to become non-flowable with less ability to manipulate its structure. However, the cement does not fully harden during these initial eight minutes and instead hardens over the first 24 hours *in vivo*. This beneficial characteristic prevents the cement from fracturing if additional fixation is being placed across the implanted biomaterial. The setting and crystallization process is not exothermic, so it will not raise the temperature of the surrounding tissue.

Porosity and Mechanical Strength:

Porosity within the CPC is a very important characteristic that can affect biological function. Micropores, mesopores, and macropores in ceramic BVFs are necessary for cells to adhere to and travel within the material and resorb it while laying down new bone; this has been well-documented in the literature¹¹⁻¹³. The overall porosity of Arthrex Quickset is 70%. Many pores are less than 10 μ m in diameter and the rest are greater than 100 μ m. The small pores provide interconnectivity and allow for nutrients to easily pass through different locations within the cement. The large pores allow for osteoclasts to enter the different sections of the defect and start the implant resorption process. This leads to vascularization and osteoblast entrance and differentiation, leading to eventual formation of new mineralized bone.

Porosity and composition also play a role in the strength of CPCs⁶. Arthrex Quickset reaches a compressive strength of 24 MPa after setting; in comparison, cancellous bone has a compressive strength of 10-15 MPa. Decreasing porosity, specifically macroporosity, can result in increased strength; however, it may have negative effects on implant resorption and bone formation. For instance, Norian SRS has a compressive strength of approximately 50 MPa. However, almost all of its porosity is microporosity without much macroporosity, resulting in minimal amounts of bone formation within the defect^{14,15}. In fact, with the exception of Quickset, all of the resorbable bone cements listed in Table 2 lack initial macroporosity, which may impede new bone formation within the implant. Once fully cured, Arthrex Quickset has a significant percentage of macroporosity.

Preclinical Studies

Arthrex Quickset™ has been tested *in vivo* in a number of different animal models. Cylindrical defects (6 mm diameter x 10 mm depth) were drilled into the distal lateral femoral condyle of skeletally mature New Zealand White rabbits at the junction of the epiphysis and the metaphysis. The defects were filled with Arthrex Quickset and the animals were sacrificed at four weeks. Samples were analyzed using back scattered scanning electron microscopy (BSEM) and histology with Movat staining. Figure 1a shows BSEM imaging of the Quickset defect at 4 weeks. The pores within the material are evident at this early time point (arrowhead), while new bone (arrow) is developing around and within the material. Figure 1b shows new osteoid (red), as well as new mineralized bone (yellowish-green) against the cement (bluish-white), without a major inflammatory reaction. A BSEM image of Norian SRS from another study at 12 weeks is shown in Figure 1c. Even with the Norian product being studied at a time point that is three times further out than Quickset (12 weeks vs. four weeks, respectively), there is minimal to no porosity within the cement, and some new bone formation is only seen around the cement, but not much within it.

