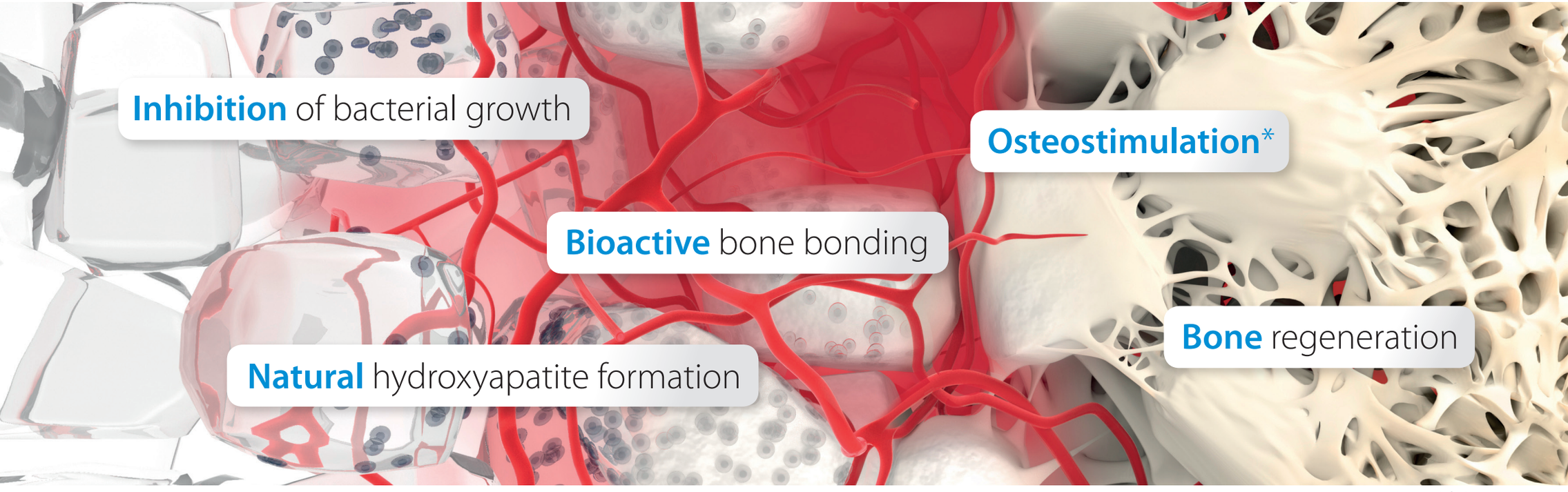
BonAlive® granules

Medical education | *Orthopedics & Trauma*



*non-osteoinductive

BonAlive® BIOMATERIALS LTD

MECHANISM OF ACTION

BonAlive® granules (bioactive glass S53P4) is a CE-marked class III medical device that is used in surgical procedures to regenerate bone. BonAlive® granules is osteostimulative* which means that it activates genes responsible for bone formation in osteogenic cells. It also has the special property of effectively inhibiting bacterial growth, which makes it a very unique material for regenerating bone.

BonAlive® granules composition:

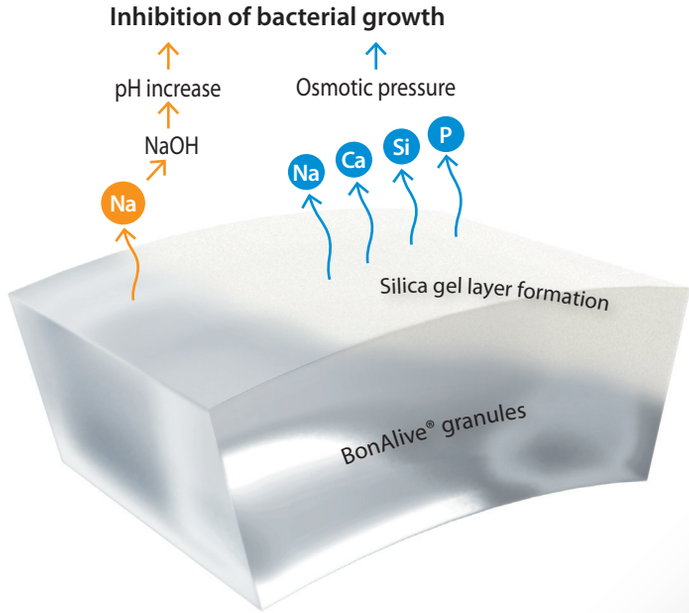
- 53% SiO_2, 23% Na_2O, 20% CaO, 4% P_2O_5

BonAlive® granules indications:

- Bone cavity filling
- Bone cavity filling in the treatment of chronic osteomyelitis

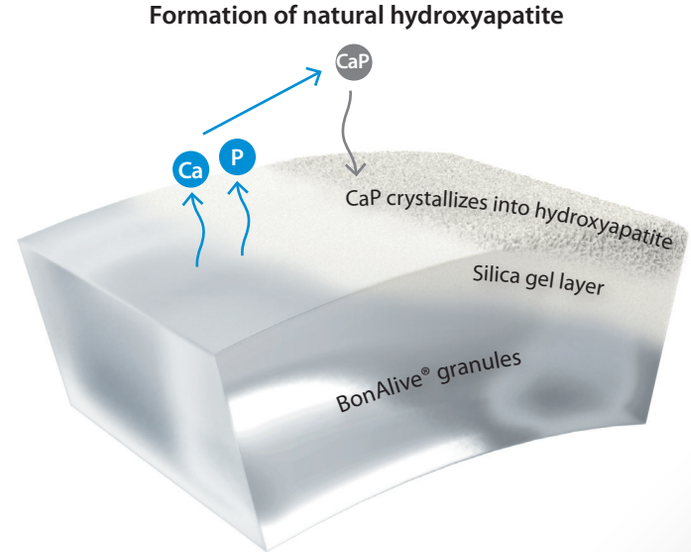
Inhibition of bacterial growth

In contact with body fluids bioactive glass works by leaching out ions leading to an alkaline environment (high pH) and increased osmotic pressure. This mechanism has been shown to effectively inhibit bacterial growth.



Bone bonding and osteointegration

The surface reactions develop a silica gel layer on the bioactive glass, which attracts the Ca and P that has been released from from the granules. The precipitated CaP crystallizes to natural hydroxyapatite, which is similar to the mineral component of bone. The newly formed natural surface will promote bone bonding and osteointegration.



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INHIBITION OF BACTERIAL GROWTH

One of the most striking features of BonAlive® granules is its ability to inhibit bacterial growth. This phenomenon has been evidenced with more than 50 clinically relevant aerobic and anaerobic bacterial species through *in vitro* studies, and indirectly by empirical observation of patient data over the past 15 years.

Chronic bone infections play a large role in surgery as the infection can be difficult to eradicate and might require several operations. Antibiotic resistance has become an increasing threat and new tools that are not based on antibiotics can bring significant benefits in fighting chronic bone infections. The efficacy of BonAlive® granules towards methicillin-resistant (MR) *Pseudomonas aeruginosa*, *Staphylococcus aureus* (*MRSA*), *Staphylococcus epidermidis* (*MRSE*) has been tested and proven effective.

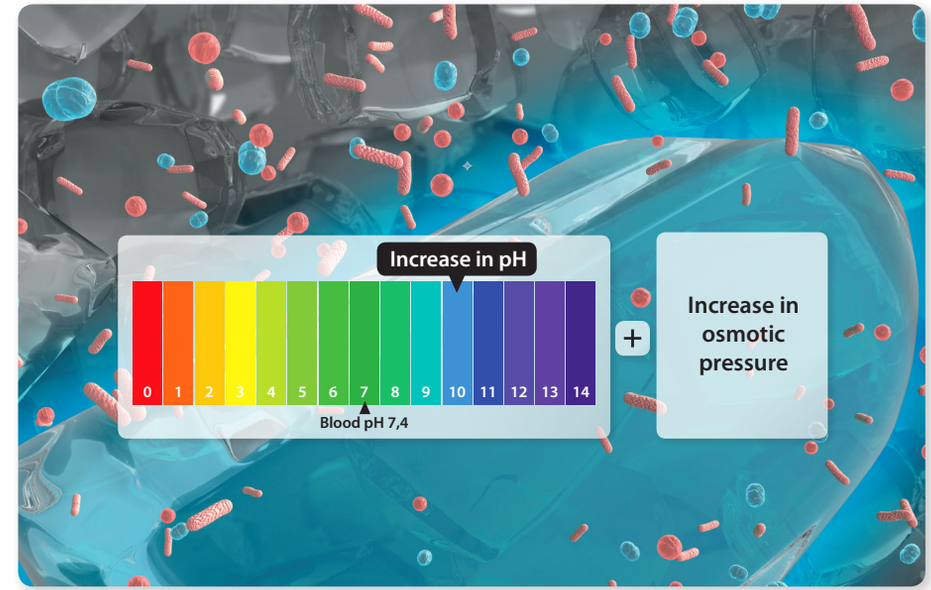
Mechanism

The bacterial growth inhibiting effect of BonAlive® granules is based on two simultaneous processes that occur when the bioactive glass reacts with body fluids.

1. Sodium is released from the surface of the bioactive glass and induces an **increase in pH** (alkaline environment), which is not favourable for the bacteria.

2. The released Na, Ca, Si and P ions give rise to an **increase in osmotic pressure** due to an elevation in salt concentration, i.e. an environment where the bacteria cannot grow.

These two mechanism will together effectively inhibit the adhesion and colonization of bacteria on the granule surface.



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Antibacterial effect of bioactive glasses on clinically important anaerobic bacteria in vitro. Leppäranta O, Vaahtio M, Peltola T, Zhang D, Hupa L, Ylänen H, et al. J Mater Sci: Mater Med. 2008;19(2):547-551.
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Interactions between the frontal sinusitis-associated pathogen Heamophilus Influenzae and the bioactive glass S53P4. Stoor P, Söderling E, Andersson OH, Yli-Urpo A. Bioceramics. 1995;8:253-258.

Broad spectrum efficacy

BonAlive® granules is effective in inhibiting bacterial growth of more than 50 common bacteria species (including *MRSA*, *MRSE*).

Gram positive bacteria

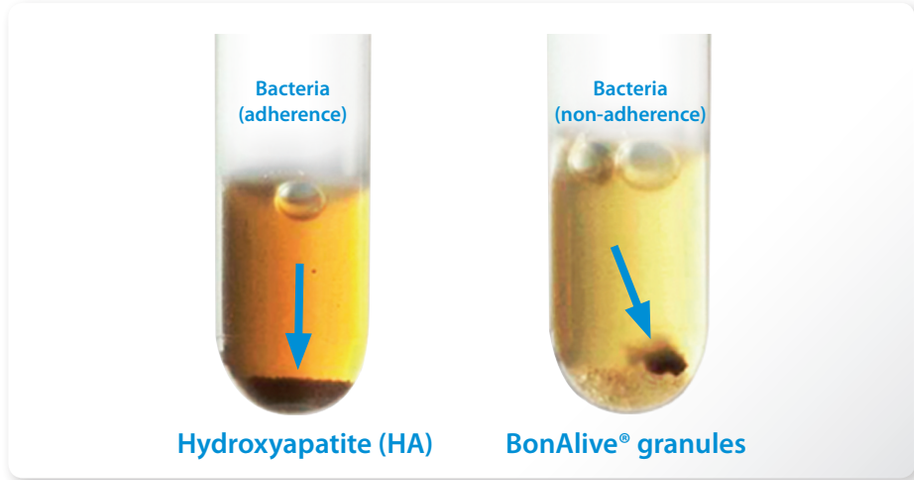
- *Bacillus cereus*
- *Bifidobacterium adolescentis*
- *Clostridium difficile*
- *Clostridium perfringens*
- *Clostridium septicum*
- *Corynebacterium ulcerans*
- *Enerobacter cloacae*
- *Enterococcus faecalis*
- *Enterococcus faecium*
- *Eubacterium lentum*
- *Listeria monocytogenes*
- *Micrococcus sp.*
- *Mycobacterium tuberculosis*
- *Peptostreptococcus anaerobius*
- *Peptostreptococcus magnus*
- *Propionibacterium acnes*
- *Propionibacterium propionicus*
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Staphylococcus hominis*
- *Staphylococcus lugdunensis*
- *Streptococcus agalactiae*
- *Streptococcus mutans*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Streptococcus sanguis*

Gram negative bacteria

- *Acinetobacter baumannii*
- *Bacteroides fragilis*
- *Bacteroides thetaiotaomicron*
- *Chryseobacterium (former Flavobacterium) meningosepticum*
- *Enterobacter aerogenes*
- *Enterobacter amnigenus*
- *Escherichia coli*
- *Fusobacterium necrophorum*
- *Fusobacterium nucleatum*
- *Haemophilus influenzae*
- *Klebsiella pneumoniae*
- *Moraxella catarrhalis*
- *Neisseria meningitidis*
- *Pasteurella multocida*
- *Porphyromonas gingivalis*
- *Prevotella intermedia*
- *Prevotella melaninogenica*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*
- *Salmonella typhimurium*
- *Shigella sonnei*
- *Veillonella parvula*
- *Yersinia enterocolitica*

Methicillin-resistant bacteria

- *Pseudomonas aeruginosa*
- *Staphylococcus aureus (MRSA)*
- *Staphylococcus epidermidis (MRSE)*



Soor P. et al. 1996

Bacteria test with pigmented *Porphyromonas gingivalis* shows that bacteria cannot adhere and grow on BonAlive® granules surface.

Courtesy of Prof. Lorenzo Drago, University of Milan, Italy

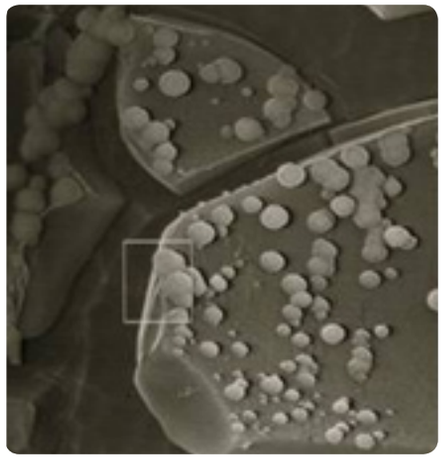
The images illustrate the impact of S53P4 on methicillin-resistant *Staphylococcus aureus, Klebsiella pneumoniae* and *Acinetobacter baumannii*. The inhibition of bacterial growth can be seen as changes in the morphology of the bacteria; deformation of the cells and hole formation in the cell membranes.

OSTEOINTEGRATION AND OSTEOSTIMULATION*

An osteoconductive material functions as a scaffold that allows bone growth on its surface or into its three-dimensional structure. BonAlive® granules is osteoconductive in nature, providing a supportive material for the osteoblast cells during bone formation. As a result of the osteoconductive process, bone grows onto and between the bioactive glass granules. Furthermore, the bioactive glass granules have been proven to activate a biological process that stimulates bone regeneration in a fashion far superior to mere osteoconductive materials. This is defined as osteostimulation*.

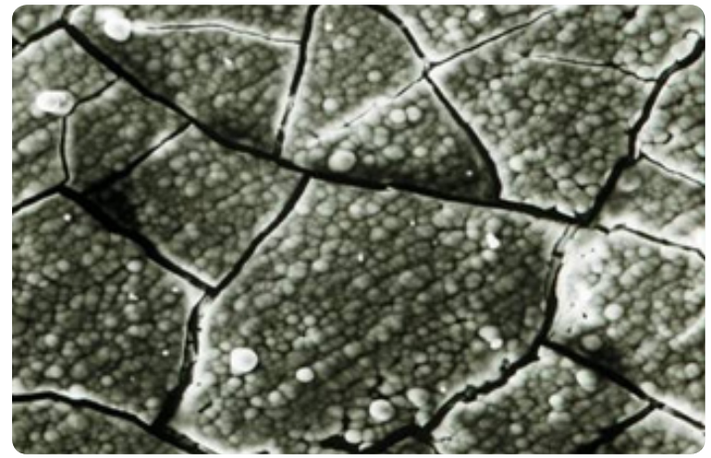
> ***"The bioactive glass surface is not only conductive but also osteoproductive in promoting migration, replication, and differentiation of osteogenic cells and their matrix production."***
>
> Virolainen et al. 1997

1 day



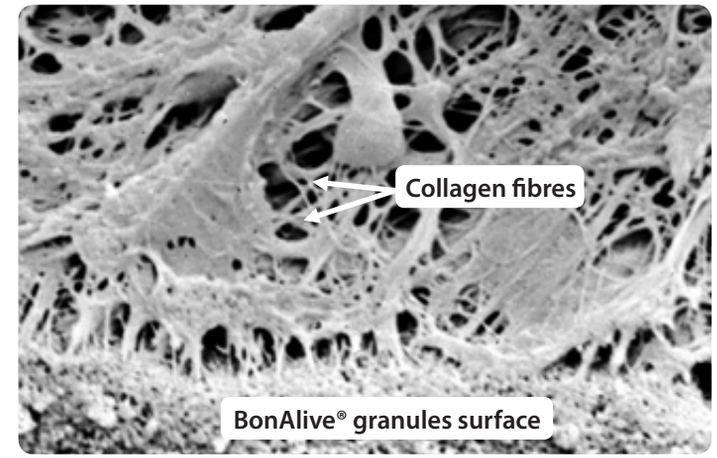
Hydroxyapatite starts to form on BonAlive® granules surface.

