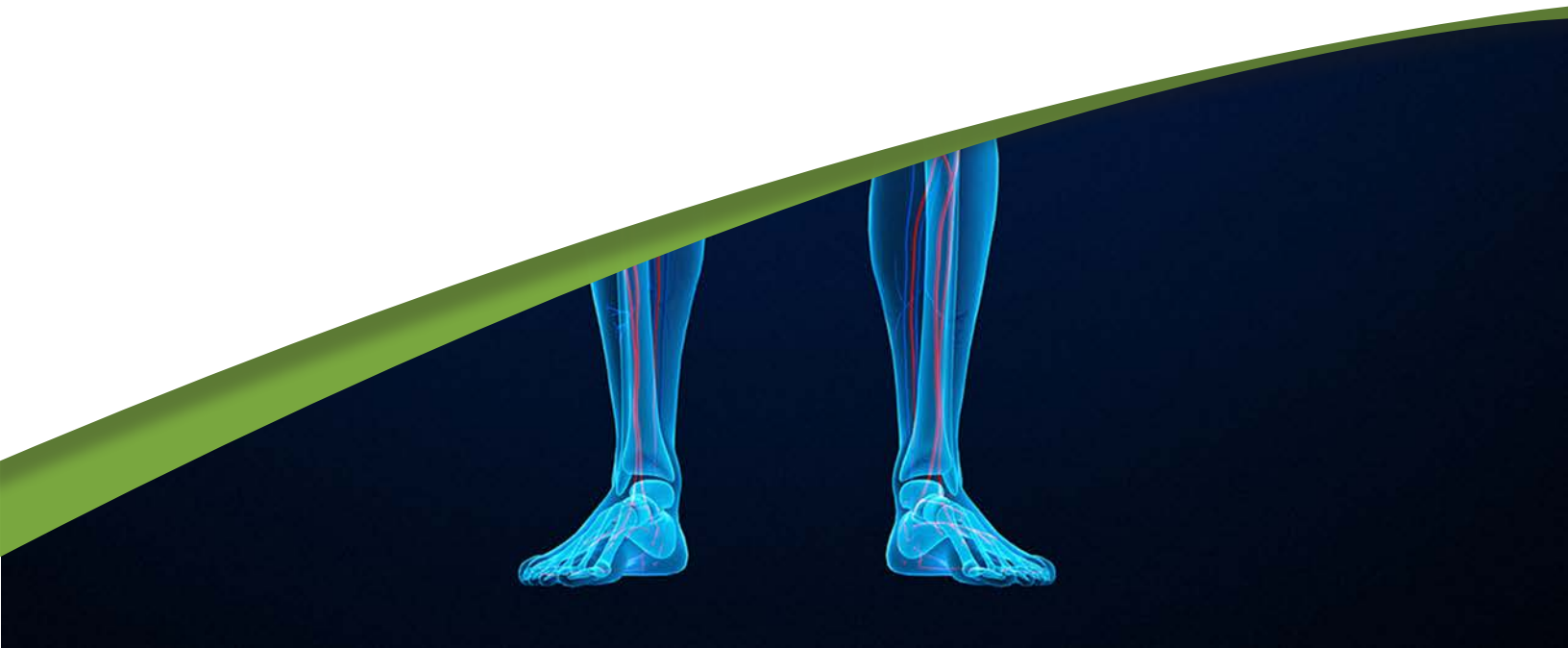
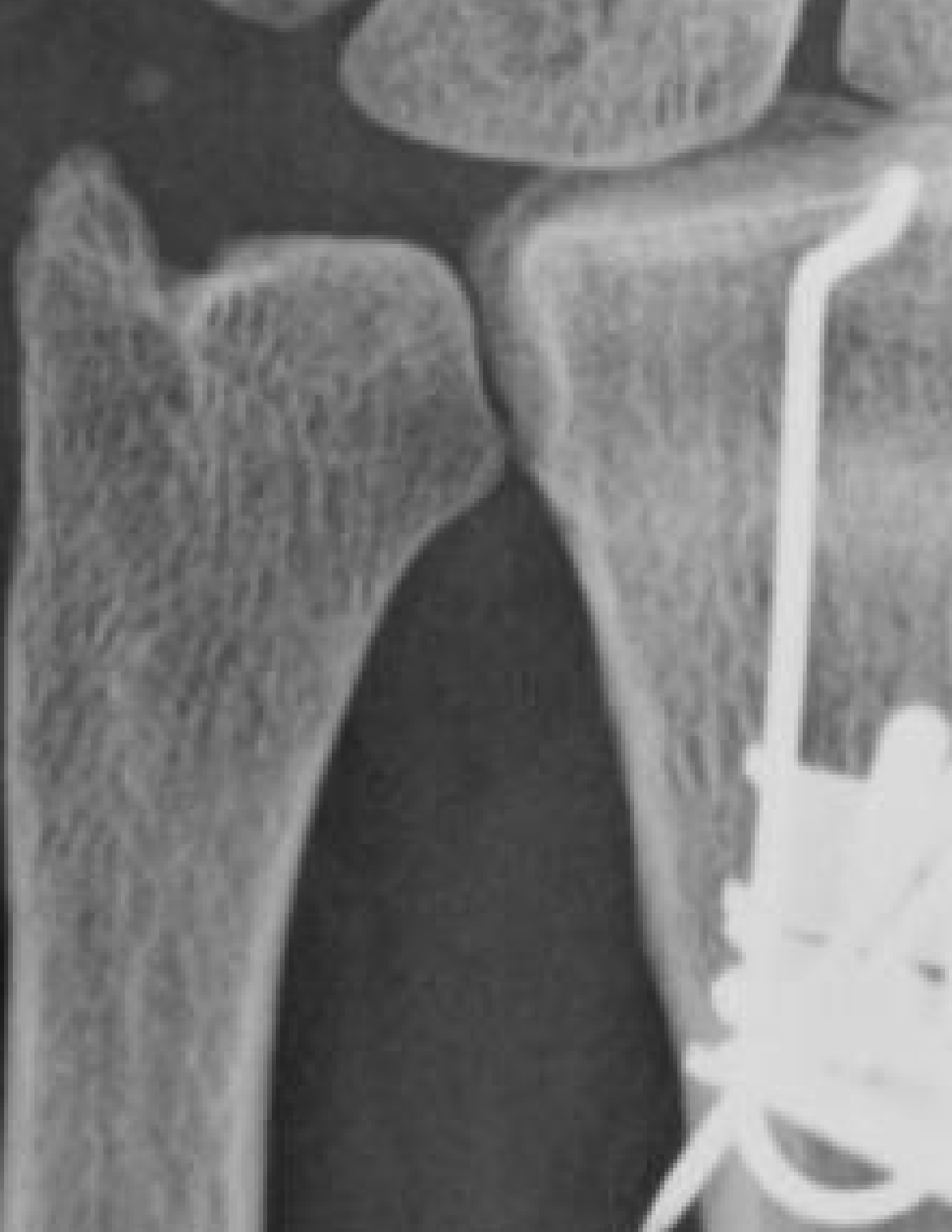
BONESUPPORT™

CERAMENT™|BONE VOID FILLER
Bone Healing Technical Monograph





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I. Overview

CERAMENT™ is a biphasic injectable bone graft substitute. It is synthetically made and has one osteoconductive component, hydroxyapatite, and one resorbable component, calcium sulfate.

Bone substitutes based on hydroxyapatite and calcium sulfate offer good potential to be used as bone repair material for clinical applications due to their:

a) osteoconductivity, with an ability to act as a matrix for cells and as a carrier of osteoinductive factors or other therapeutic substances

b) injectability, making it possible to utilize in minimally invasive surgery techniques

c) adequate strength and controllable resorption

CERAMENT™ also includes a radio-opacity enhancing component which makes the material suitable in applications guided by fluoroscopy, including mini-invasive surgery.

The material is easy to mix and handle. It hardens in situ and all *in vivo* studies have shown good biocompatibility, adequate resorption rate and good bone healing.