Figure 1a

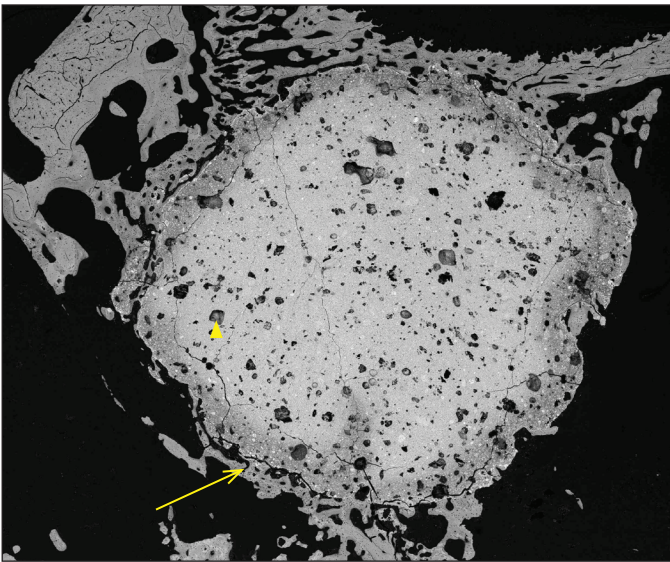


Figure 1b

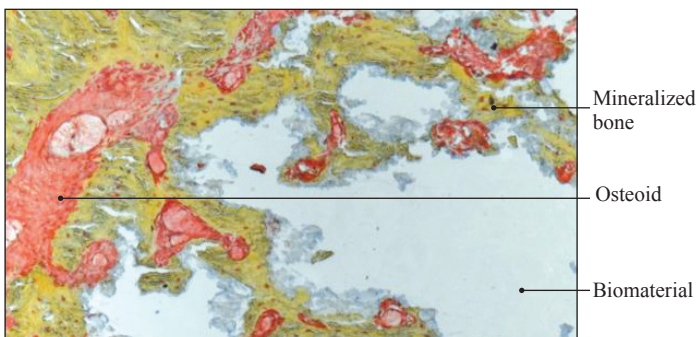
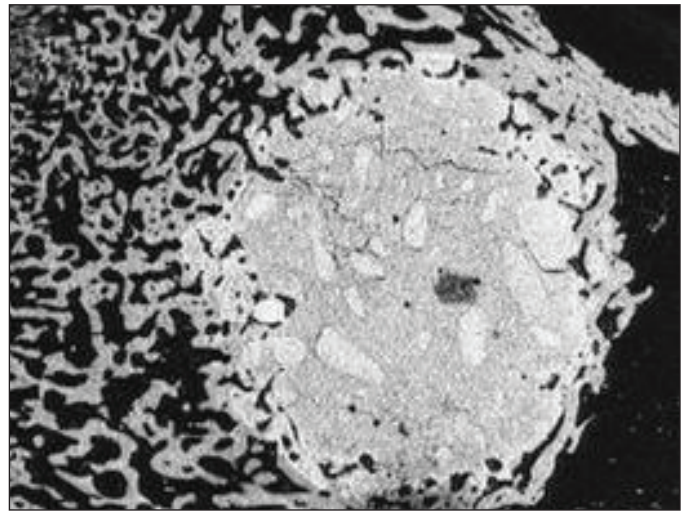


Figure 1c



Cylindrical defects (9 mm diameter x 20 mm length), were also implanted in sheep for 6 months. Figure 2a shows a BSEM image of the Quickset implant after sample processing. Again, there is new bone formation around the periphery of and within the cement. One item of note is that after 6 months' implantation, porosity is retained within the cement, which helps to promote continued bone ingrowth. Movat pentachrome histology is shown in Figure 2b. New lamellar bone and osteoid are apposed against the cement. These two animal studies give evidence to show that Arthrex Quickset generates new bone within and around the cement.

Figure 2a

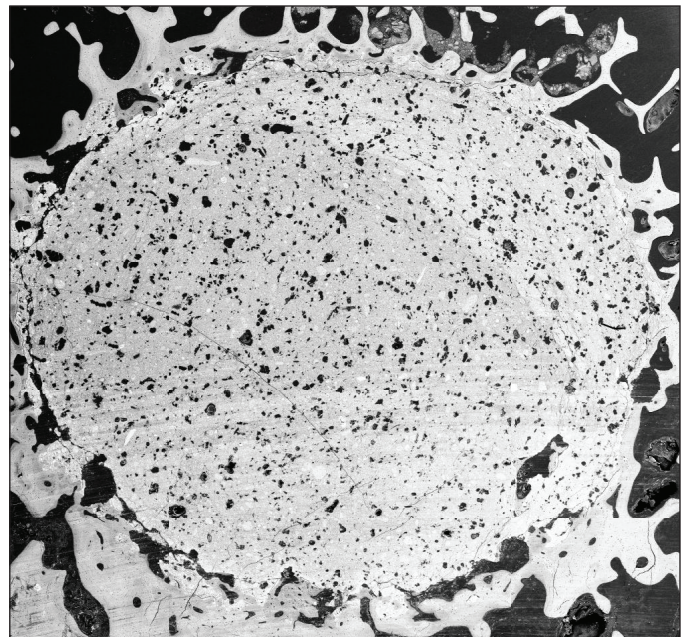
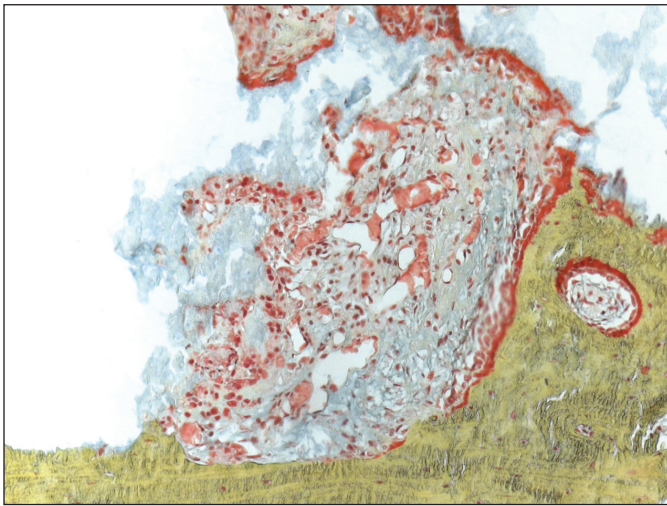