1 week



Hydroxyapatite covers BonAlive® granules surface.

6-12 weeks



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BonAlive® granules bond to bone and stimulate new bone formation (osteostimulation*).

*non-osteoinductive

Formation of natural hydroxyapatite and osteointegration

The bioactive surface of the BonAlive® granules is characterized by its ability to attach firmly to living tissue, facilitate tissue growth and bond chemically with surrounding bone. Osteogenic cells, such as osteoblasts and osteoclasts will be stimulated by the released Si and Ca and the natural hydroxyapatite surface. Subsequently the bone formation pathway will be initiated.

Reaction layers of BonAlive® granules

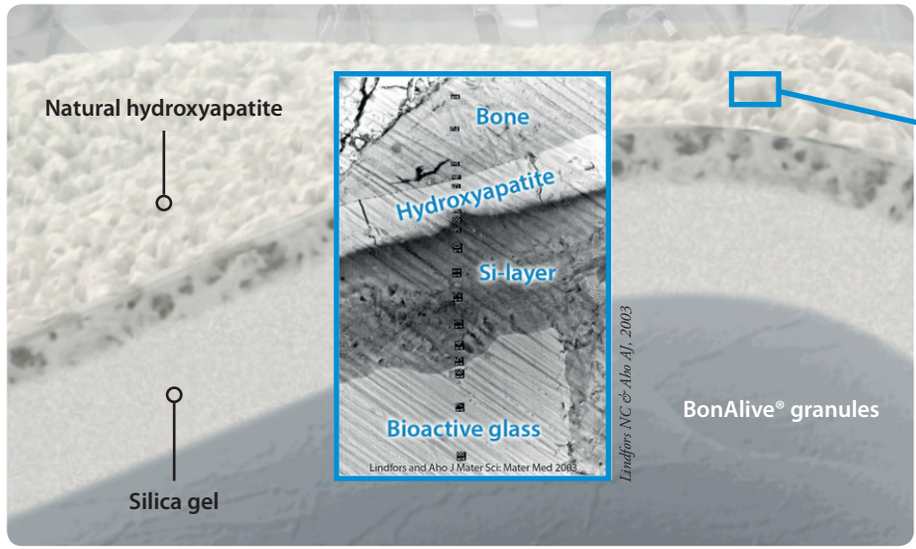
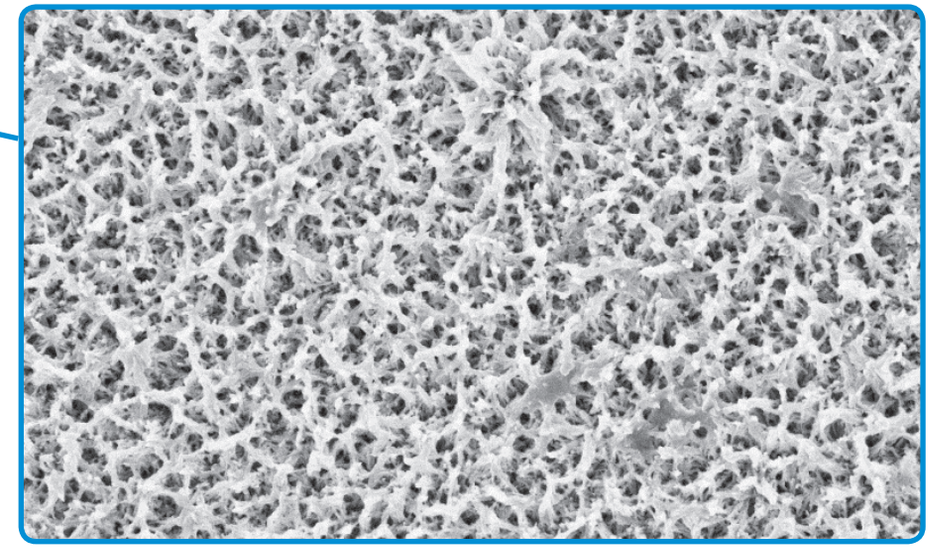


Illustration of a BonAlive® bioactive glass granule to show the characteristics of the reaction surface.

Natural hydroxyapatite surface on BonAlive® granules



Scanning electron microscopy (SEM) image (10 000 x magnification) presenting the hydroxyapatite surface that resembles the mineral phase found in natural bone.

References

Genetic design of bioactive glass. Hench L. J Eur Cer Soc. 2009;29:1257-1265.
Molecular basis for action of bioactive glasses as bone graft substitute. Välimäki VV, Aro HT. Scand J Surg. 2006;95(2):95-102.
Intact surface of bioactive glass S53P4 is resistant to osteoclastic activity. Wilson T, Parikka V, Holmbom J, Ylänen H, Penttinen R. J Biomed Mater Res. 2005;77A(1):67-74.
Granule size and composition of bioactive glasses affect osteoconduction in rabbit. Lindfors NC, Aho AJ. J Mater Sci: Mater Med. 2003;14(4):265-372.
Histomorphometric and molecular biologic comparison of bioactive glass granules and autogenous bone grafts in augmentation of bone defect healing. Virolainen P, Heikkilä J, Yli-Urpo A, Vuorio E, Aro HT. J Biomed Mater Res. 1997;35(1):9-17.
Long term behaviour of bioactive glass cone and granules in rabbit bone. Heikkila JT, Salonen H, Yli-Urpo A, Aho AJ. Bioceramics. 1996;9:123-126.
Bone formation in rabbit cancellous bone defects filled with bioactive glass granules.Heikkila JT, Aho HJ, Yli-Urpo A, Happonen R, Aho AJ. Acta Orthopaedica. 1995;66(5):463-467.

Osteostimulation*

The mechanism of bone regeneration with bioactive glass has been demonstrated to be based on both **surface-mediated** (natural hydroxyapatite surface) and **solution-mediated** (release of Si and Ca) processes. The effect is seen on a cellular level as promotion of particular cell stages of the osteogenic cell lineage through specific gene activation. This active role in osteogenesis has been defined as osteostimulation*. *In vitro* and preclinical studies with BonAlive® granules give evidence that it acts as an osteostimulative* material.

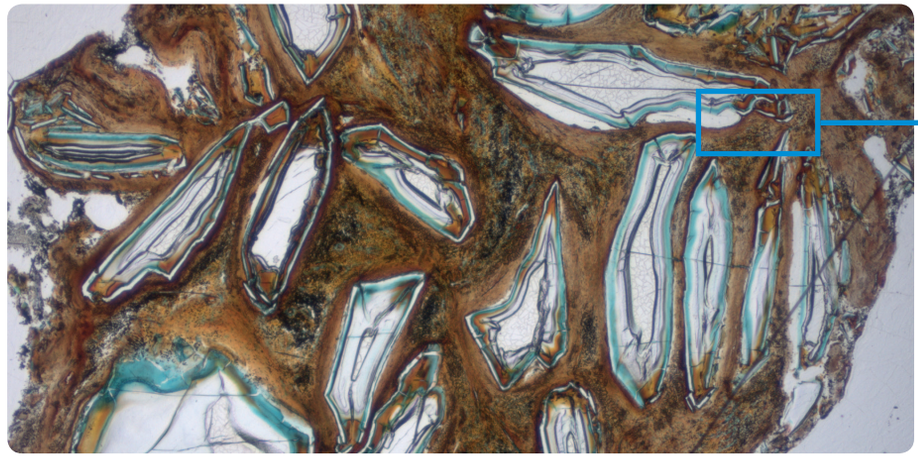
BonAlive® granules plays an active role in:

- recruitment and differentiation of osteogenic cells
- promotion of osteogenic cells to increase the remodeling rate of bone
- activation of specific genes in osteogenic cells as a response to ion dissolution and the natural HA surface

Definition of osteostimulation*

'Activation of genes responsible for bone formation in osteogenic cells'

Histology 3 months post-op



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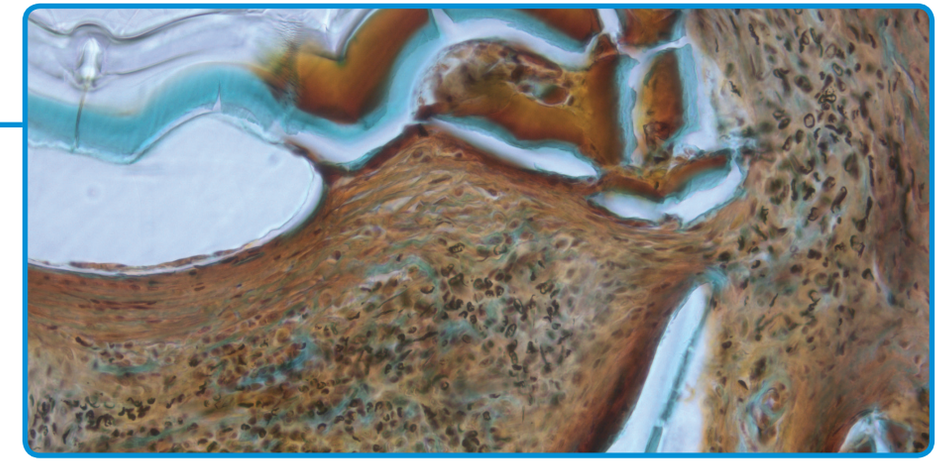
Histological 20µm-thick section from the mastoid area at 3 months after BonAlive® granules implantation (human biopsy).

Stimulation of tissue formation



The natural hydroxyapatite layer that has been formed on the BonAlive® granules conducts and stimulates new tissue formation in the grafted area. Tissue formation can be clearly visualized around the BonAlive® granules in the microscopy image.

References

Molecular basis for action of bioactive glasses as bone graft substitute. Välimäki VV, Aro HT. Scandinavian Journal of Surgery. 2006;95(2):95-102.
Osteoblast differentiation of bone marrow stromal cells cultured on silica gel and sol-gel-derived titania. Dieudonné SC, van den Dolder J, de Ruijter JE, Paldan H, Peltola T, van 't Hof MA, Happonen RP, Jansen JA. Biomaterials. 2002;23(14):3041-3051.
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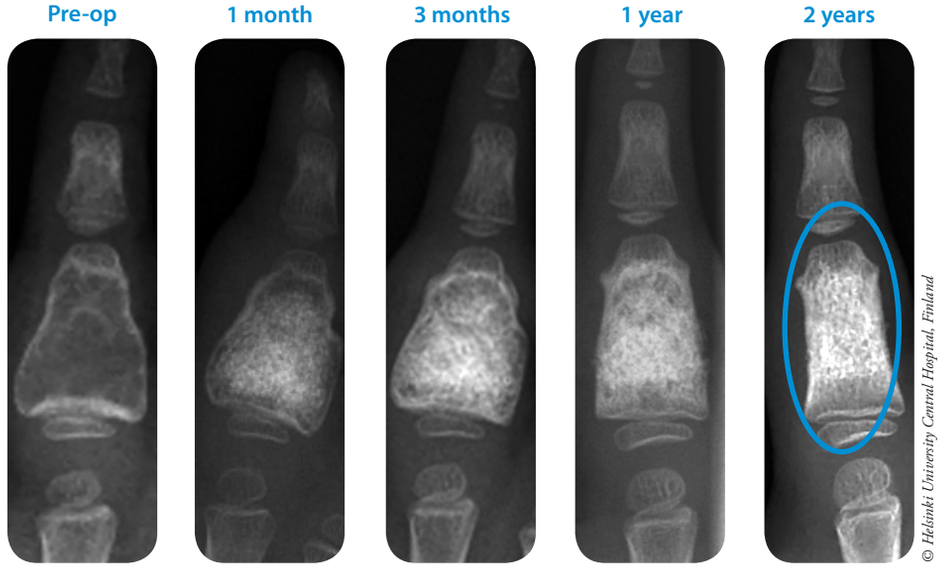
**non-osteoinductive*

RESORPTION PROFILE AND BONE REMODELING

BonAlive® granules is a fully resorbable biomaterial that remodels completely into bone over a period of several years to allow sufficient time for bone regeneration. These results have been presented in randomized prospective clinical trials, which show that BonAlive® granules is a safe and effective biomaterial for bone cavity filling applications.

Furthermore, BonAlive® granules has been proven to induce a high but local turnover through the simultaneous stimulation of osteoblast and osteoclast activity that promotes bone remodeling.



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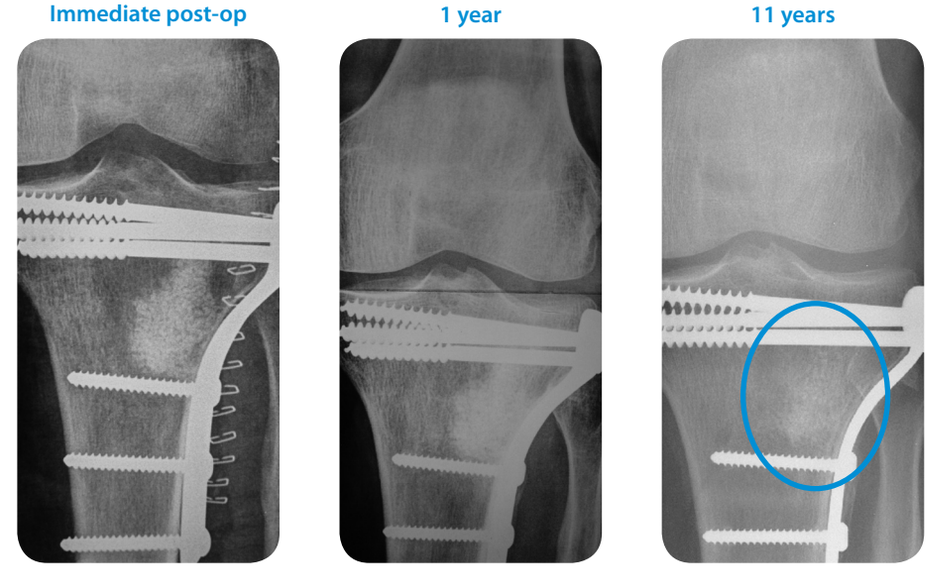
BonAlive® granules does not disturb the normal remodeling process of bone. In pediatric orthopedic patients the BonAlive® granules can be safely implanted in close vicinity of the growth plate. Small (0.5-0.8 mm) granules were used in this patient case.



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BonAlive® granules remodels slowly to bone and allows sufficient time for bone regeneration. At 1-year post-op a solid dense mass of bone can be visualized in the grafted area. At 11 years post-op BonAlive® granules has completely remodeled to bone. Medium (1.0-2.0 mm) granules were used in this patient case.

Reference

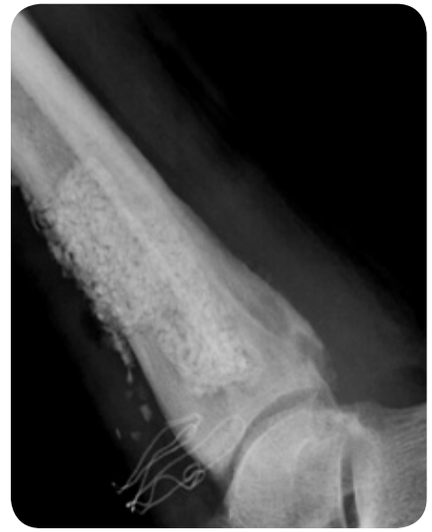
Treatment of a recurrent aneurysmal bone cyst with bioactive glass in a child allows for good bone remodelling and growth. Lindfors NC. Bone. 2009;45:398-400.

Reference

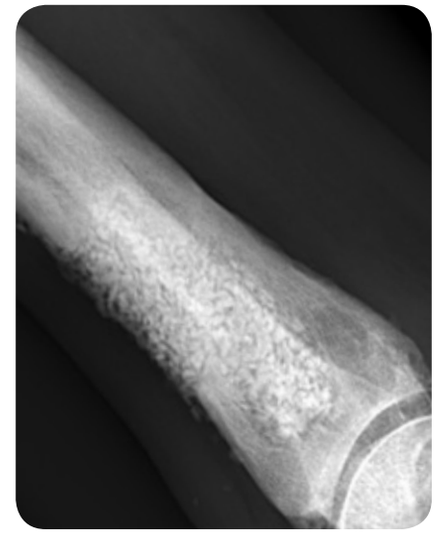
Bioactive glass S53P4 and autograft bone in treatment of depressed tibial plateau fractures. A prospective randomized 11-year follow-up. Pernaa K, Koski I, Mattila K, Gullichsen E, Heikkilä J, Aho AJ, Lindfors N. J Long-term Eff Med Impl. 2011;21(2):139-148.

The bone remodeling process in the grafted area visualized with x-ray and computer tomography (CT) as the BonAlive® granules resorb slowly and remodel into bone.