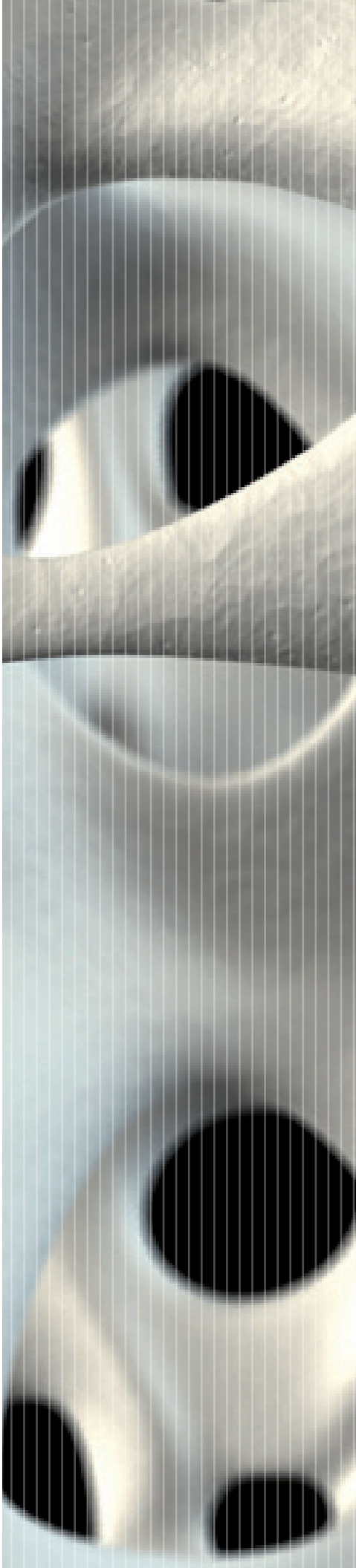
By filling a bone defect with CERAMENT™, which contains 40% bone mineral, i.e. hydroxyapatite, three important needs for bone healing are fulfilled:

a) The void is filled with a bone mineral and can therefore not be invaded by fibrous tissue

b) CERAMENT™ hardens ***in*** *situ,* augments the bone, and provides some mechanical stability

c) CERAMENT™ acts as a scaffold for the ingrowth of bone

When bone-forming cells are in direct contact with CERAMENT™, the hydroxyapatite particles get incorporated into the newly formed bone which increases the bone strength. After treatment with CERAMENT™, complete bone healing is demonstrated within 6-12 months.



II. Conditions for bone healing

1. VASCULARITY
Vascular ingrowth and blood supply is critical for bone formation. Blood contains circulating osteoprogenitor cells and extracellular matrix proteins necessary to initiate osteoclast and osteoblast. In a fracture or a bone defect, this cell proliferation initiates cartilage growth followed by immature bone formation. If the mechanical situation is stable, woven and lamellar bone will follow. To activate healing in a void not created by surgery or a recent fracture, it is preferable to provoke bleeding to attract cells and to promote angiogenesis and subsequent bone healing.

2. FIXATION
Excess motion in a fracture or bone defect may interrupt the development of new bone which may lead to fibrous tissue formation instead of bone.

3. BONE TISSUE FORMATION
Fracture healing, with bridging of bone defects, occurs if the defect is small enough and the above mentioned conditions are fulfilled. Healing of bone with large gaps often fails because there is no scaffold for the osteoblast to climb on. The healing process in such defects starts from the edges of the defect in order to fill it completely with new bone tissue. If the defect site gets filled by fibrous tissue instead of bone, a non-union will be the result.

4. MINERALIZATION
Mineralization and maturation of the bone tissue are the final stages in the bone healing process, and it can only occur if the bone is adequately loaded. Unloaded immature bone tissue will be resorbed by osteoclasts since it is considered "not needed" by the body. However, loading the immature bone tissue will stimulate the remodeling to result in a strong and load-bearing bone structure.

Too strong bone substitute material might be expected to shield the immature bone from the load leading to bone resorption, while a weak bone substitute material might lead to early collapse. It is therefore important to match the strength of the bone substitute to the mechanical demands.

III. History of bone graft substitutes

i) Calcium sulfate

The use of synthetic bone grafts started over 100 years ago with the implantation of calcium sulfate. The first reported case, where calcium sulfate was used to treat cavities in bone, is from 1892 by Dreesmann in Germany, who operated on eight patients with large bone defects grafting them with β-calcium sulfate hemihydrate[1]. Subsequent reports showed good results with complete bone regeneration and concluded that calcium sulfate was biocompatible, did not add complications even in infected cavities, and was resorbed quickly[2-6].

The majority of recent studies have been performed on calcium sulfate pellets produced from hemihydrate with crystals of regular shape and size, i.e. α-calcium sulfate hemihydrate. These pellets show less variation in solubility and resorption[7-11]. The most important advantages with calcium sulfate are the excellent biocompatibility and the dissolution rate making it suitable for drug release. The drawback is rapid resorption caused both by passive dissolution and by osteoclasts activity[12].

ii) Calcium Phosphate

The most common calcium phosphate compound used in bone grafting is hydroxyapatite (HA; $Ca_{10}(PO_4)_6(OH)_2$). Its structure is similar to that of the mineral phase of bone and it shows excellent biocompatibility. HA is osteoconductive due to its chemical similarity to natural bone mineral and is also bioactive, i.e. bone chemically binds to it[13,14]. A study on the proximal tibia of 30 rabbits demonstrated that HA (50 wt-%) + calcium sulfate was highly osteoconductive, giving 52% bone formation after 4 weeks and 90% after 24 weeks[15]. Although the calcium sulfate component had disappeared after 8 weeks, the HA continued to guide bone ingrowth[15]. At 24 weeks, the HA particles were surrounded by, and incorporated in, thick trabecular bone.

HA is often synthesised at high temperature (typically above 1800 F) to form granules or blocks, but can also be precipitated from a supersaturated solution of calcium (Ca^{2+}) and phosphate (PO_4^{2-}) ions. High temperature treatments provide a more crystallized HA that shows minimum resorption by osteoclast activity and may remain at the implant site for years or even decades[16,17]. This may be an advantage for certain applications, but a drawback for others. In younger patients or growing children resorbable implants are, however, preferable since the material is replaced over time by bone tissue.

Due to partial resorption, biphasic calcium phosphate (BCP) has been used[18-22]. It may give bone ingrowth and mechanical stability at the implant/bone interface, but BCP will not resorb completely[20].

IV. Importance of porosity and chemistry

To achieve bone healing a bone substitute has to be porous to allow penetration of living cells. Blood capillaries, osteoblasts and osteoclasts have to be able to invade the material to allow bone remodeling.

For many years it was believed that only macroporosity (pore size > 100 µm) was critical for good bone ingrowth. More recently the importance of microporosity has been highlighted, with convincing results showing cell attachment on microporous surfaces[23] and a need for microporosity around 1-50 microns to allow penetration of body fluids and subsequent vessel ingrowth[24]. In vivo studies show that manipulation of the microporosity in calcium phosphate bioceramics may accelerate osteointegration[25,26], improve the adsorption of proteins and the adhesion and proliferation of human bone cells[27].

Conclusively, both micro- and macroporosity are important for the bone ingrowth[28,29] as well as the chemistry of the bone graft substitute[30].

Ideally, the resorption of an implant material has to correspond to the bone ingrowth rate in order to optimize the healing of the defect:

- Too slow resorption of the implant will obstruct the growth of new bony tissue and will slow down the healing process.
- Too fast resorption of the implant will leave a gap between the implant and the ingrowing bone with a risk of fibrous tissue interpositioning.

The resorbing material leaves space for the bone tissue to grow and the osteoconductive material guides the bone cells and facilitate bone formation. Eventually this results in full transformation of the bone substitute into mature bone.

With CERAMENT™|BONE VOID FILLER there is controlled resorption of CaS to match the rate of bone ingrowth and support new bone growth.