Figure 2b



Clinical Case Studies

A recent meta-analysis of randomized trials published in the *Journal of Bone and Joint Surgery* demonstrated that CPCs compared to autograft reduced the incidence of loss of fracture reduction (68% reduction), as well as reduced the amount of pain at the fracture site compared to controls managed with no graft (56% reduction)¹⁶. Based on these results, there is substantial data demonstrating that CPC plays a significant role with orthopedic surgery. In addition, this helps show the potential importance of Arthrex Quickset™ when used in a clinical setting. To analyze this further, a clinical case study was performed by Dr. Sebastien Parratte at Sainte Marguerite University Hospital in Marseille, France using Quickset within a tibial plateau fracture site. Figure 3a shows the preoperative scan of the injury, and Figure 3b shows the immediate postoperative x-ray where Quickset was injected (yellow arrow). After four months, the wires and a screw were removed in order to start early mobilization. At this time, a biopsy was taken from the fracture site where Quickset was used in order to analyze tissue incorporation into the graft. The histological analysis within Figures 3c (10X magnification) and 3d (20X magnification) demonstrate good osteointegration of Quickset. The cement is in direct contact with new bone trabecula without a fibrous interface. The histology was also able to highlight the intertwining network that develops as the biomaterial resorbs and mineralized lamellar bone is laid down. Osteoblastic cells (cuboid) were found along the osteoid borders (red) going through mineralization (yellow-brown), osteoclastic cells (multinuclear cells) representative of the resorption process were isolated along the borders of the cement (bluish-white), and numerous blood vessels had been established within the implant. At eight months, follow-up x-rays were taken and demonstrated fracture healing and good osteointegration of the Quickset (Figure 3e, yellow arrow). At 20 months, the rest of the hardware was removed and another biopsy was taken from

the site of injection (Figure 3f). There was very good osteointegration with a only a small amount of cement (bluish-white) remaining, and it was in direct contact with new mineralized lamellar bone (yellow-brown). In addition, there was recolonization of the affected area with bone marrow, with an absence of unwanted fibrous tissue. The 22-month follow-up x-ray confirms new bone formation (Figure 3g).