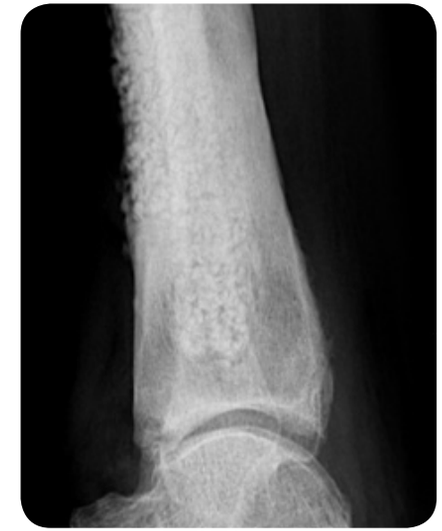
1-day post-op X-ray



1-year post-op X-ray



2-year post-op X-ray



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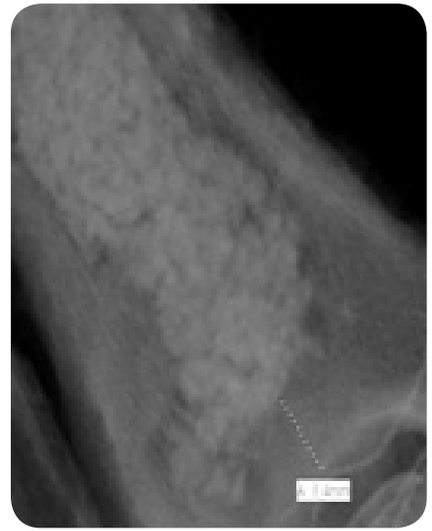
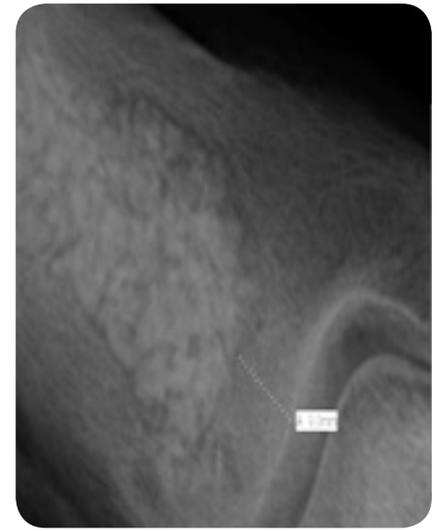
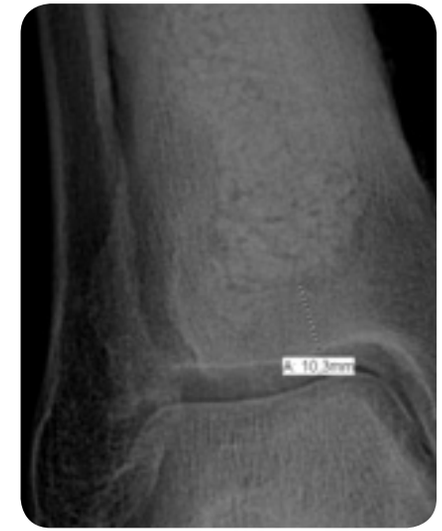
1-day post-op CT



1-year post-op CT



2-year post-op CT



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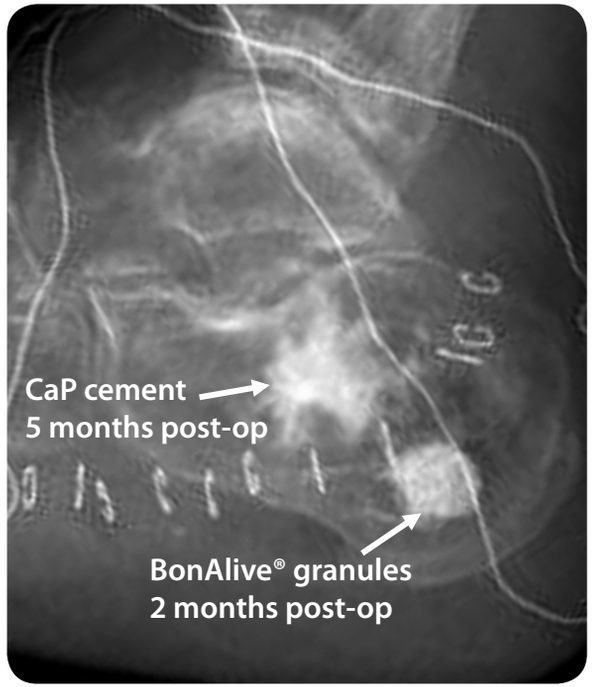
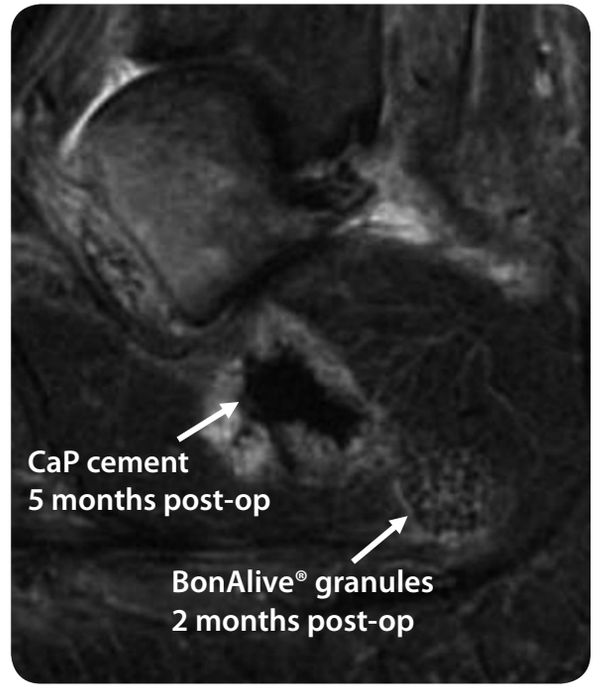
VISUAL APPEARANCE

The radio-opaque nature of the bioactive glass brings significant benefits. The BonAlive® granules can be visualized with imaging during surgery and the progression of the healing (resorption, remodeling and bone regeneration) can be followed post-operatively.

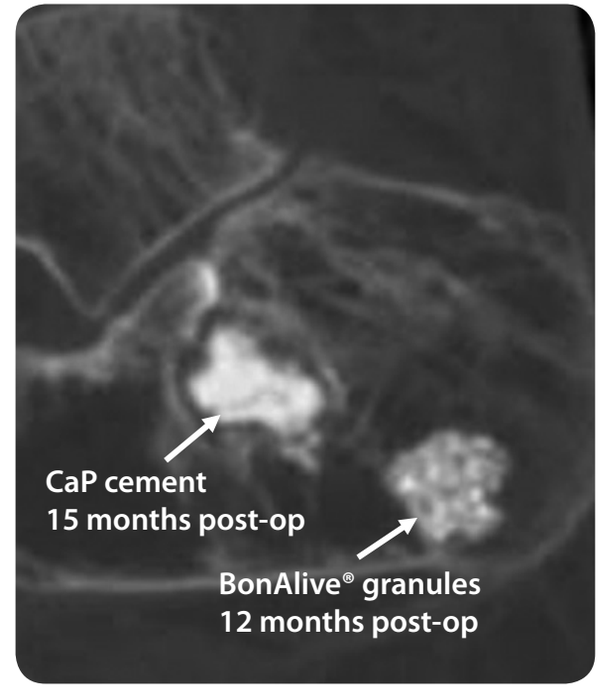
X-ray



MRI



CT



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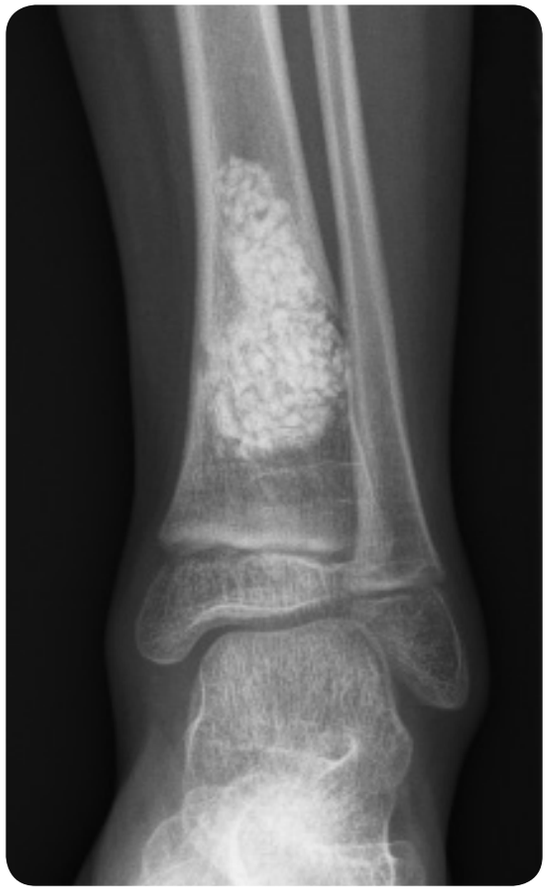
PEDIATRIC ORTHOPEDICS

Pediatric orthopedic surgery is a special focus area for the BonAlive® products. The long-term use of BonAlive® granules for treating bone defects created by benign bone tumors, e.g. enchondromas, simple cysts and aneurysmal bone cysts, has showed that BonAlive® granules resorbs slowly and the grafted area remodels to bone over time without disturbing the normal growth of bone in children.

BonAlive® granules induces a high but balanced local bone turnover by stimulating new bone formation through osteostimulation*. The proven performance of BonAlive® granules shows that it is a well tolerated and safe bone graft substitute for filling benign bone tumour cavities in pediatric patients.

BonAlive® granules indications

- Bone cavity filling
- Bone cavity filling in the treatment of chronic osteomyelitis



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References

Treatment of a recurrent aneurysmal bone cyst with bioactive glass in a child allows for good bone remodelling and growth. Lindfors NC. Bone. 2009;45:398-400.
Clinical experience on bioactive glass S53P4 in reconstructive surgery in the upper extremity showing bone remodelling, vascularization, cartilage repair and antibacterial properties of S53P4. Lindfors N. J Biotechnol Biomaterial. 2011;1(5) (An open access journal).

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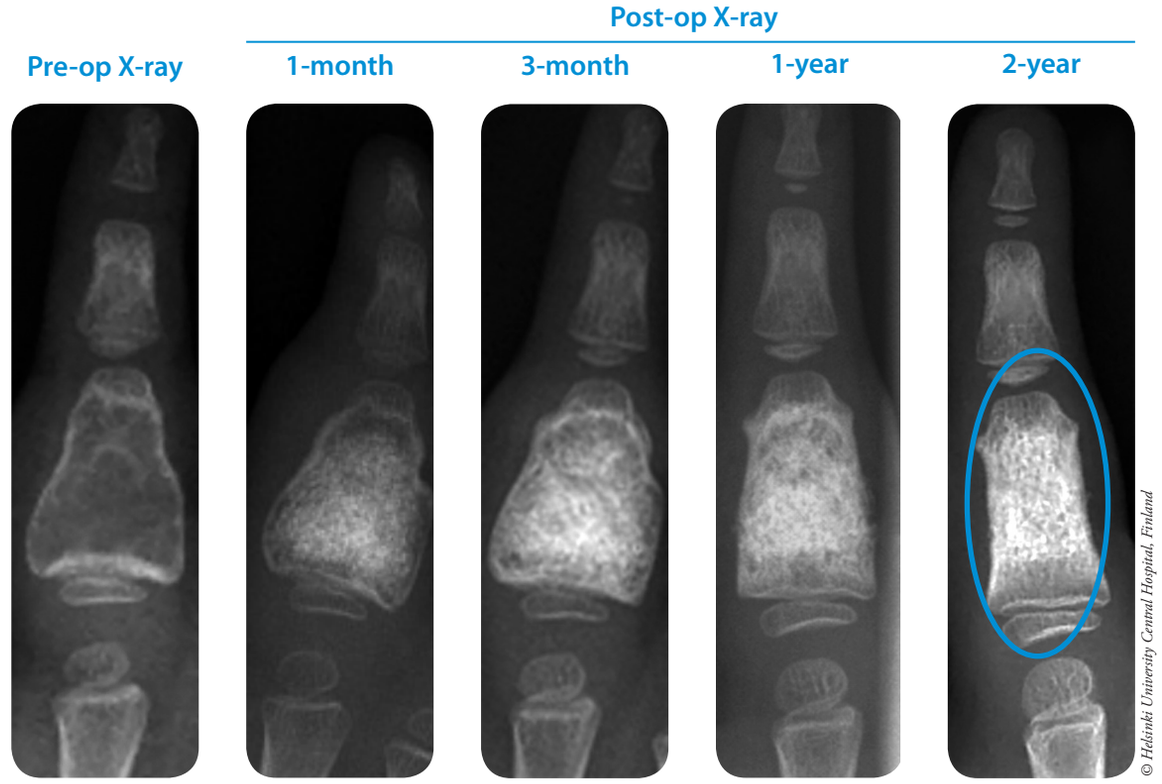
Proximal phalanx aneurysmal bone cyst

Patient: A 3-year old child with a recurrent aneurysmal bone cyst (ABC) of the proximal phalanx of the index finger.

Operation: The bone tumor was removed and the defect was grafted with 2 cc/0.5-0.8 mm (small) BonAlive® granules and two 2-3 mm pieces of autogenous bone.

Clinical outcome: Follow-up was at 1, 3, 12 and 24 months post-op. At 24-month post-op, no cavity was observed and the homogenous region resembled normal trabecular bone. The phalanx had grown in length and remodeled to almost normal shape. BonAlive® granules does not disturb the natural growth of bone in children.



Reference

Treatment of a recurrent aneurysmal bone cyst with bioactive glass in a child allows for good bone remodelling and growth. Lindfors N. Bone, 2009;45(2):398-400.

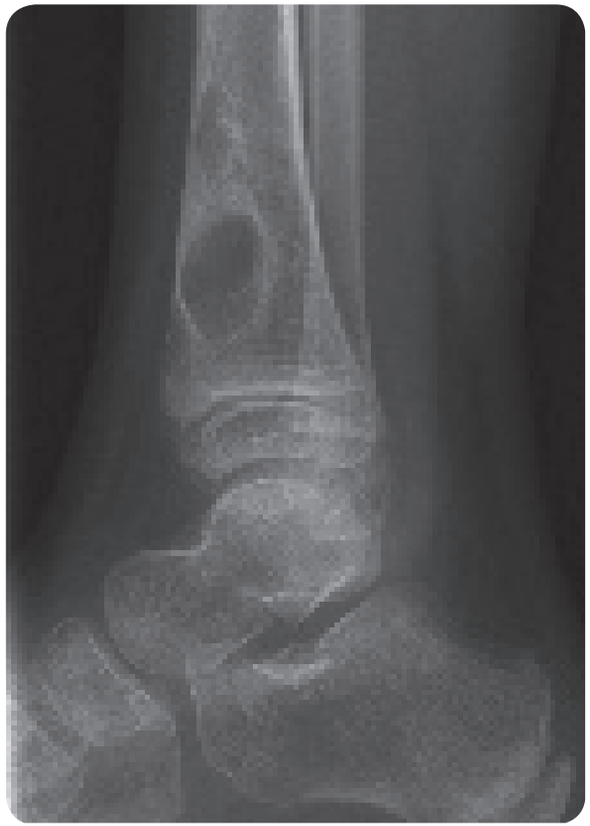
Distal tibial aneurysmal bone cyst

Patient: 6-year old girl with a distal tibial pathological fracture.

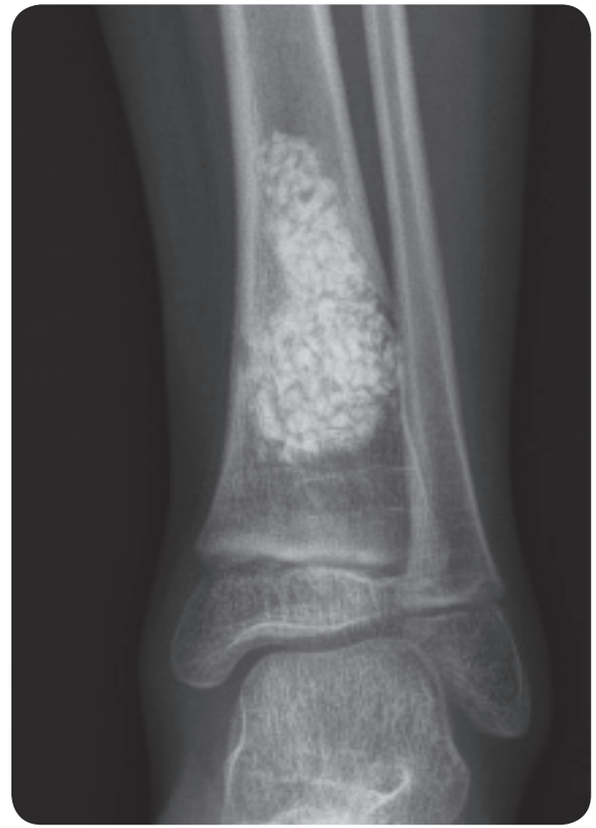
Operation: After the fracture had healed conservatively, the large bone cyst was evacuated. The defect was fenolized and filled with 1.0-2.0 mm (medium) BonAlive® granules.

Clinical outcome: At 6 months post-op the patient had fully healed and was free of any symptoms.