V. The Science of CERAMENT™

i) Biphasic

CERAMENT™ is an injectable biphasic ceramic material, indicated for the filling of bone voids. CERAMENT™ consists of a powder which is mixed with a liquid and becomes an injectable paste which hardens *in situ*. The powder has two components:

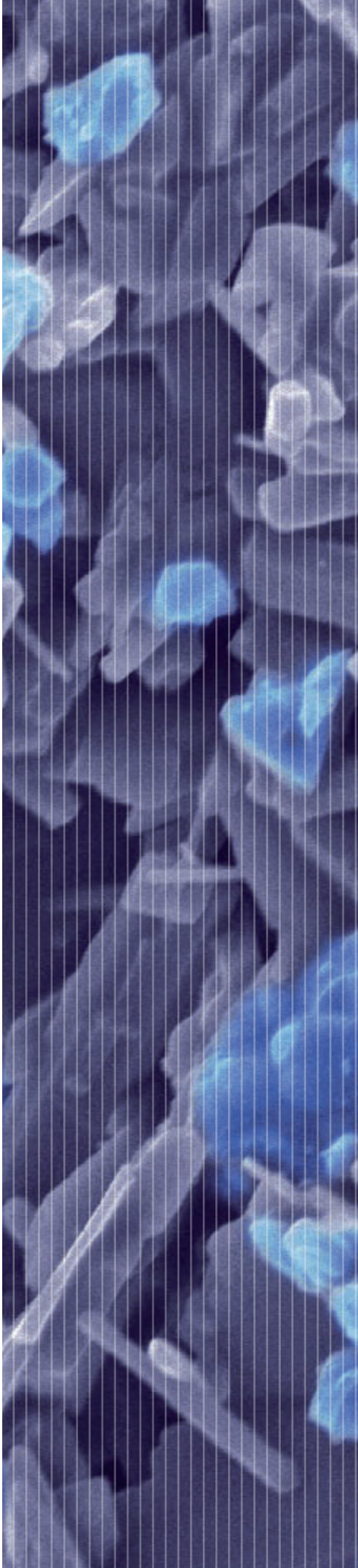
- 40 wt% hydroxyapatite (HA)
- 60 wt% α-calcium sulfate hemihydrate

HA is the mineral phase of bone. It is highly osteoconductive[18] and will guide the bone ingrowth throughout CERAMENT™ *in vivo*. The HA used in CERAMENT™ is engineered to be stable. It offers high injectability and gives long term support to the defect. The HA particles form an osteoconductive scaffold augmenting the calcium sulfate to retard its resorption rate[31]. The HA particles are embedded into newly formed bone with no adverse inflammatory response[31].

Calcium sulfate is used for its tissue integration and biocompatibility. It has been used for bone repair for more than 100 years with excellent tissue response[2-4,6,32]. No adverse reactions have been reported during its resorption[3,9,10], showing that calcium sulfate degradation products are very unlikely to be harmful for the body. The calcium sulfate used in CERAMENT™ is of medical grade. It gives short term stability to the bone defect after repair and will dissolve and be actively resorbed by octeoclastic activity[12] within 6-12 months[33]. Dissolution of calcium sulfate creates space for new bone growth.

Both the calcium sulfate and the HA component of CERAMENT™ are synthetically produced to assure high purity and reproducibility.

The ratio 40/60 of HA/calcium sulfate provides maximum osteoconductivity while keeping a strength suitable for augmentation of cancellous bone defects[34]. The mechanical properties closely match cancellous bone[35] thereby avoiding stress shielding and providing a mechanically stimulating environment for bone growth. A too strong and stiff material may cause bone resorption since the force will be transmitted through the material instead of through the bone[36]. It is important to load the treated region adequately to regenerate and remodel bone[37].



ii) Injectable

The alpha-form of calcium sulfate hemihydrate delivers much better injectability compared with the beta-form[34]. The alpha-form has a higher density and absorbs less liquid, which also makes the calcium sulfate stronger[38] and gives the material a slower resorption rate[39]. The injectability is also enhanced by the round shape of the HA particles[40]. Round particles flow easily and the injection may be performed without high pressure. The liquid used in CERAMENT™, iohexol solution, further increases the lubrication of the powder and ensures that no filter pressing occurs[41]. Filter pressing is a phenomenon seen when particles mixed with liquid are put under pressure, where the material separates and the liquid is pressed out through the particle phase, resulting in dry powder left if in a syringe during injection.

High injectability enables injection through narrow needles and ensures an excellent spread in the trabecular system. It also allows HA particles to be carried into the bone defect. The calcium sulfate component of CERAMENT™ not only delivers the osteoconductive HA, but also prevents migration of the particles. It binds the HA particles which is important for subchondral applications and in joint prosthetic revision surgery avoiding the risk for abrasive wear.The liquid component is a water soluble radio-opacity enhancing component called C-TRU™ consisting of iohexol and water. It is safe[42] and has been used clinically under the brand name Omnipaque® since the 1980s. By adding a radio-opacity enhancing component to the material, transcortical injections using minimally invasive techniques may be performed safely. Injection of CERAMENT™ can thus be followed visually under fluoroscopy which decreases the risk of leakage into e.g. the joint space in the presence of intra-articular fracture lines.

Iohexol is a non-inflammatory, non-ionic radiocontrast agent[42], that doesn't metabolize and is cleared from the body through renal excretion[43].

When mixing the powder with the liquid an injectable and moldable paste is formed. Once the paste hardens it forms a microporous ceramic material designed to facilitate bone formation in the bone void and result in complete healing.

CERAMENT'S **40/60 ratio of HA/calcium sulfate provides maximum osteoconductivity while keeping a strength suitable for augmentation of cancellous bone defects.**

iii) Bioactive

CERAMENT™ is bioactive, which means that a nanolayer of carbonated apatite will spontaneously form on the material surface approximately 1-3 days after implantation (Fig 1). Calcium ions from the calcium sulfate react with phosphate ions from the body fluids and a layer of apatite precipitates on the material surface[31]. It is hypothesized that this passive precipitation of endogenous HA stabilizes the CERAMENT™ implant and explains the substantially retarded resorption of the calcium sulfate component seen with CERAMENT™. This precipitation has also been observed on other highly biocompatible materials like titanium[44] and Bioglass® [45], and it has been shown to encourage new bone ongrowth onto the material[46]. It basically enhances the direct contact between material and bone because bone cells recognize the apatite layer as bone mineral.

Not all bone graft substitutes are bioactive. Pure calcium sulfate, which always presents with a low pH, does not have the ability of forming this apatite layer[47]. The HA particles are thus needed to induce HA precipitation, which might be explained by a combination of neutralized pH and necessary surface properties not present with calcium sulfate[47].

CERAMENT™ is bioactive and has been shown to encourage new bone ongrowth onto the material because bone cells recognize the apatite layer as bone mineral.

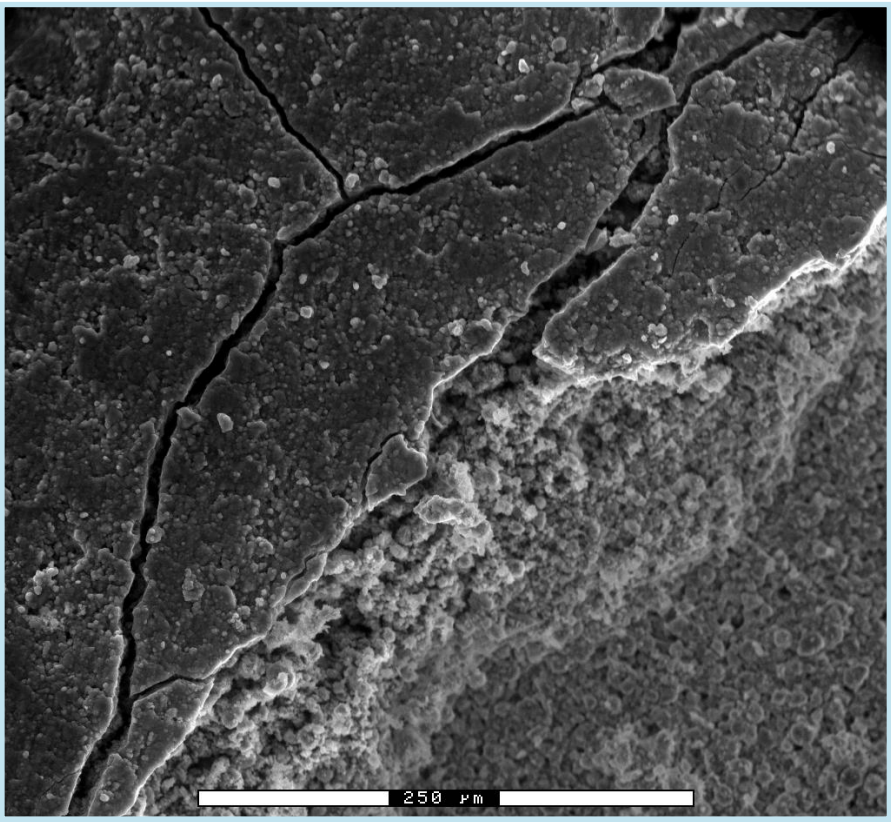


Fig 1: A layer of HA has been formed on the surface of CERAMENT™. This layer makes the material bioactive, retards the calcium sulfate resorption and enhances the direct contact between material and bone[34].