Figure 3a



Figure 3b



Figure 3c

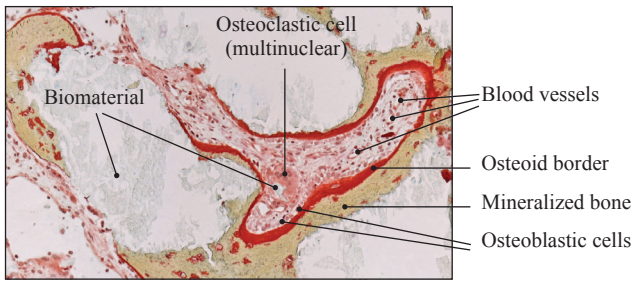


Figure 3d

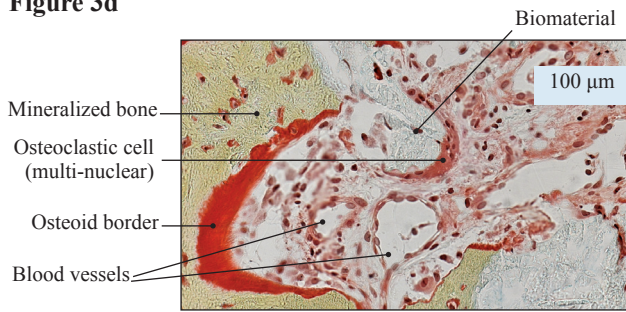


Figure 3e

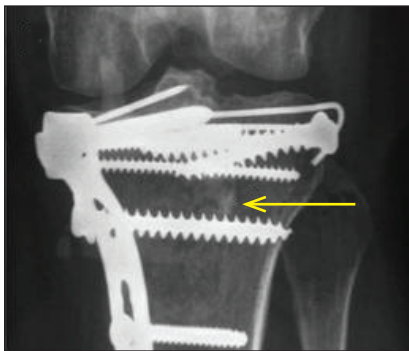


Figure 3f

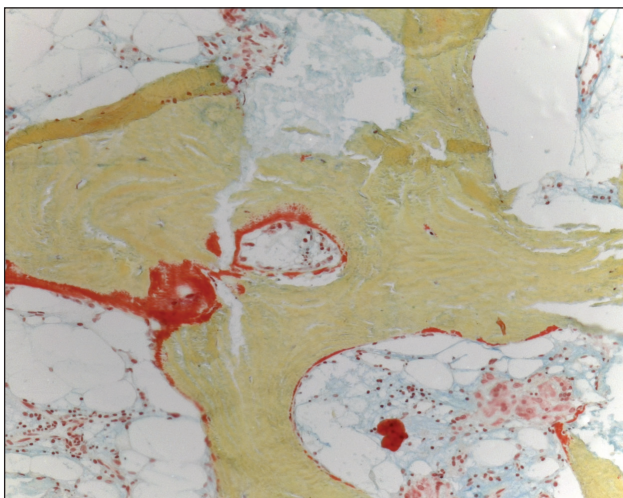


Figure 3g



Another clinical case performed by Dr. Parratte illustrates the use of Arthrex Quickset™ in a proximal humeral fracture. Figure 4a shows the immediate post-operative x-ray of the fracture with the injected Quickset (yellow arrow). Figures 4b and 4c show the site at 1 and 2 months post-surgery, respectively. The Quickset is integrated well into the humerus (yellow arrows) and appeared to be supporting new bone formation.

Figure 4a

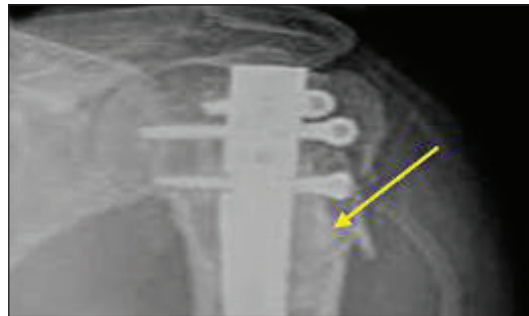


Figure 4b

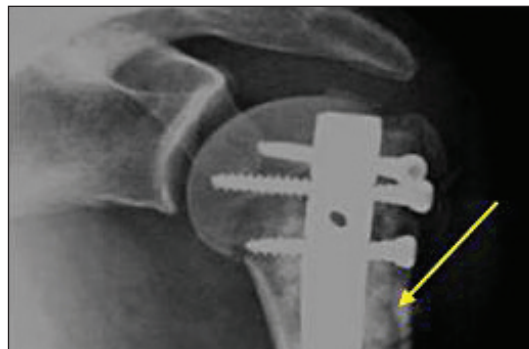
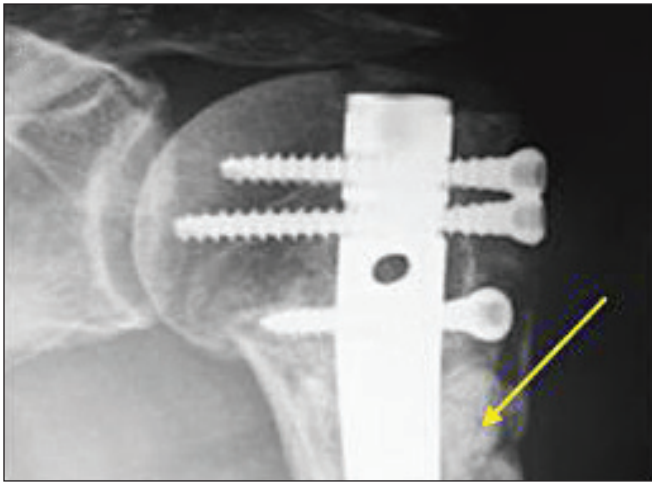


Figure 4c



Conclusion

Arthrex Quickset™ is an injectable macroporous CPC that has been well-researched and well-received in Europe before it received clearance in the United States. It provides a balance of porosity and strength, making it an optimal CPC to incorporate into a vast array of orthopedic procedures. Consider using this product for either surgically created osseous defects or osseous defects created from traumatic injury to bones within the extremities and pelvis. Quickset, in turn, will be able to fill the osseous void, provide an intertwining scaffold, resorb naturally, and will be replaced with bone during the healing process.

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