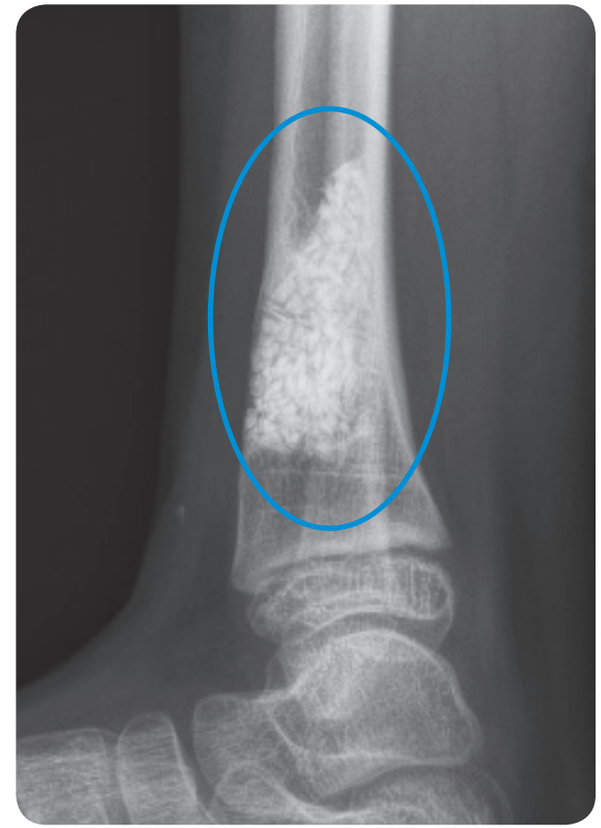
Pre-op X-ray



6-month post-op X-ray



6-month post-op X-ray



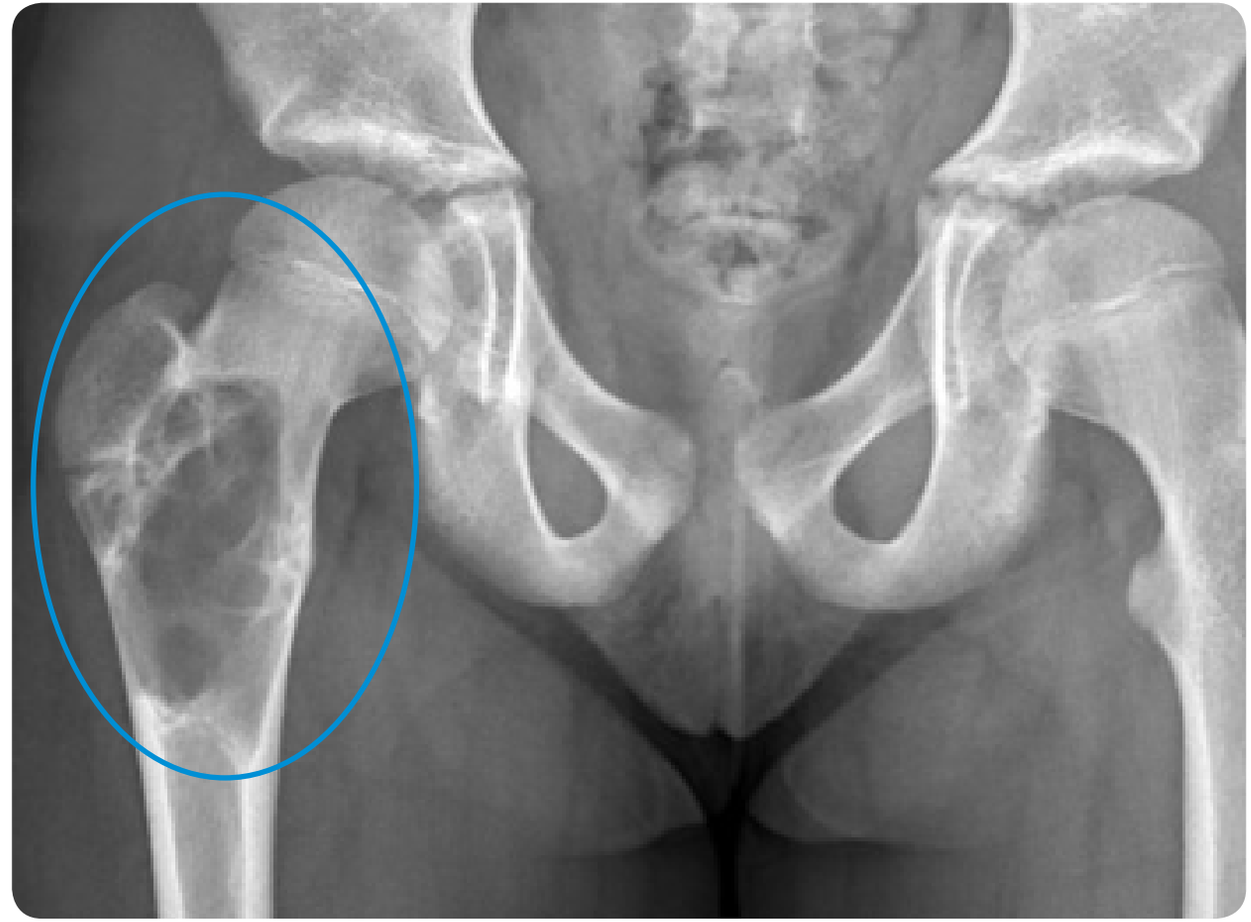
Courtesy of Dr. Ilkka Helenius, Turku University Hospital, Finland

Proximal femur aneurysmal bone cyst

Patient: 11-year old girl with a proximal femur aneurysmal bone cyst (ABC).

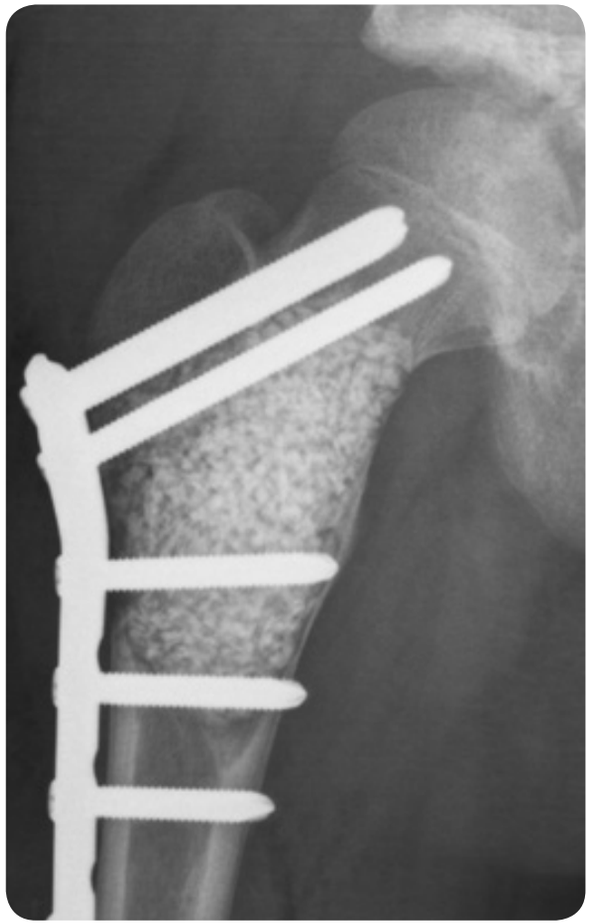
Operation: The large bone cyst was evacuated with high-speed drilling and prophylactic plating was performed. The defect was filled with 1.0-2.0 mm (medium) BonAlive® granules.

Pre-op X-ray

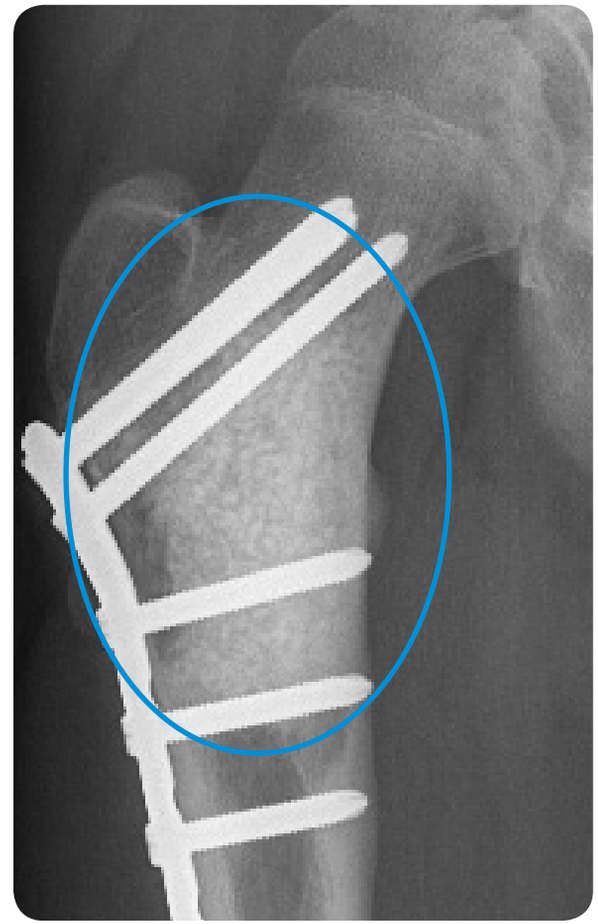


Clinical outcome: At 2 years post-op the patient was fully asymptomatic and active in sports. The progression of bone remodeling was clearly visible at follow-up.

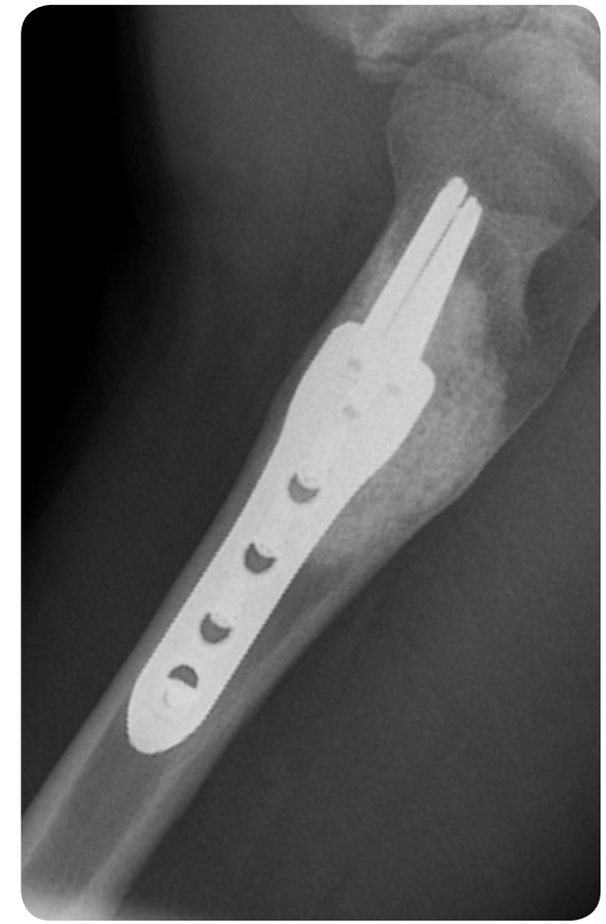
Post-op X-ray



2-year post-op X-ray



2-year post-op X-ray



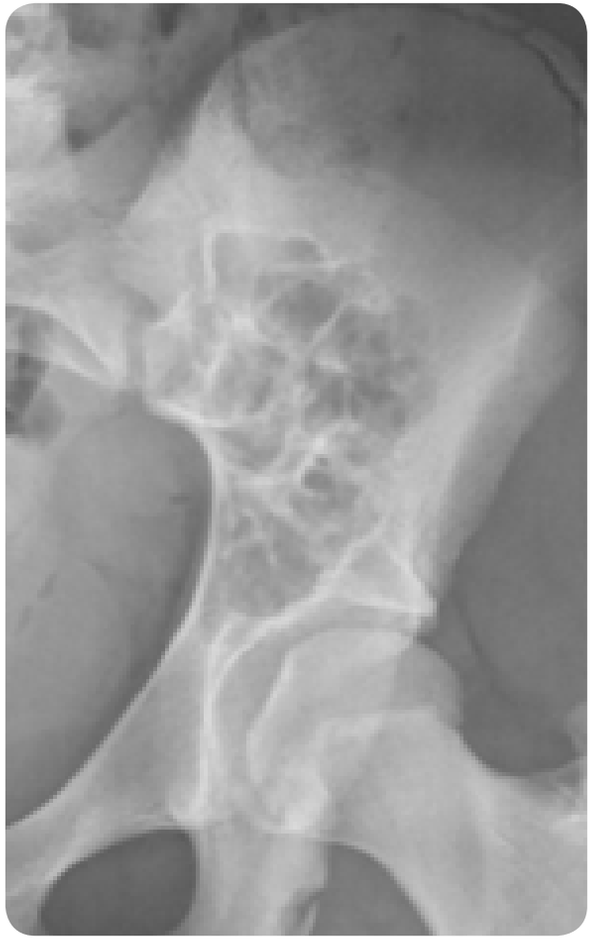
Large pelvic aneurysmal bone cyst

Patient: 15-year old girl with a large pelvic aneurysmal bone cyst (ABC).

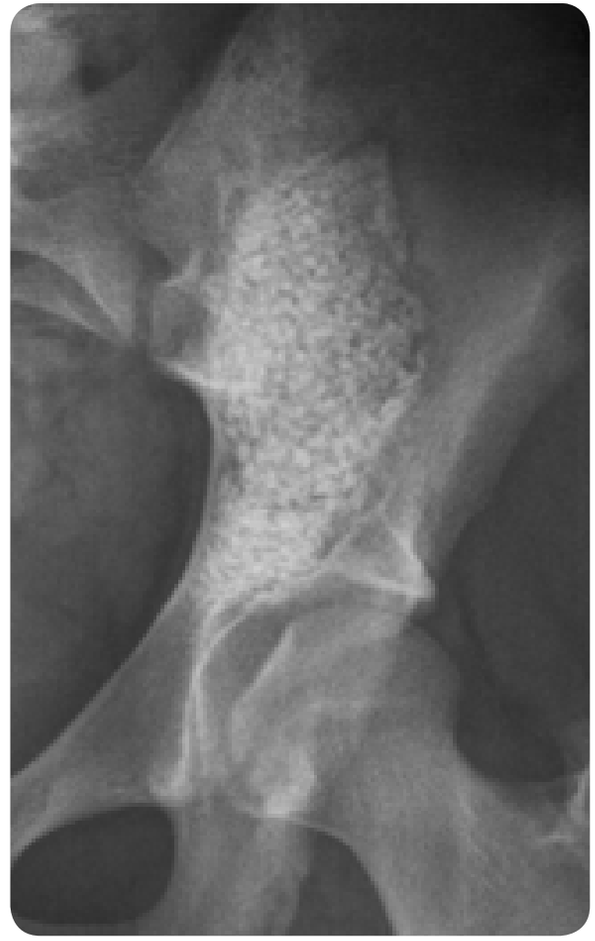
Operation: The large bone cyst was evacuated, the defect was fenolized and filled with 60 cc/2.0-3.15 mm (large) BonAlive® granules.

Clinical outcome: At 9 months post-op the patient had fully healed and was free of any symptoms and signs of recurrence of the ABC.

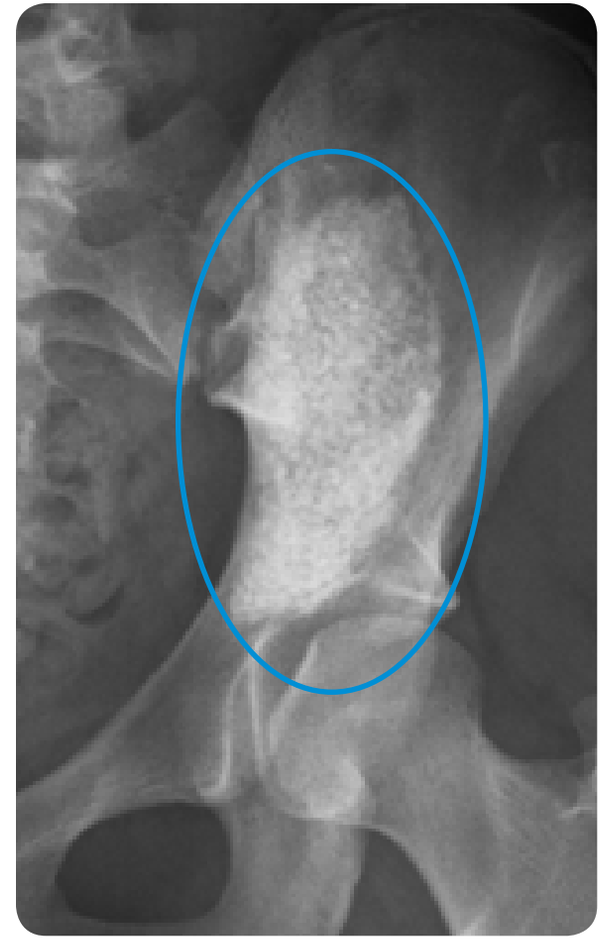
Pre-op X-ray



Immediate post-op X-ray



9-month post-op X-ray



ORTHOPEDICS & TRAUMA

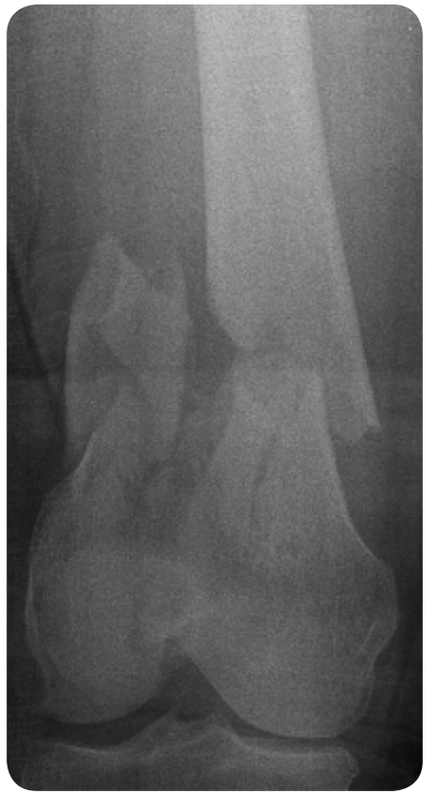
The clinical use of BonAlive® granules in orthopedic and trauma surgery is supported by a program of long-term randomized prospective clinical trials with follow-up extending to 11 years in patients with tibial plateau fractures and 14 years in patients with benign bone tumors. The results from these studies show that the long-term performance of BonAlive® granules in bone cavity filling applications is comparable to autograft.