VI. Preclinical findings

i) Biocompatibilty and no inflammatory reaction

CERAMENT™ has been studied in innumerous animals, including in rats, rabbits, and sheep[31,48-53].

It has shown good tissue response both in muscle pockets and in bone defects[31]. A close contact was found between material and bone tissue in a bone harvest chamber model in rabbits[31] (Fig 2), with trabecular bone completely surrounding and embedding the HA particles (Fig 3). No inflammatory reactions or fibrous tissue were observed after 3 and 6 weeks.

The incorporation of the HA particles and fragments of the material, both calcium sulfate and HA, was observed in greater detail in femur defects in rats[50] (Fig 4 on pg.10) at 21 days, and in rabbits[51] (Fig 5 on pg.10) at 12 weeks after implantation of CERAMENT™.

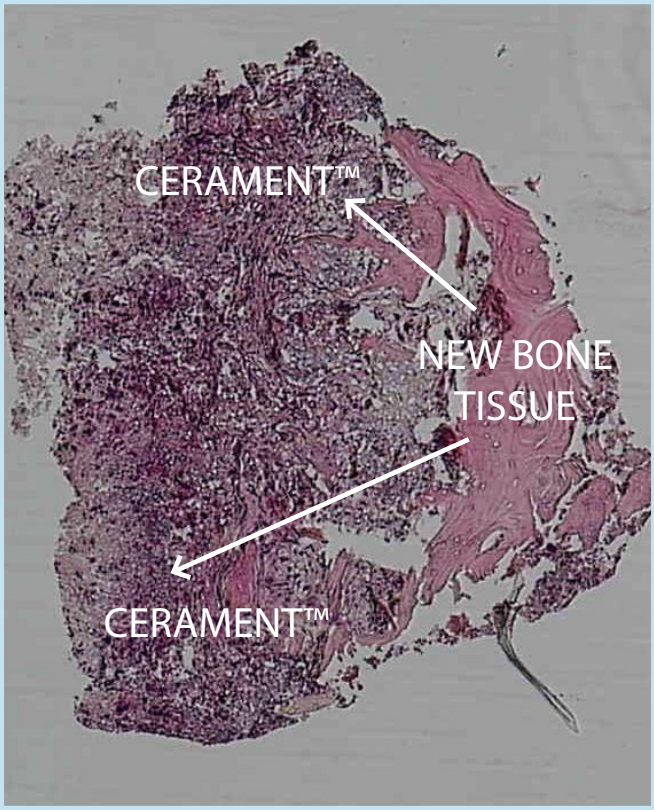


Fig 2: A close contact was found between CERAMENT™ (to the left) and new bone tissue (to the right) at 6 weeks post implantation[31] of CERAMENT™. The new bone tissue invaded CERAMENT™ and no sharp bone/implant interface was observed.

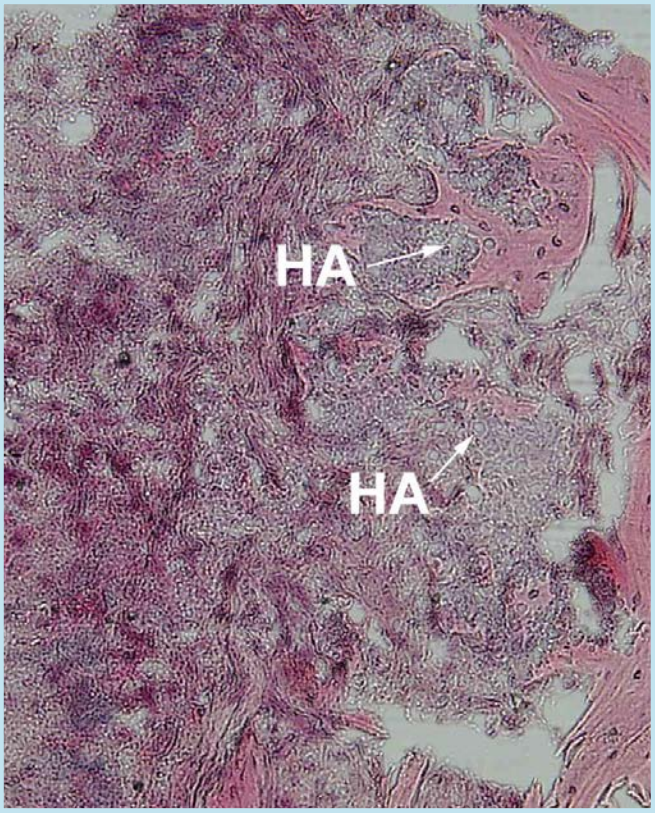


Fig 3: Bony tissue completely surrounded and embedded the HA particles.

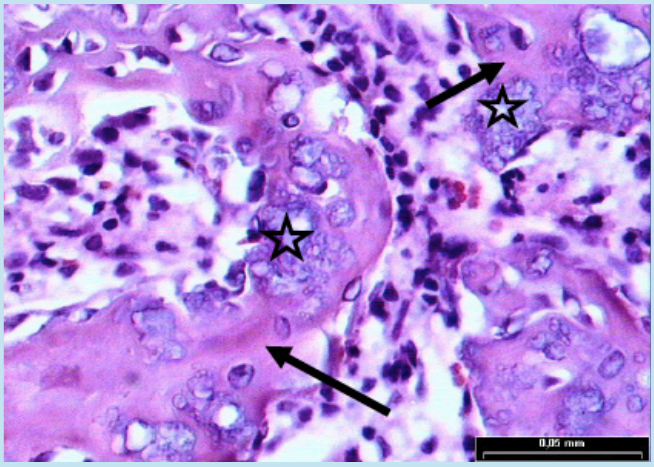


Fig 4: Shows fragments of CERAMENT™ (star) incorporated in new, immature bone tissue (arrow).

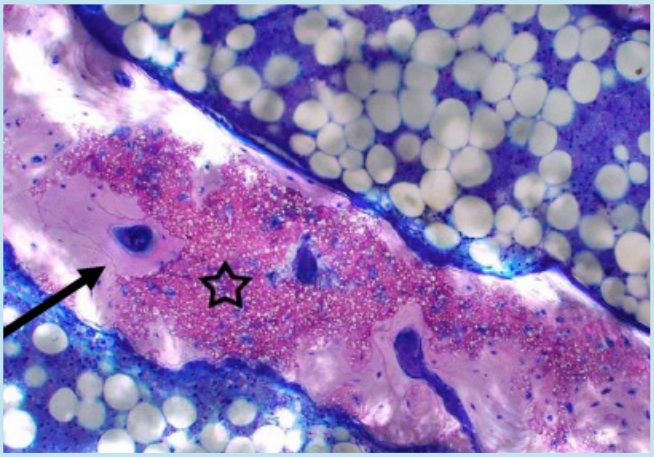


Fig 5: Show CERAMENT™ with translumiscent HA particles (star) inside a newly formed bone trabecula (arrow).

It was concluded that calcium sulfate in combination with HA resulted in the formation of new bone that completely surrounded and embedded the HA particles once the calcium sulfate had resorbed[50]. The new trabeculae became thicker and denser, which increased the mechanical strength of the newly formed bone as demonstrated by indentation tests (Fig 6)[50].

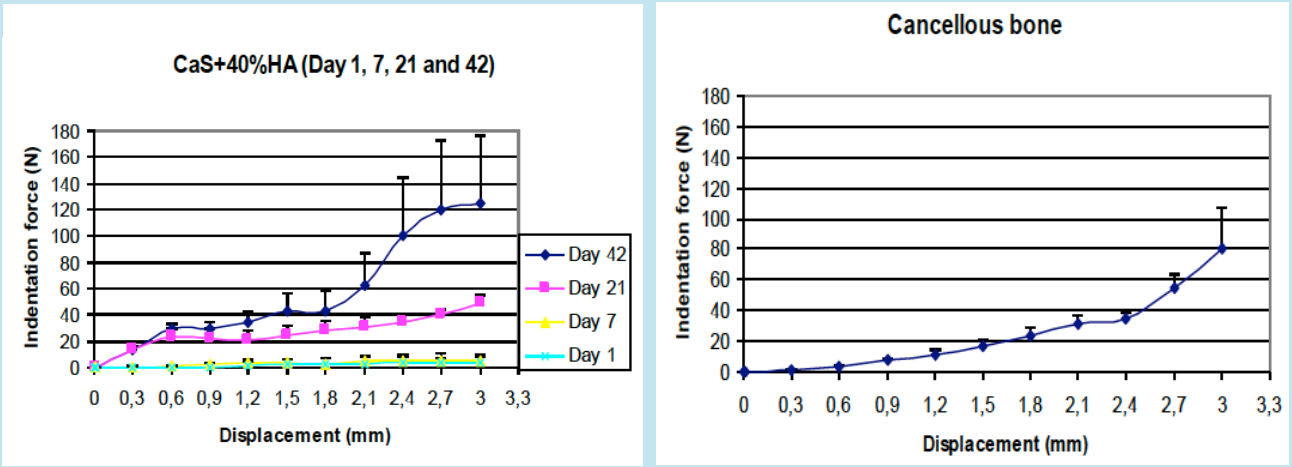


Fig 6: Showing the mechanical strength of newly formed bone after CERAMENT™ implantation (left)vs. normal cancellous bone (right). Forty-two days after CERAMENT™ implantation (blue line to the left) mechanical strength of the newly formed bone was higher compared to intact cancellous bone (to the right).

ii) Osteoconductivity

Calcium sulfate alone is not an osteoconductive material. Bone will form with time but early results show that fibrous tissue is first formed between the new bone and the remaining material[50], probably because of the rapid resorption of the calcium sulfate. HA particles can be added to the calcium sulfate based bone substitute to provide osteoconductivity. It has been clearly shown that between 30 and 50% of HA is necessary to obtain an osteoconductive material that still provides sufficient strength[15,54]. In a study using 40% HA in calcium sulfate, osteoconductivity was observed in defects in the distal part of rabbit femora[50].

iii) Bone regeneration – transformation into bone

The first generation of synthetic bone substitutes consisting of either pure calcium sulfate or pure HA have had limited advantages due to their static behavior. It was thus stated by Hench in 1998[55] that "we need to shift the emphasis of biomaterial research towards assisting or enhancing the body's own reparative capacity".

Most calcium phosphate-based bone substitute materials have a too slow resorption rate and are followed by new bone tissue formation through a creeping substitution from the surface towards the center of the defect[56]. New bone tissue is only present at the surface of the material and the material remains in the defect center until complete healing occurs, which might take years[16,17,57]. The mechanism of action for CERAMENT™ is different. Through initial microporosity and later macroporosity, early vascularization and invasion of osteoblasts enable a multiple site formation of bone throughout the cured CERAMENT™ implant (Fig 7).

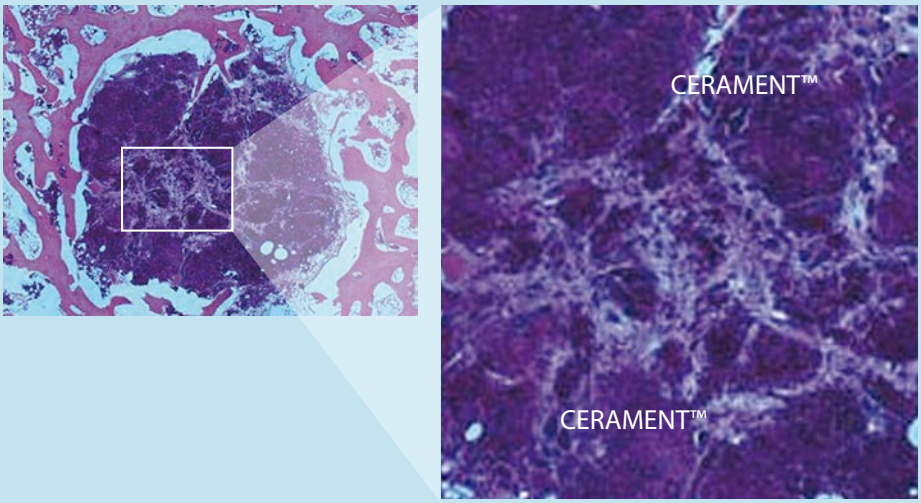


Fig 7: New bone tissue formed throughout CERAMENT™ after 12 weeks, as opposed to the creeping substitution seen with many calcium phosphate-based bone substitutes. Rabbit study with a critical defect (> 5 mm) created in the lateral femoral condyle and filled with CERAMENT™ [51].

Immature bone tissue is first formed by the osteoblasts but is later mineralized and remodeled into new trabecular bone[51] (Fig 8).

The bone remodeling process includes both osteoclasts and osteoblasts and they are both seen at the material/bone interface (Fig 9).

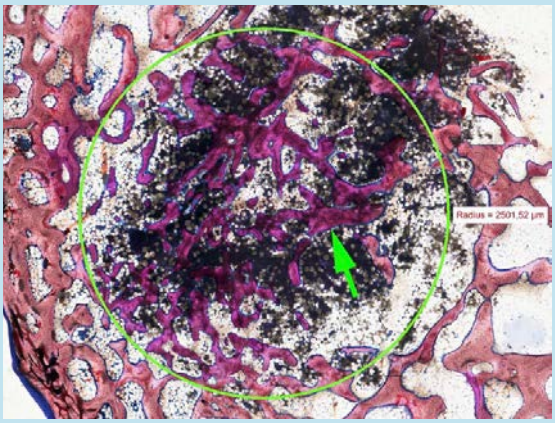


Fig 8: Deep pink color (green arrow) shows newly formed bone which is transformed into trabeculae, i.e. mature bone. Remaining CERAMENT™ stained black. Animal study with a critical defect (> 5 mm) created in the lateral femoral condyle and filled with CERAMENT™[51].

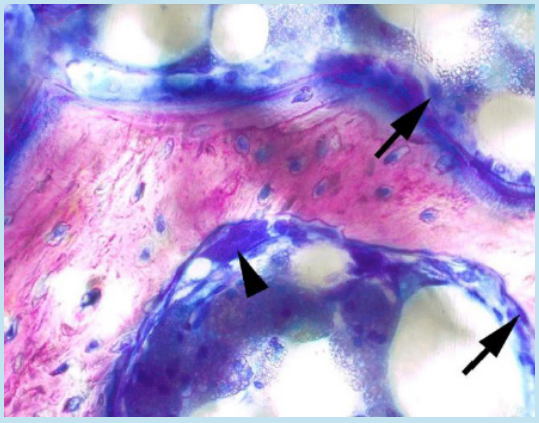
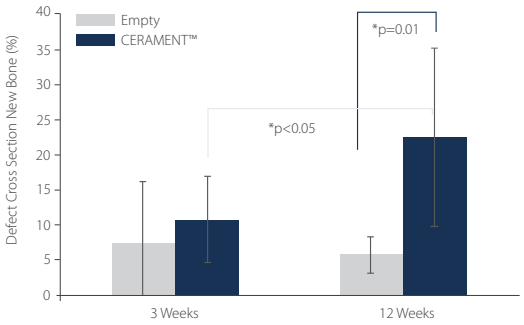


Fig 9: Newly formed bone trabeculae rimmed with multiple osteoblasts (arrows) and osteoclasts (arrow heads)[51]. Rabbit study with a critical defect (> 5 mm) created in the lateral femoral condyle and filled with CERAMENT™[51].