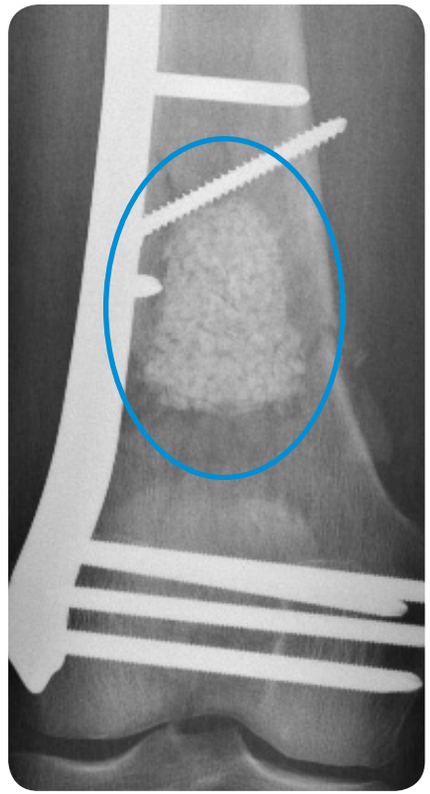
The solid nature of BonAlive® granules provides specific benefits, such as allowing the granules to be impacted into the bone defect. The granules maintain their volume effectively, hence they do not shrink or expand.

BonAlive® granules produces a high and balanced local bone regeneration by stimulating new bone formation through osteostimulation*.

BonAlive® granules indications

- Bone cavity filling
- Bone cavity filling in the treatment of chronic osteomyelitis





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Bioactive glass granules: a suitable bone substitute material in the operative treatment of depressed lateral tibial plateau fractures: a prospective, randomized 1 year follow-up study. Heikkilä JT, Kukkonen J, Aho AJ, Moisander S, Kyyrönen T, Mattila K. J Mater Sci: Mater Med. 2011;22(4):1073-1080.
Posterolateral spondylodesis using bioactive glass S53P4 and autogenous bone in instrumented unstable lumbar spine burst fractures - A prospective 10-year follow-up study. Rantakokko J, Frantzén J, Heinänen J, Kajander S, Kotilainen E, Gullichsen E, Lindfors N. Scand J Surg. 2012; 101:66–71.

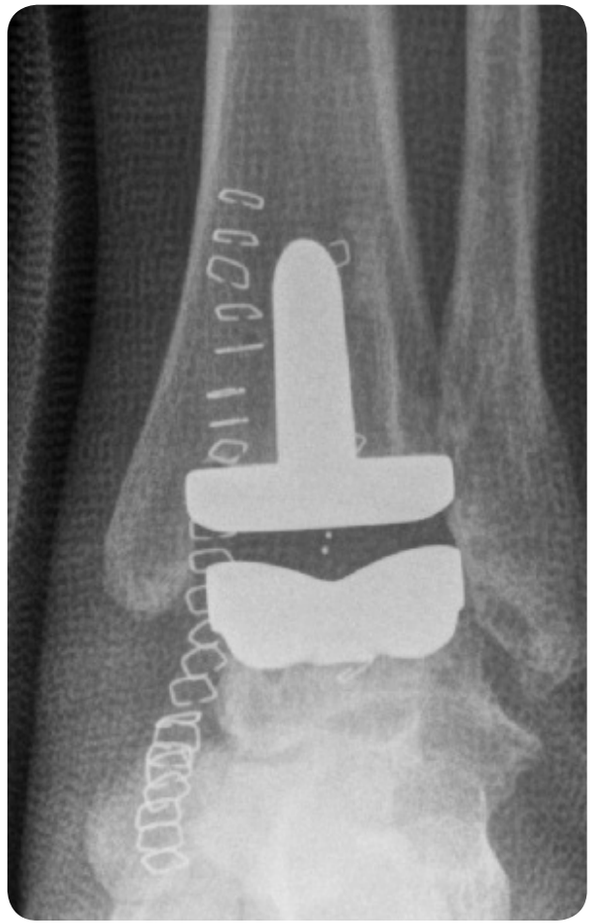
**non-osteoinductive*

Periprosthetic osteolysis in the distal tibia

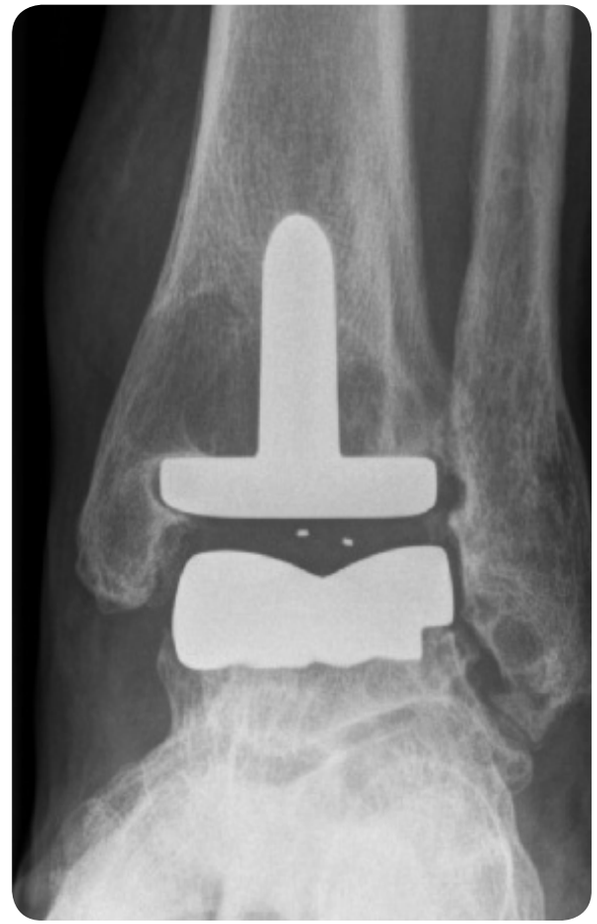
Patient: 44-year old female with arthrosis of the ankle.

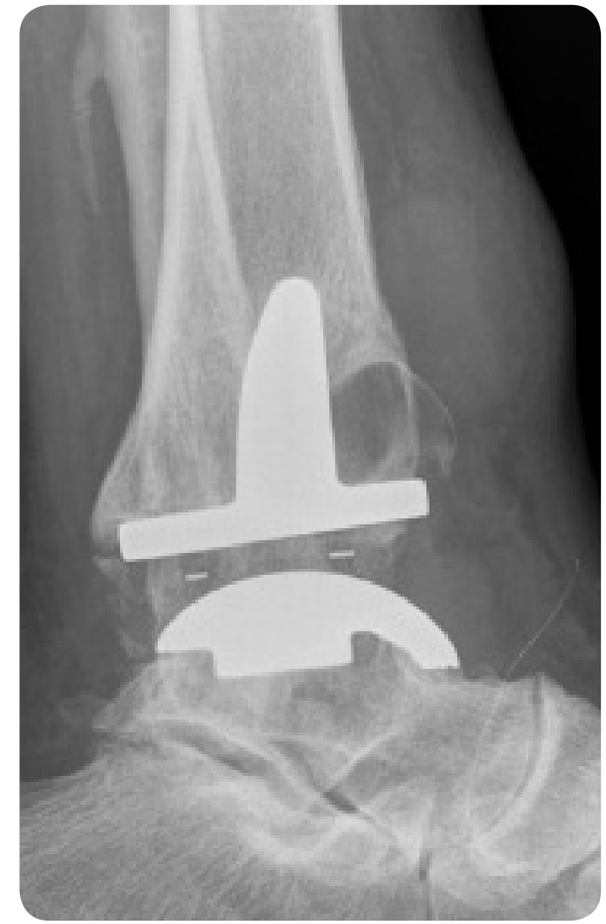
Operation: Arthroplasty was performed in 2005 and periprosthetic osteolysis was observed in December 2007. The periprosthetic osteolytic space was cleaned and the dead space was filled with 6 cc/1.0-2.0 mm (medium) BonAlive® granules to stimulate new bone formation around the prosthesis.

Arthroplasty in 2005



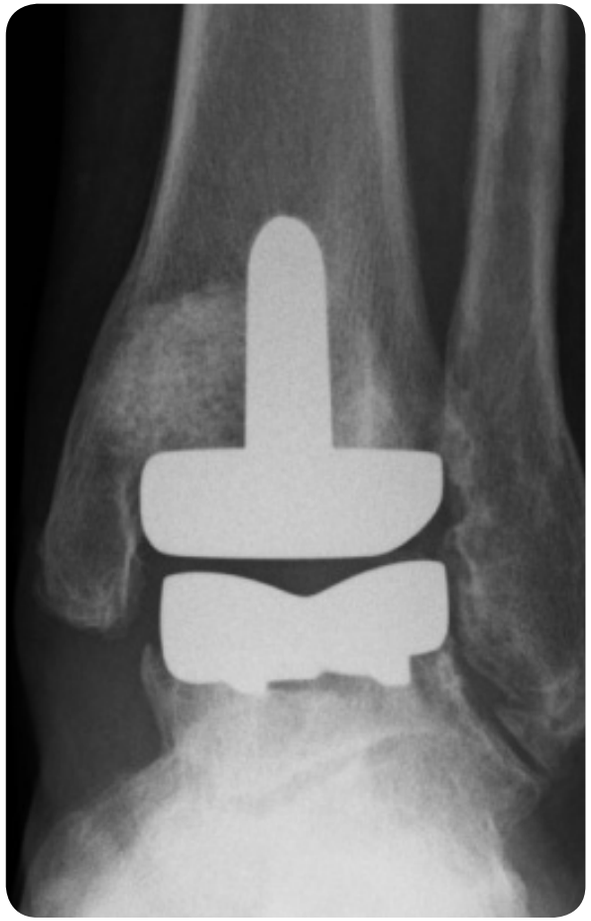
Osteolysis detected in 2007

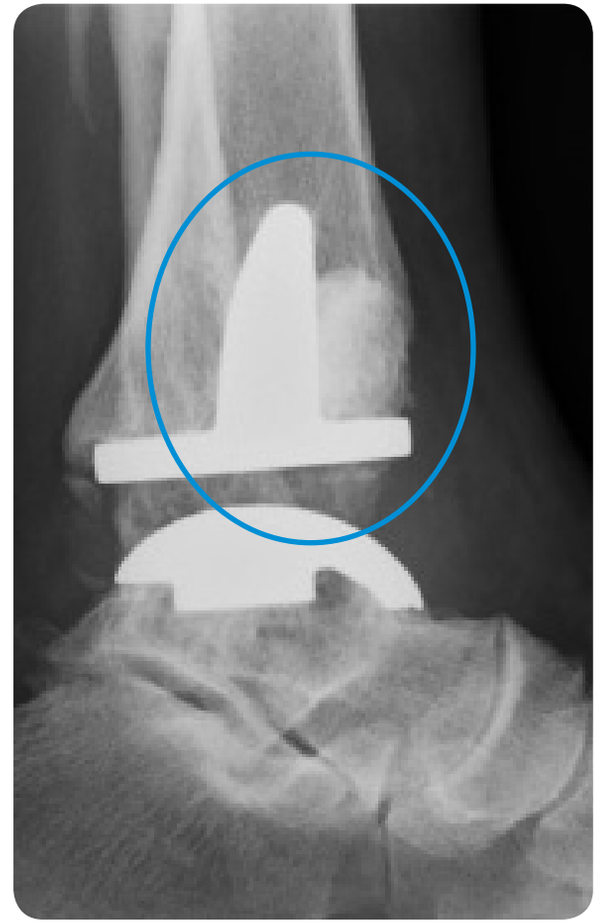




Clinical outcome: The soft tissue healed well and the ankle has been fully functional and painless during the course of follow-up. No sign of osteolysis or other complications have been observed at 2.5-year post-op.

2.5-year post-op X-ray





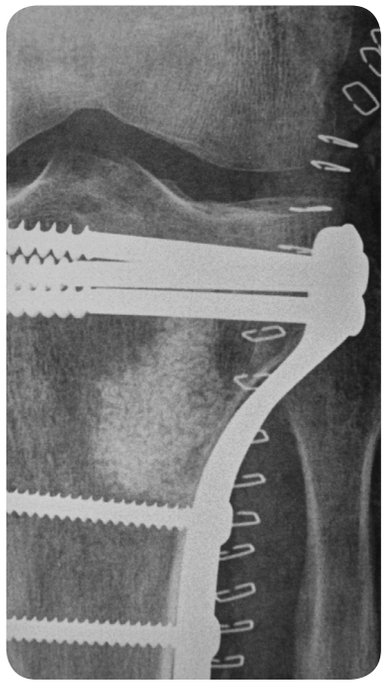
Depressed tibial plateau fracture

Patient: 57-year old male with a depressed lateral tibial plateau fracture.

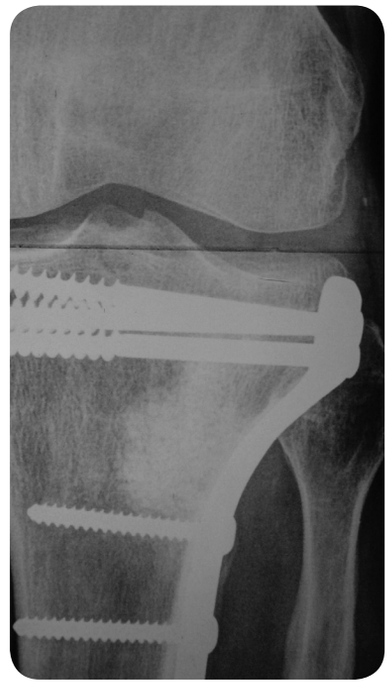
Operation: The lateral tibial condyle was exposed through an anterolateral, posteriorly curved incision. The subchondral cavity, which was caused by the fracture and the manual elevation of the fractured bone, was filled with 15 cc/1.0-2.0 mm (medium) BonAlive® granules. The fractured lateral tibial condyle was supported with an anatomical condylar plate.

Clinical outcome: No complications, current status is excellent. BonAlive® granules is a slowly resorbing biomaterial, but has completely remodeled to bone during the 11-year follow-up.

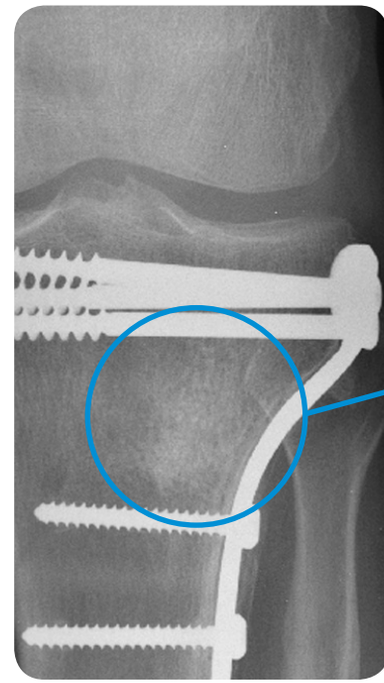
Immediate post-op X-ray



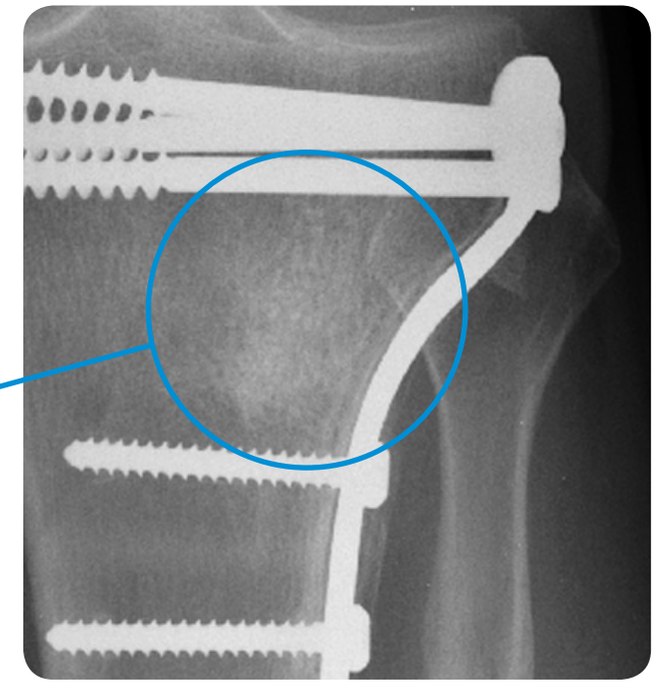
1-year post-op X-ray



11-year post-op X-ray



11-year post-op X-ray



Reference

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CHRONIC OSTEOMYELITIS & SEPTIC BONE SURGERY

Chronic osteomyelitis, or chronic bone infection, is defined and characterized by progressive infection of the bone marrow and cortex, resulting in destruction of bone, bone necrosis. It may occur at any age and can involve any bone. Often, a multidisciplinary approach is required, involving expertise in orthopedic surgery, infectious diseases and plastic surgery.