CERAMENT™ has been shown to be biocompatible, bioactive, and osteoconductive. But most importantly when used as a bone void filler, CERAMENT™ has proven to carry the ability to form new bone in a bone defect. This was clearly demonstrated by Voor et al[48], implanting CERAMENT™ in critical size defects in rabbit distal femurs with examination of new bone formation (Fig 10) and defect healing grade (Fig 11) after 3 and 12 weeks. Substantially more bone was formed in the defects filled with CERAMENT™ compared to those that were left empty[48].



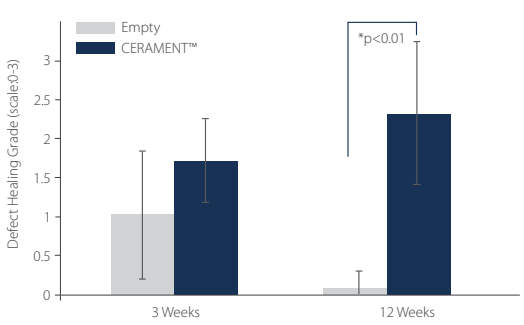


Fig 10 and 11: Both the amount of new bone formation and the healing grade* were greater for CERAMENT™ filled defect compared to empty at both 3 and 12 weeks. The difference was statistically significant at 12 weeks.

* A grade from 0 to 3 [0=no cellular activity, 1=minimal cellular activity only at the defect boundary, 2=cellular activity with new bone formation at the defect boundary, 3=extensive cellular activity with new bone extending to the defect center] was assigned to each histological section

VII. Clinical results

Case 1

Osteotomy after distal radius fracture malunion

A man (40 years old) was included in a clinical study by Abramo *et al*[58]. He underwent osteotomy after distal radius fracture malunion.

Fixation was performed using Trimed system. CERAMENT™ was applied in the gap formed during surgery. Fig A shows the osteotomy directly post-operatively and Fig B shows the same osteotomy one year later. Complete bone healing was achieved and new trabecular and cortical bone were formed where CERAMENT™ had been implanted.

Credit:
Antonio Abramo (1), Mats Geijer (2),
Philippe Kopylov (1), Magnus Tägil (1)

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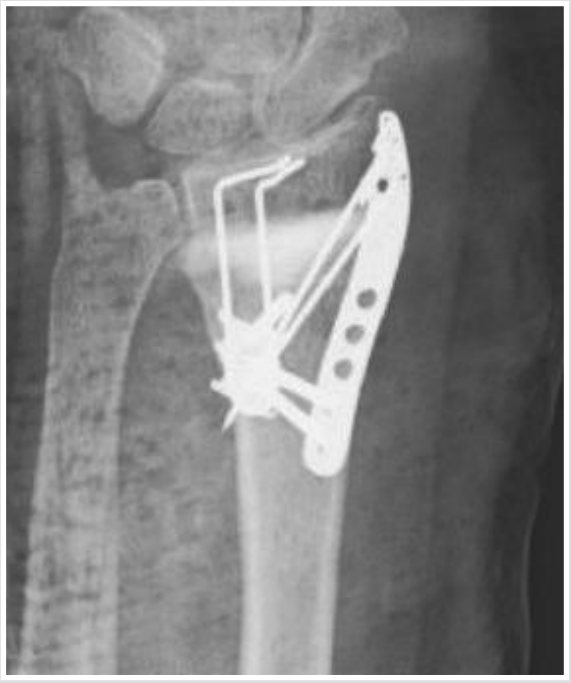

Figure A: Post-operative picture of osteotomy in distal radius.

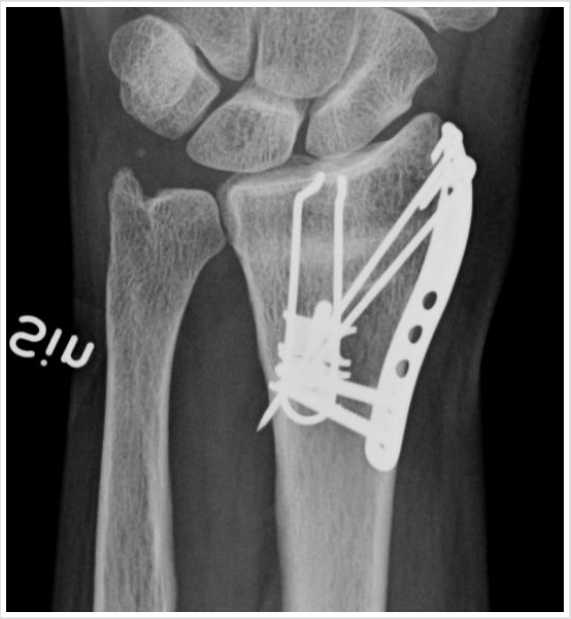

Figure B: 1 year follow up shows complete bone healing and new trabecular and cortical bone in wrist osteotomy.

Case 2

Treatment of displaced intra-articular calcaneal fracture

A female (54 years old) with a displaced intra-articular calcaneal fracture had open reduction and internal fixation (ORIF) Fig. A. The resulting bone void after fracture reducation was filled with CERAMENT™|BONE VOID FILLER.

Removal of the plate at 4 months due to pain (no signs of infection) facilitated a bone biopsy which showed early signs of new bone growth Fig B.

At 7 months the patient demonstrates a good result. Fig C & D.

Credit:
Damiano Papadia

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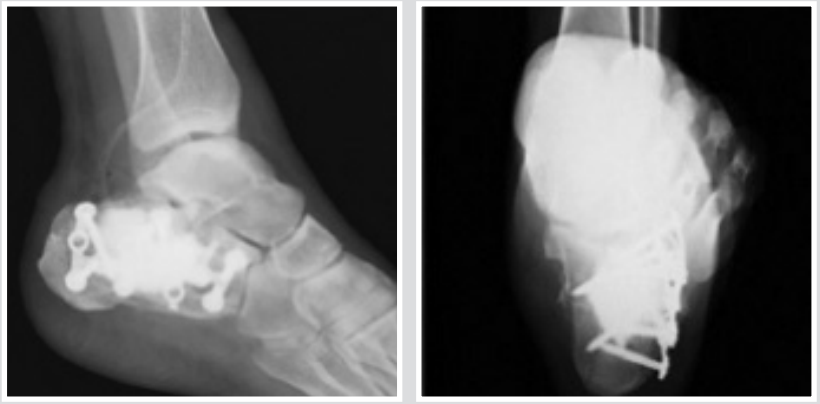


Figure A. X-ray immediately post surgery.

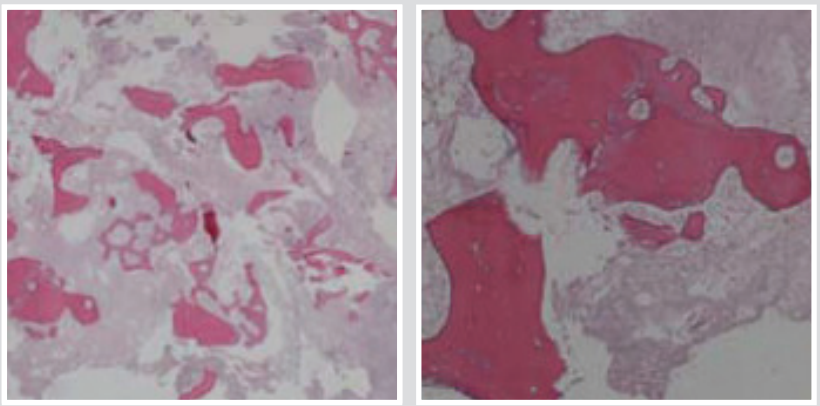


Figure B. Histology at 4 months showing new bone growth.

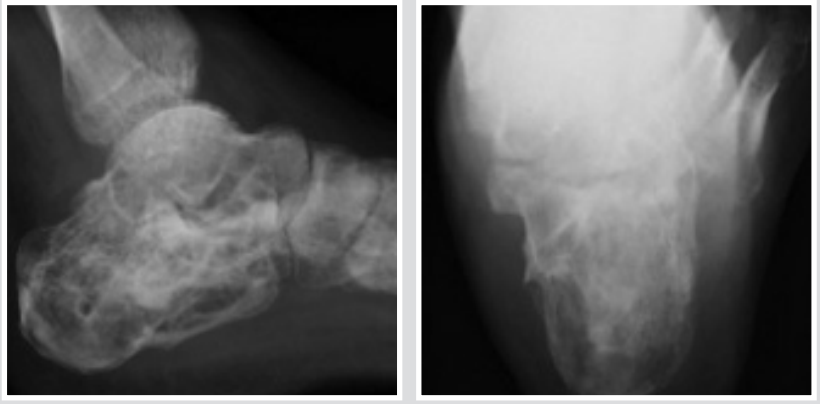


Figure C. X-ray after removal of the plate.

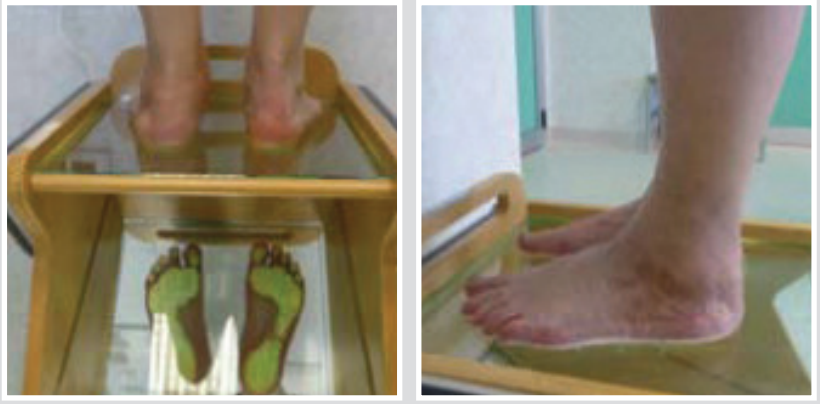


Figure D. Patient full weight bearing.

Case 3

Bicondylar osteoporotic tibial plateau fracture

A female (88 years old) underwent open reduction and internal fixation of angulated, impacted, displaced and unstable left tibial plateau bicondylar fracture, with percutaneous lateral plate application.

CERAMENT™|BONE VOID FILLER was injected to fill resulting void after fracture reduction. Fig A & B.

At 18 months patient was clinically improved and ambulating well. Radiographs showed remodeling of CERAMENT™|BONE VOID FILLER into bone. Fig C & D.

Credit:
Dr. Prashant Desai DO

Lakeland Regional Medical Center, Lakeland, Florida, USA

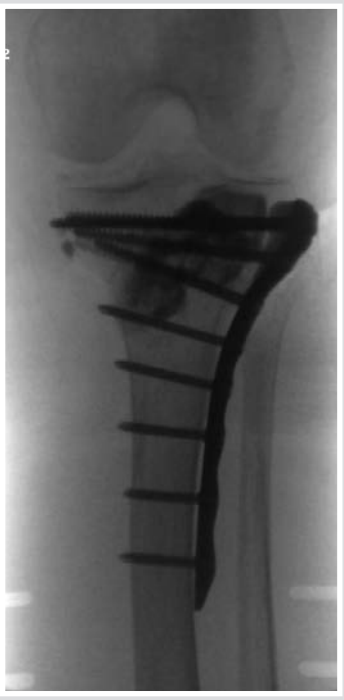


Figure A. Intra operative anterior radiograph placement of CERAMENT™|BONE VOID FILLER

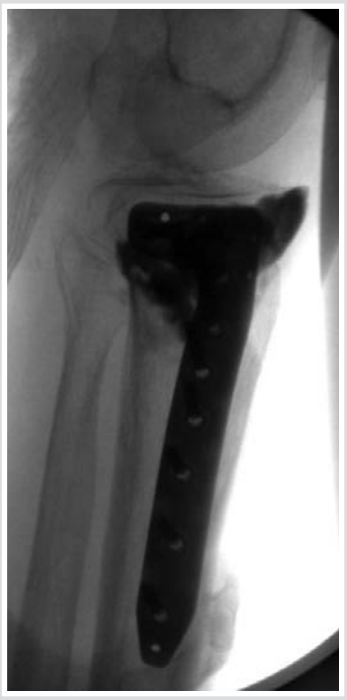


Figure B. Intra operative lateral radiograph placement of CERAMENT™|BONE VOID FILLER

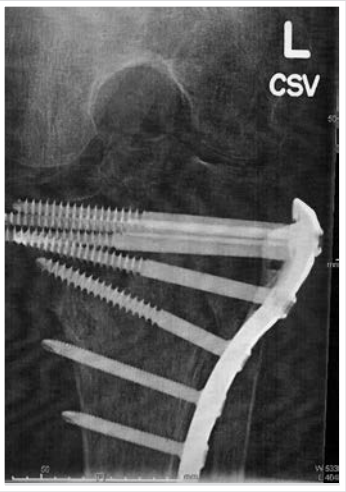


Figure C. At 18 months anterior radiograph demonstrating excellent incorporation of CERAMENT™|BONE VOID FILLER by new bone

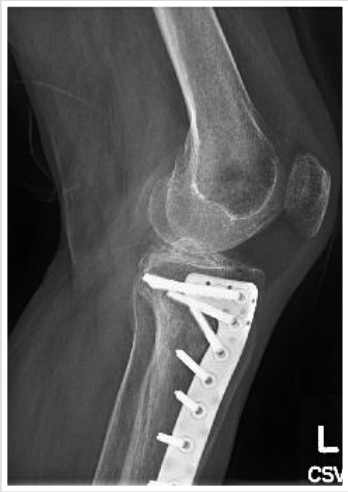


Figure D. At 18 months lateral radiograph demonstrating excellent incorporation of CERAMENT™|BONE VOID FILLER by new bone

Case 4

Hip Revision

A 61-year old male with a history of well-positioned, well functioning bilateral uncemented THAs presented with progressive left hip pain over 6 months.

X-rays showed a large cystic osteolytic lesion in the left acetabulum involving the superior dome and the medial wall with extension into the ischium. CT scan confirmed extensive amount of osteolysis.

Intraoperatively, significant wear of the polythylene liner allowing subluxation of the femoral head was found. The cup was solidly fixed and was not revised. The femoral head was exchanged for a new 32 mm head and the liner was exchanged to a10-degree elevated lip liner.

A 2x2cm window was made above the acetabulum at the level of the cyst.

The cyst was curetted and filled with 32cc CERAMENT™|BONE VOID FILLER (Fig. 1). Once CERAMENT™ solidified, the wound was irrigated and closed.

At 6 weeks post-op, the patient had good and painless range of motion and was weight-bearing without aides. X-rays confirmed good positioning of the acetabular implant CERAMENT™|BONE VOID FILLER is still visible (Fig. 2).

At 8 months post-op, the patient was doing well and was pain-free. X-rays demonstrated CERAMENT™|BONE VOID FILLER to be nearly completely resorbed and replaced with new cancellous bone (Figs. 4 & 5).

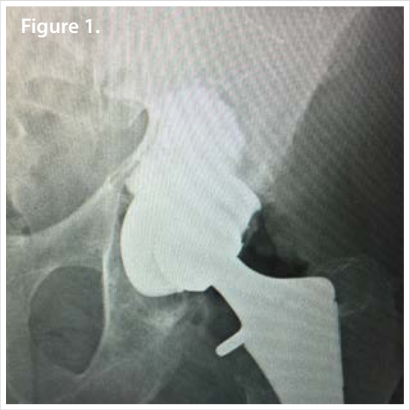


Figure 1.

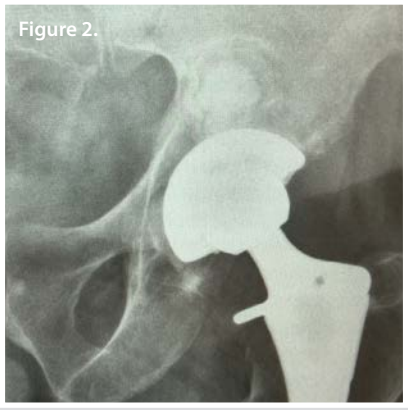


Figure 2.

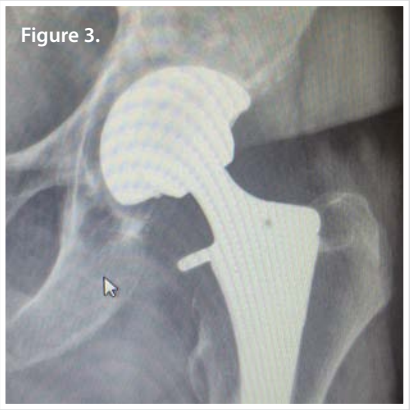


Figure 3.