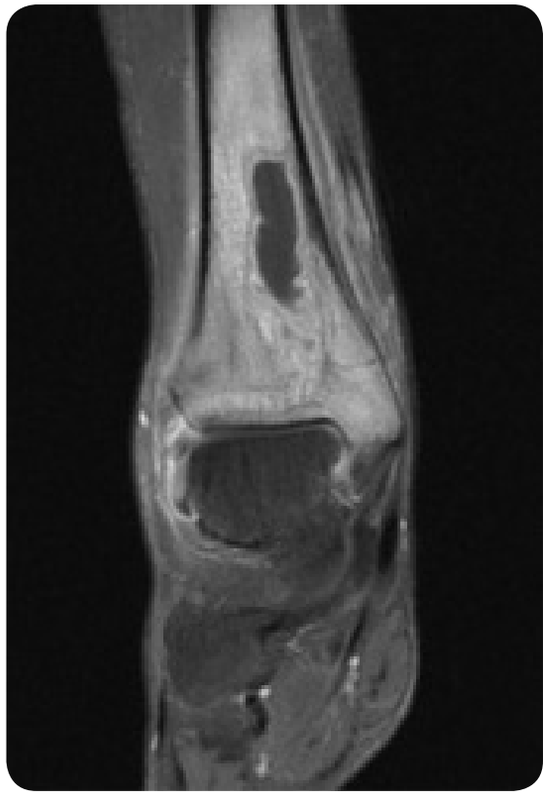
BonAlive® granules is a unique bone graft substitute that inhibits bacterial growth in a vast number of bacterial species that are related to orthopedic complications, including e.g. *MRSA* and *MRSE*.

BonAlive® granules indications

- Bone cavity filling
- Bone cavity filling in the treatment of chronic osteomyelitis

"We found that BAG-S53P4 is as effective as two different calcium-based antibiotic-loaded bone substitutes, with a significant reduction in prolonged wound serum leakage and a trend towards reduction in hospital stay."

Romanó et al. 2014



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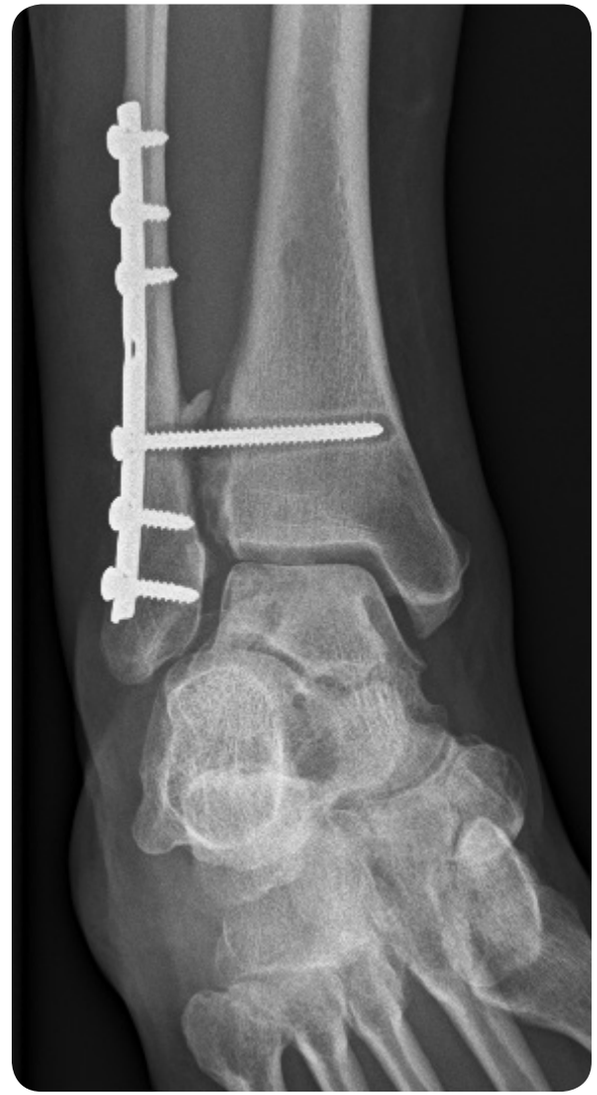
Chronically infected screw in the distal tibia

Patient: 48-year old female with a chronically infected screw in the distal tibia.

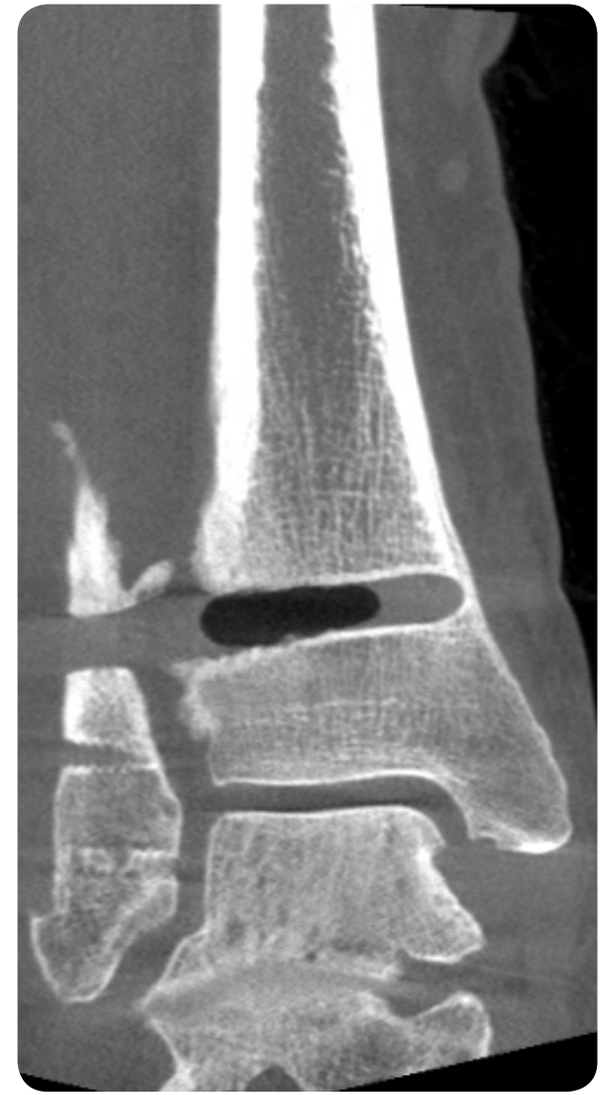
Bacterial culture: *Streptococcus agalactiae*

Operation: The plate and screws were removed and the screw hole was thoroughly debrided. The defect was filled with 0.5-0.8mm (small) BonAlive® granules.

Pre-op X-ray

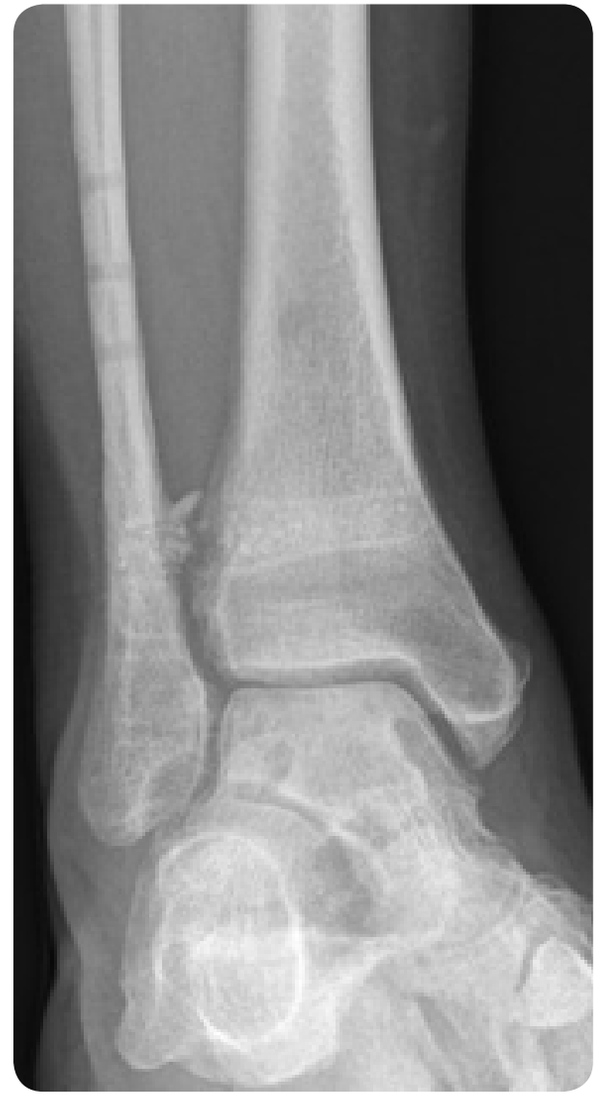


CT after hardware removal

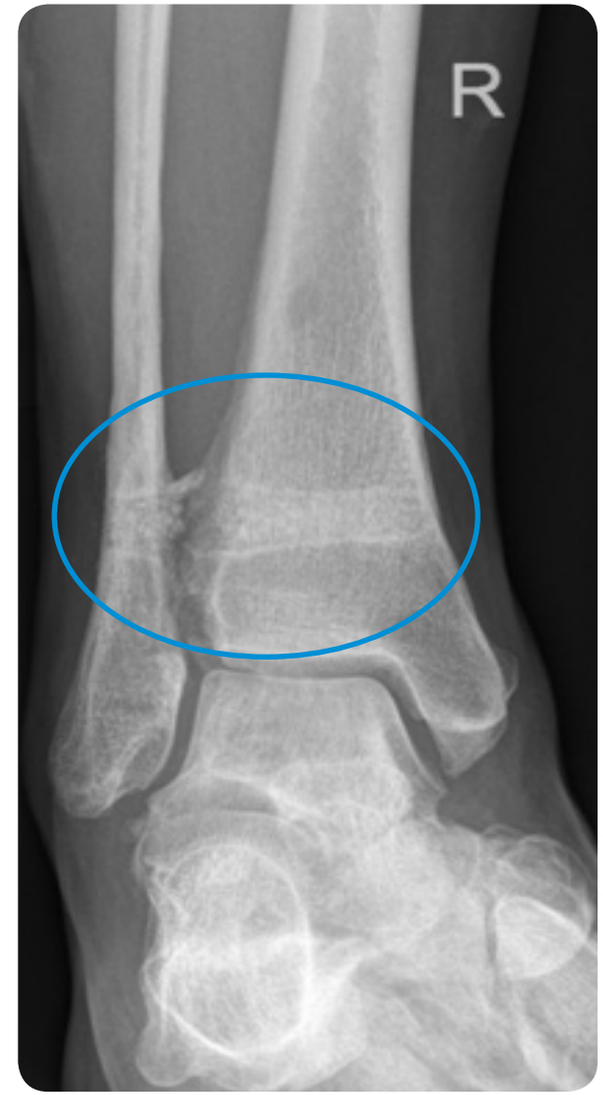


Clinical outcome: At 1-year post-op the patient had fully healed and was free of any signs of infection.

1.5-month post-op X-ray



1-year post-op X-ray



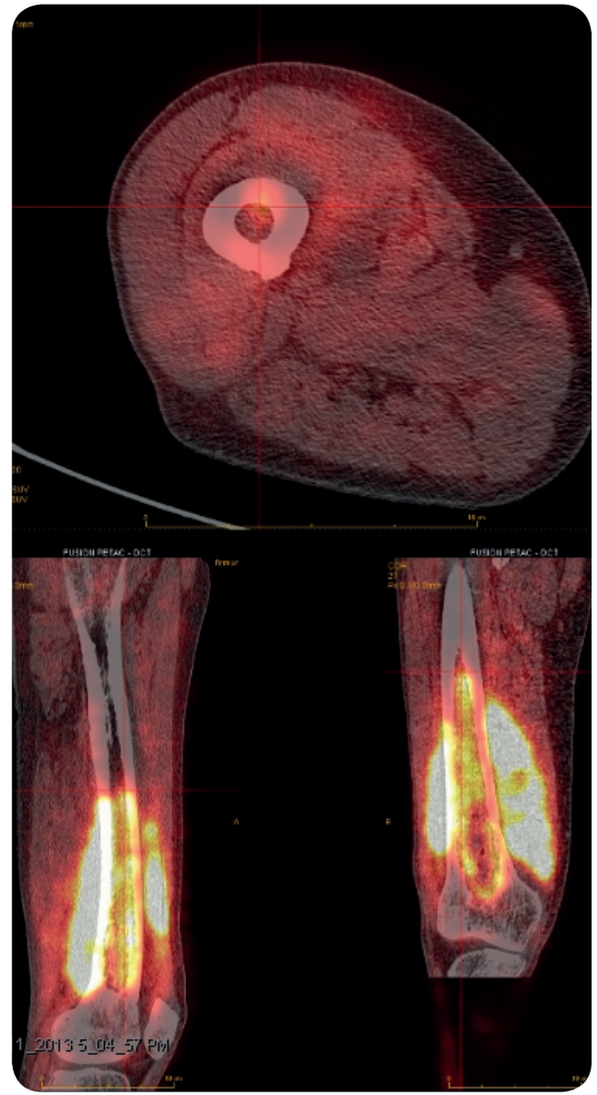
Chronic osteomyelitis in the distal femur

Patient: 64-year old male with an infected implantable cardioverter defibrillator. As a consequence of hematogenous spread, osteomyelitis appeared in the right femur, accompanied by infection of surrounding tissues.

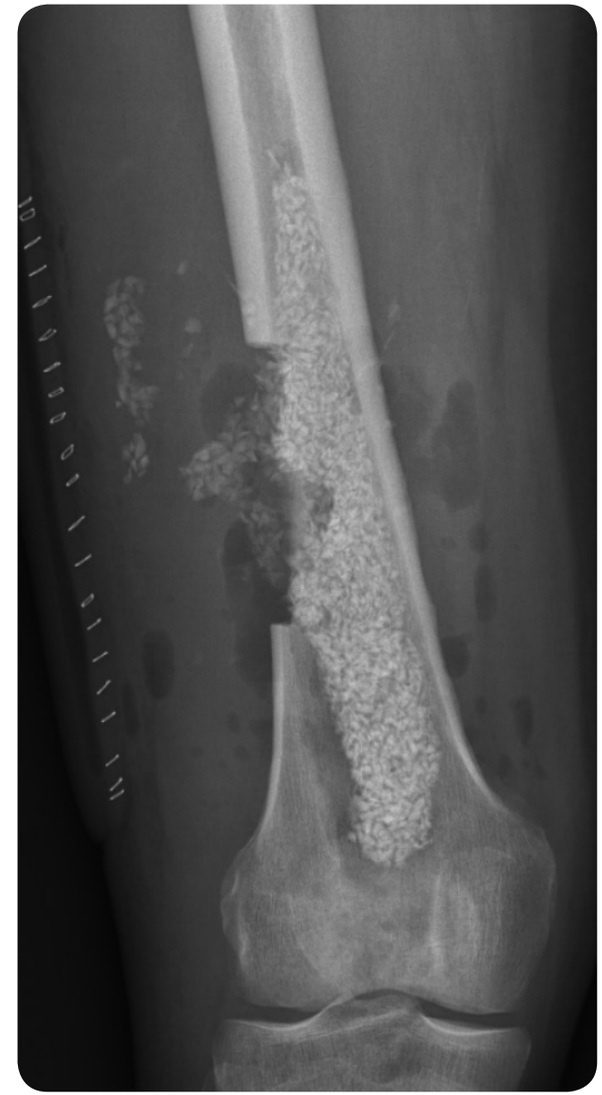
Bacterial culture: *Staphylococcus aureus*

Operation: Debridement of the femur was performed and surrounding soft tissues were removed through the large cortical window. The defect was filled with 60 cc/2.0-3.15 mm (large) BonAlive® granules.