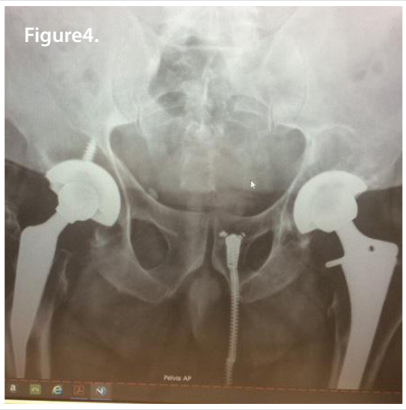


Figure4.

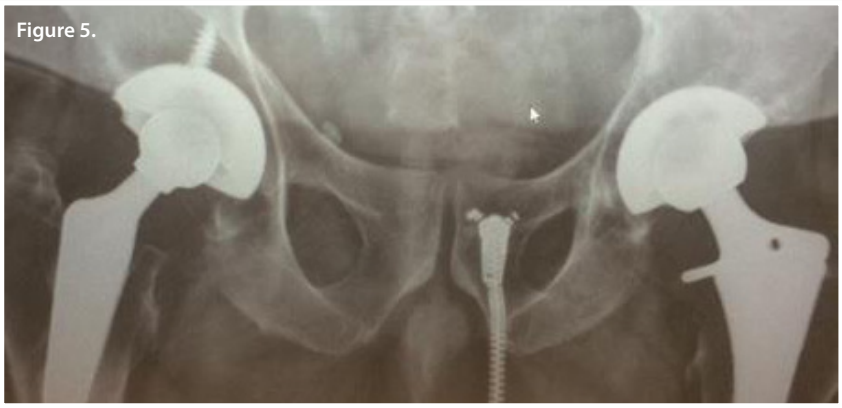


Figure 5.

Credit:
Thomas Baier,, M.D.

Advocate Condell Medical Center, Libertyville, IL UsA

Case 5

Minimally Invasive Treatment of a Benign Proximal Humeral Cyst

Large benign proximal humeral cyst with thinning of proximal cortices (Fig. 1).

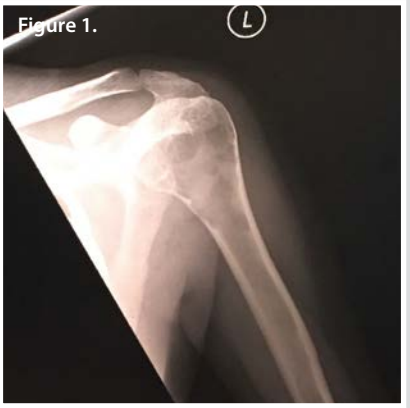
The cyst was aspirated using a large-bore needle then exchanged for a cannula for pressure relief during injection of CERAMENT™|BONE VOID FILLER (Fig. 2, 3).

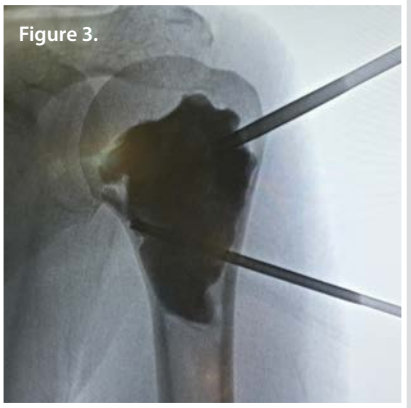
An additional cannula was placed into the distal-most extent of the cyst. The CERAMENT™|BONE VOID FILLER delivery syringe was attached to the end of the distal cannula and injected one minute after mixing to ensure complete fill of the void via a bottom-to-top (distal to proximal) technique.

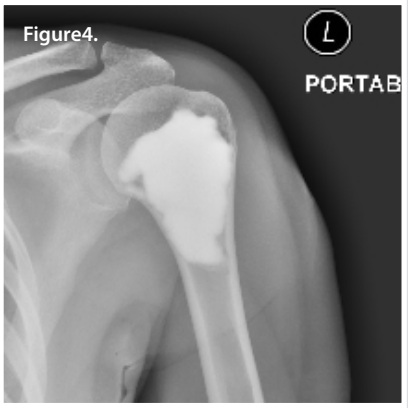
30cc of CERAMENT™| BONE VOID FILLER was injected. Iohexol provides visibility of product under fluoroscopy (Fig. 3, 4).

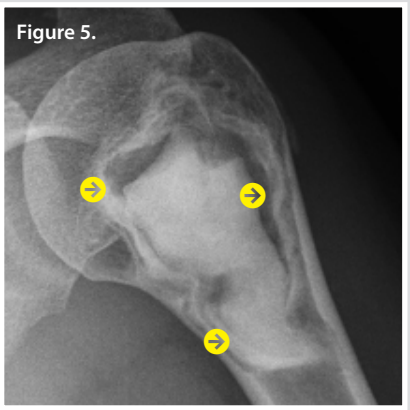
6 week X-ray demonstrates a white 'halo effect' outlining the cyst (Fig. 5). At 3 months, early bone remodeling is seen, along with a 'puddling effect' at bottom of cyst (Fig. 6).

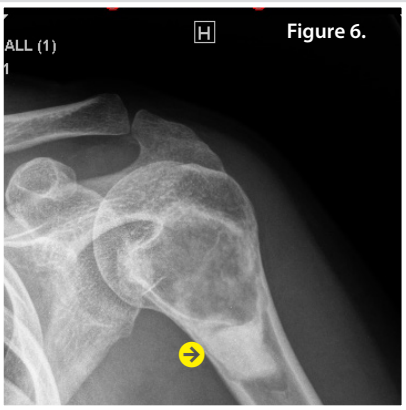
5 month X-ray shows on-going replacement of CERAMENT™| BONE VOID FILLER with new cancellous bone (Fig. 7).

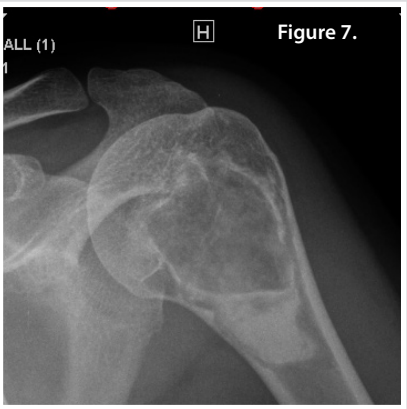












Credit:
Joseph Benevenia, M.D.

Rutgers University Hospital, Newark, NJ

VIII. Conclusion

CERAMENT™ is an easy to use, injectable bone graft substitute that will transform into bone within 6-12 months[33, 59]. Unlike bone substitutes based on calcium phosphates alone, and with a slow resorption rate due to creeping substitution starting from the surface, CERAMENT™ will facilitate bone ingrowth based on its micro-and macro porosity, which results in multiple islets of de novo bone formation throughout the implant[51]. The resorption rate of the material is designed to match the speed of new bone tissue ingrowth. By using calcium sulfate as a complement to the osteoconductive hydroxyapatite, the material resorption will be complete and the hydroxyapatite particles will guide the bone ingrowth and ultimately get incorporated into the newly formed bone trabecuale[31,33,48]. The bioactivity of the material initiates an endogenous precipitation of hydroxyapatite resulting in a thin layer of apatite on the implant surface[34], which enhances the material-bone cell contact[46] and retards the calcium sulfate resorption[34]. New bone will not only be deposited on the outside of the material but the bone generation will occur at multiple sites throughout the material[51], which accelerates the transformation of CERAMENT™ into bone.

Biphasic, providing osteoconductivity and complete resorption

Hydroxyapatite guides bone ingrowth

Hydroxyapatite makes the material bioactive

Hydroxyapatite gets completely incorporated into the bone and potentially strengthens it

Remodels completely

Proven to be safe and efficacious

Can be used at metal-bone interfaces

Will transform into both cancellous and cortical bone

Easy to use

Radiopaque to facilitate safe injection

Bone regeneration occurs everywhere in the material, not only on the surface

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