Pre-op PET-CT



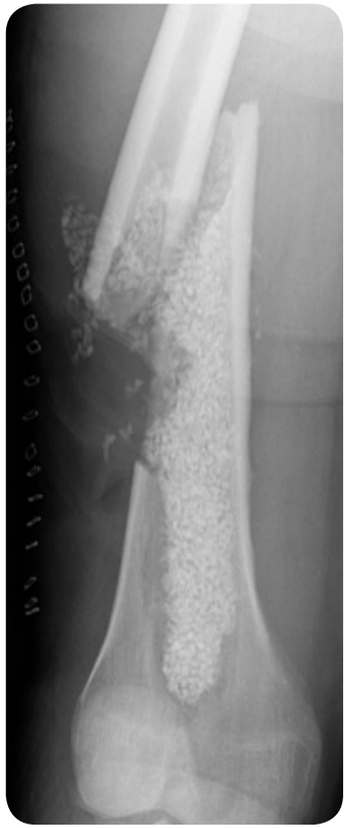
Post-op X-ray



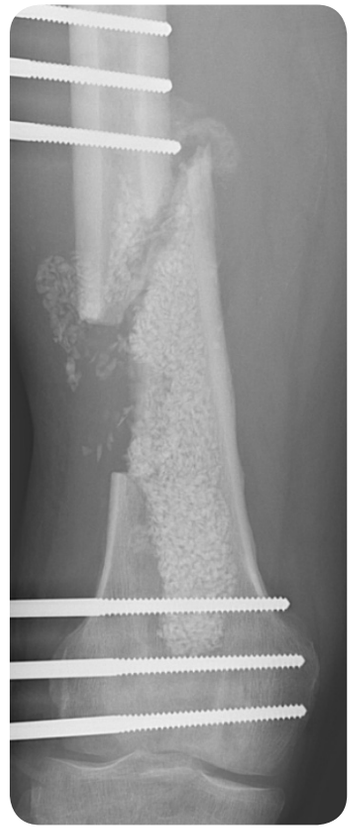
10 days post-op: Fracture appearance through cortical window due to non-compliance of the weight-bearing. Internal fixation could not be used because of the active infection; external fixation was applied to achieve acceptable alignment.

Clinical outcome: Bone healing was achieved in 4 months from implantation. The soft tissue healed well, with no clinical or laboratory signs of infection recurrence. The external fixation was removed 4 months post-op due to persistent pin tract problems. The patient was fully functional and only slight residual shortening of the right femur was found. There were no signs of recurrence of infection and blood markers were normal. The granules in the soft tissues were resorbed.

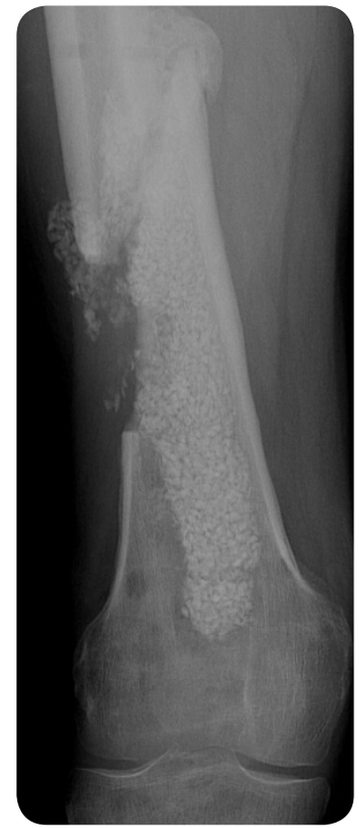
10-day post-op



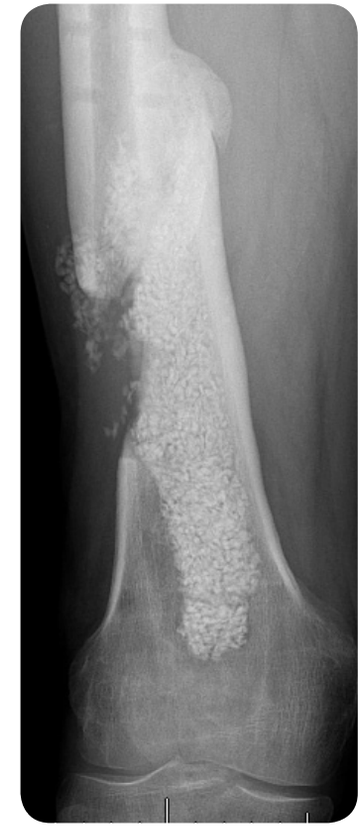
1.5-month post-op



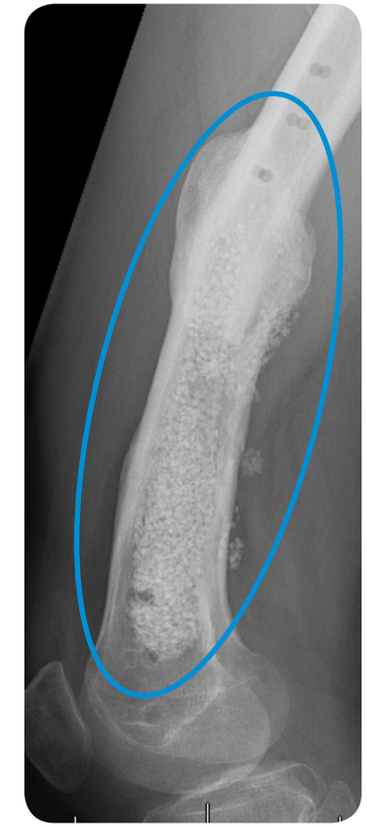
4-month post-op



1-year post-op



1-year post-op



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Ulnar fracture with post-op chronic infection

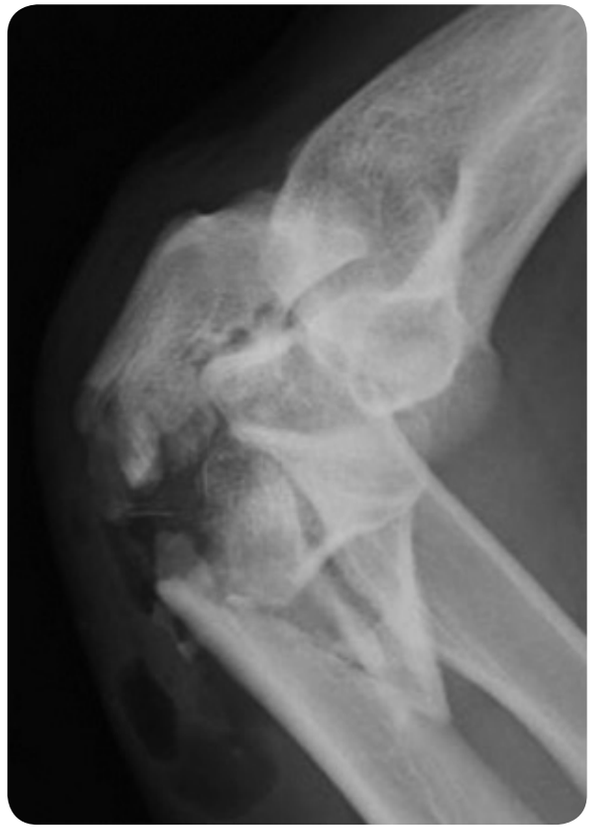
Patient: 45-year old male with an ulnar fracture.

Bacterial culture: *Staphylococcus epidermis*

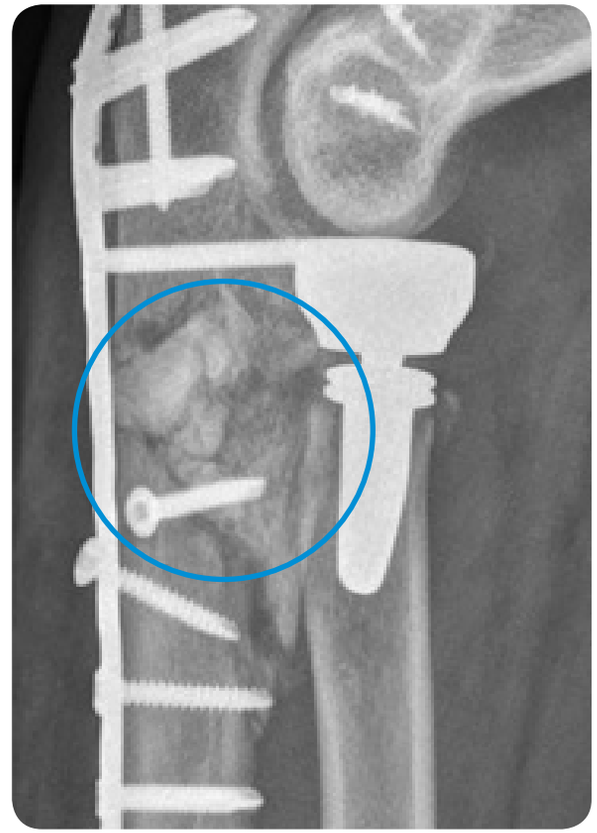
Operation: The fracture was stabilized and CaP cement was applied to the bone defect. At 2 months post-op, fistula formation to CaP with *Staphylococcus epidermis* infection was observed. A two-stage revision was performed using antibiotic beads, radical debridement and grafting with 1.0-2.0 mm (medium) BonAlive® granules.

Clinical outcome: At 7 months after revision surgery the patient had healed well and the clinical outcome was considered to be good.

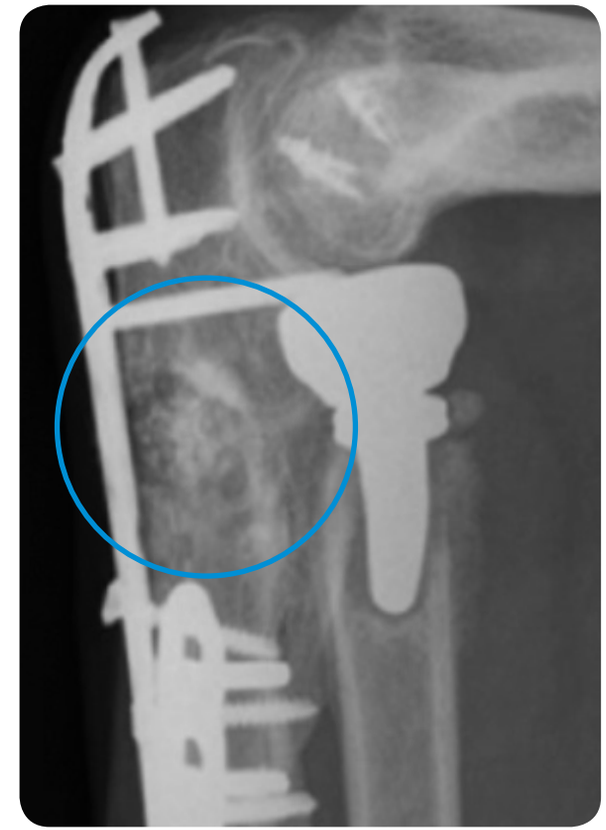
Pre-op X-ray



CaP in 2-month post-op X-ray



BonAlive® granules in 7-month post-op X-ray



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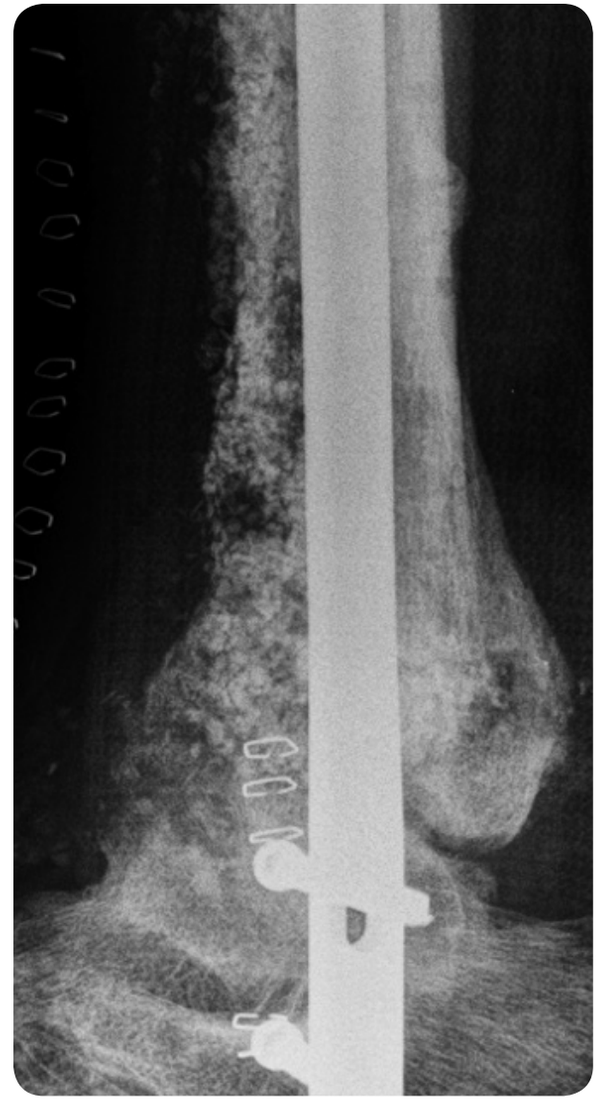
Chronic osteomyelitis in the distal tibia

Patient: 36-year old male with a chronic osteomyelitis in the distal tibia. After surgical debridement the defect size was 100 cc.

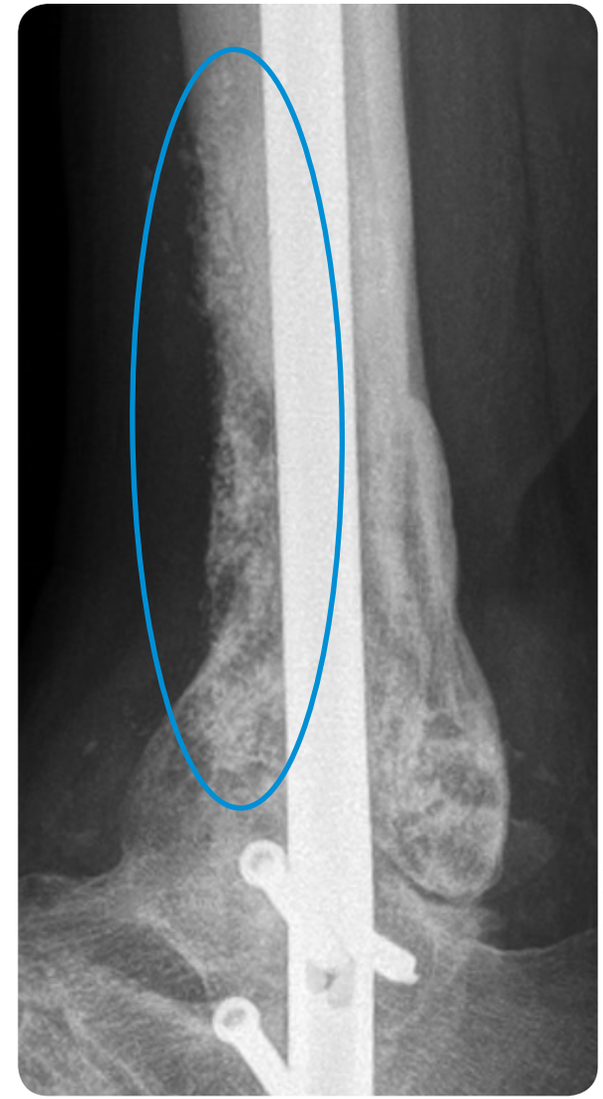
Operation: The patient received a pilon fracture in a car crash and the fracture was stabilized with an anterior plate in the distal tibia. The patient was diagnosed with severe chronic osteomyelitis with extensive pus formation in the distal tibia. The anterior fixation plate was removed and the area was surgically cleaned through radical debridement. The defect was filled with 48 cc/2.0-3.15 mm (large) BonAlive® granules mixed with an equal amount of autologous bone.

Clinical outcome: The soft tissue healed well. Although a significant part of the anterior cortex of the distal tibia was removed, new cortical bone was formed. At 2.5 years post-op the fusion was stabile and the patient outcome continued to be successful.

Immediate post-op X-ray



2.5-year post-op X-ray



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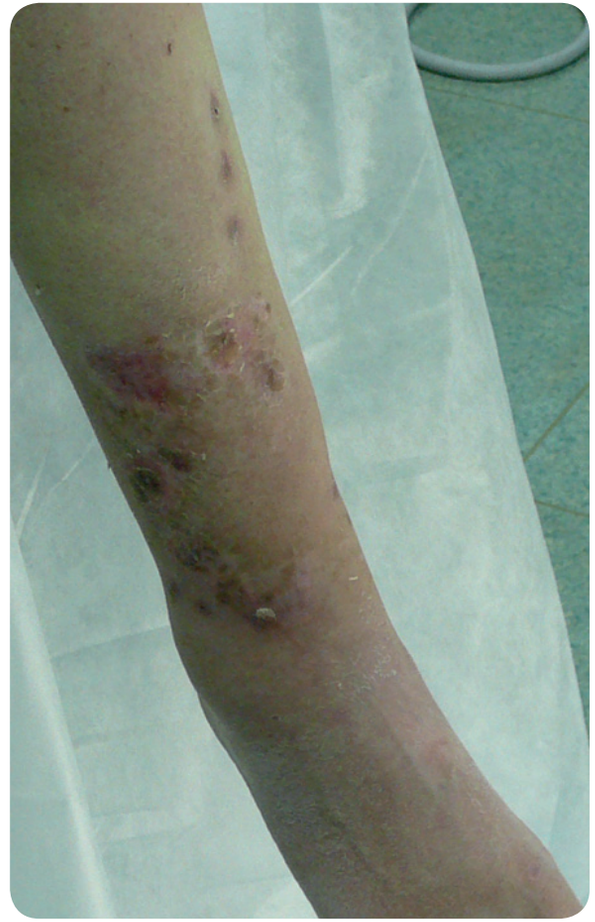
Chronically infected non-union of the distal tibia

Patient: 32-year old female, type A host, was in a car crash and received an exposed pilon fracture that was stabilized with an external fixator.

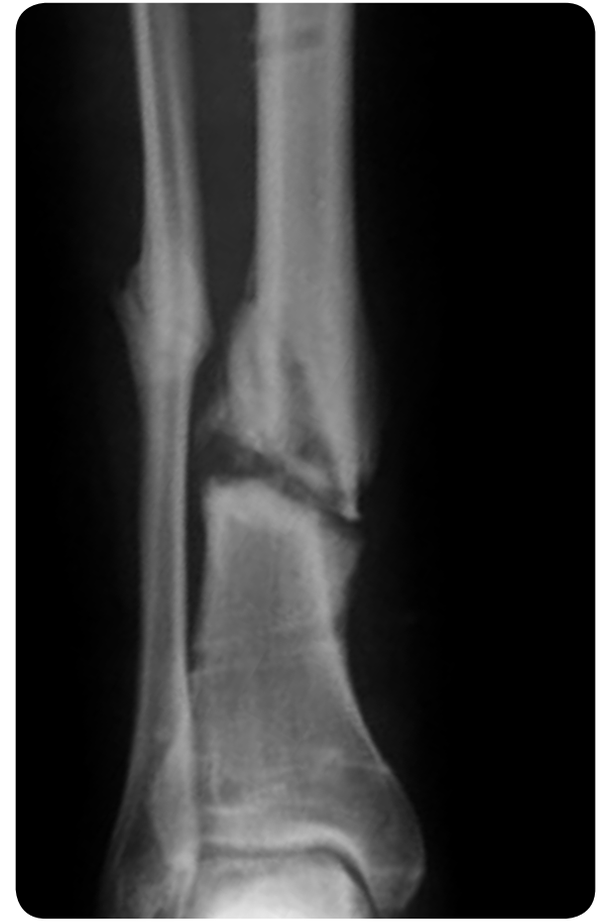
Bacterial culture: *Staphylococcus aureus*

Operation: The patient was diagnosed with septic non-union 9 months after trauma. The patient refused new external fixation. The external fixator was removed and, after 15 days, the following procedure was carried out: osteotomy of the fibula, debridement of the non-union septic focus, local application of 20 cc/1.0-2.0 mm (medium) BonAlive® granules mixed with autograft in a 50/50 ratio, intramedullary nailing.

Pre-op

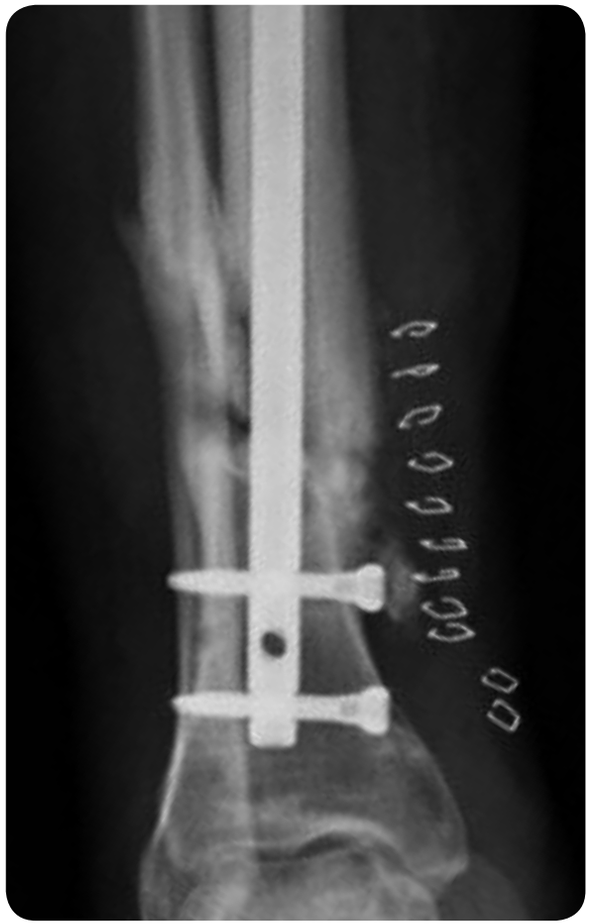


Pre-op X-ray

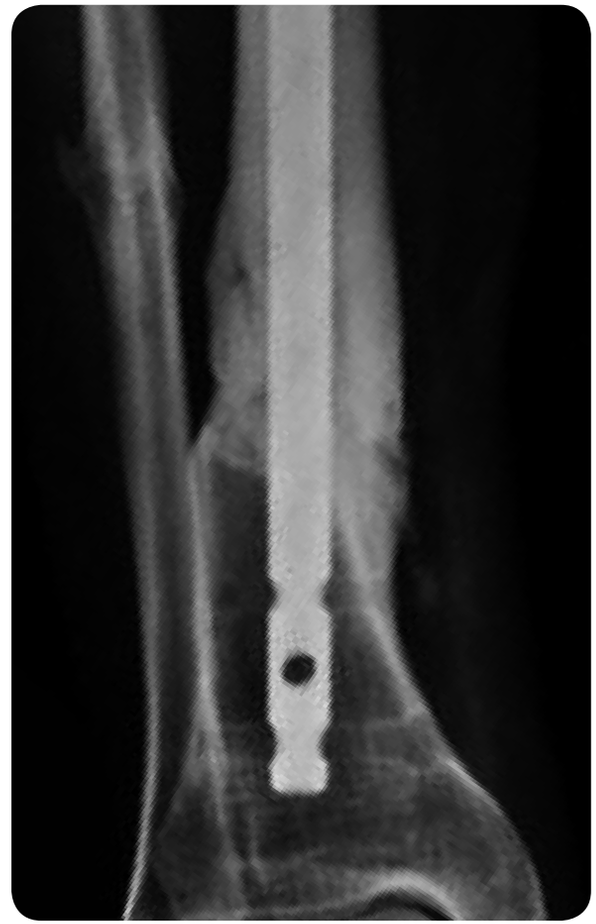


Clinical outcome: Bone healing was achieved in 6 months from implantation. The soft tissue healed well, with no clinical or laboratory signs of infection recurrence. Dynamization of the nail was performed 14 months post-op and the nail was removed 2 years post-op.

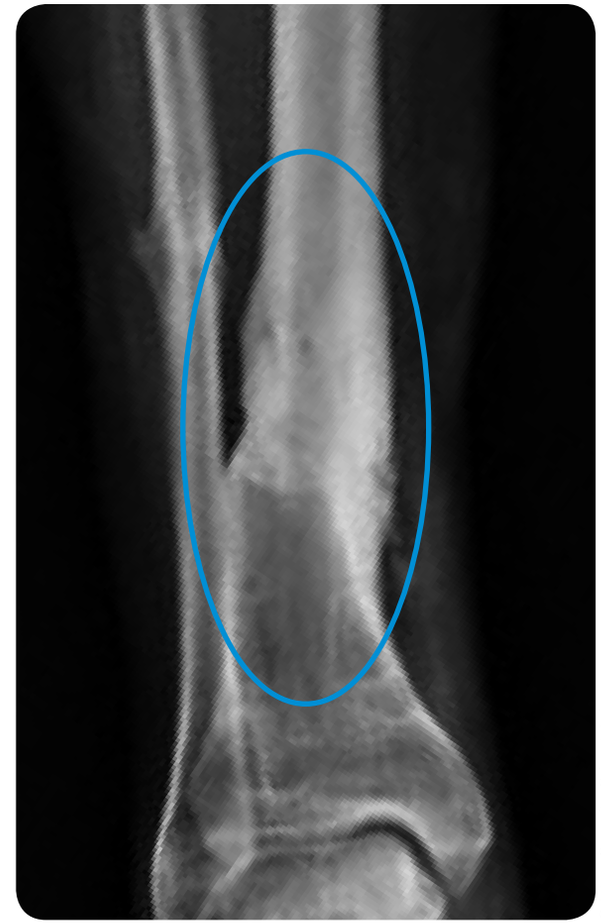
Immediate post-op X-ray



14-month post-op X-ray



2-year post-op X-ray



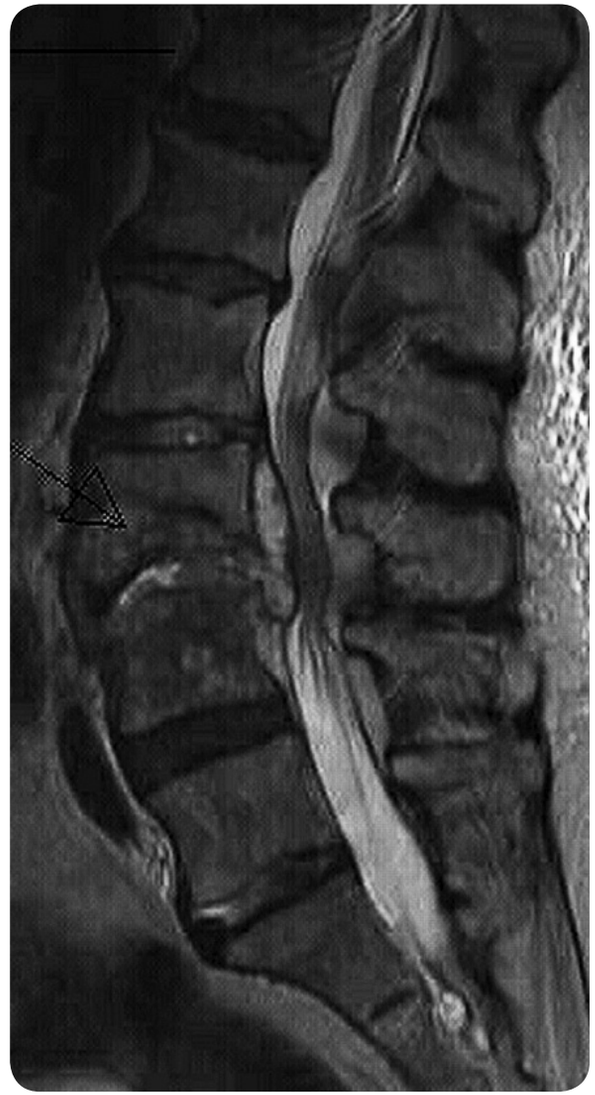
Chronic osteomyelitis in the spine

Patient: 75-year old female, abscess formation in the spine.

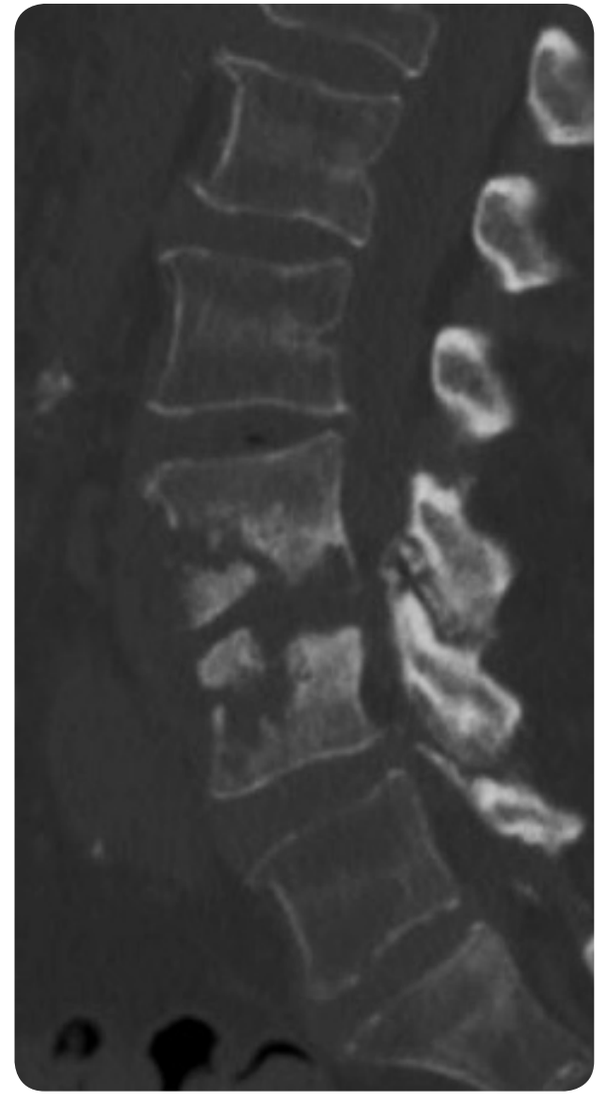
Bacterial culture: *Mycobacterium tuberculosis*

Operation: Posterior decompression L2-L3 and L3-L4, posterolateral spondylodesis L2-L5 with autogenous bone, lumbotomy, canalisation of paravertebral abscess, resection of L3-L4, anterior decompression and reconstruction using an expandable spinal implant covered with 32 cc of BonAlive® granules.

Pre-op MRI

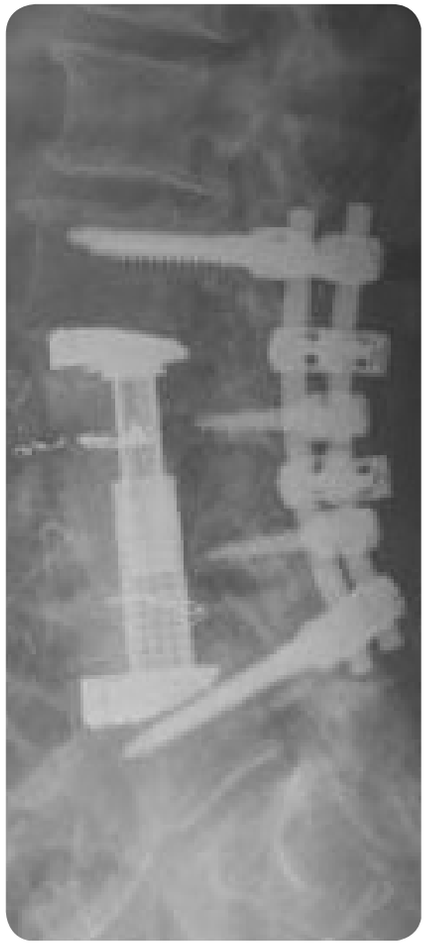


Pre-op CT

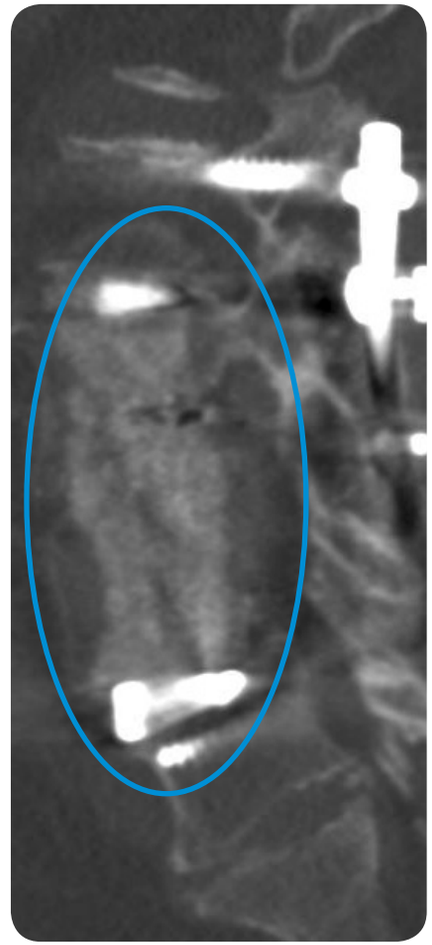


Clinical outcome: Complete fusion at 2 years post-op. The patient was fully healed.

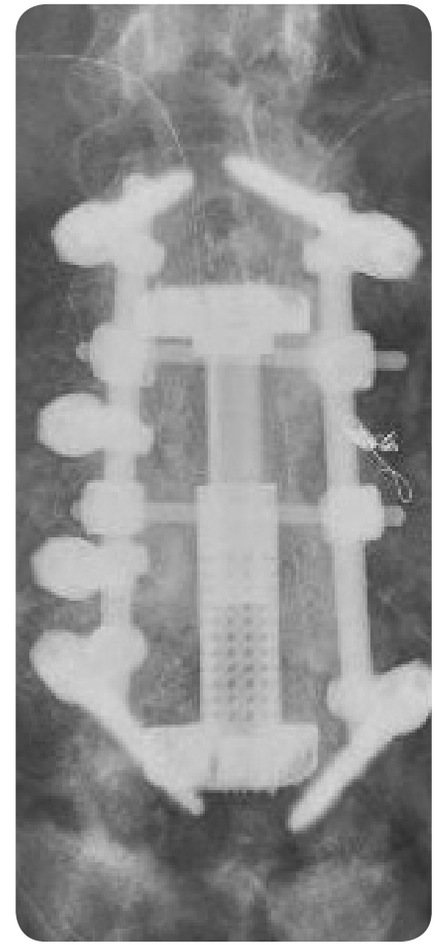
Immediate post-op X-ray



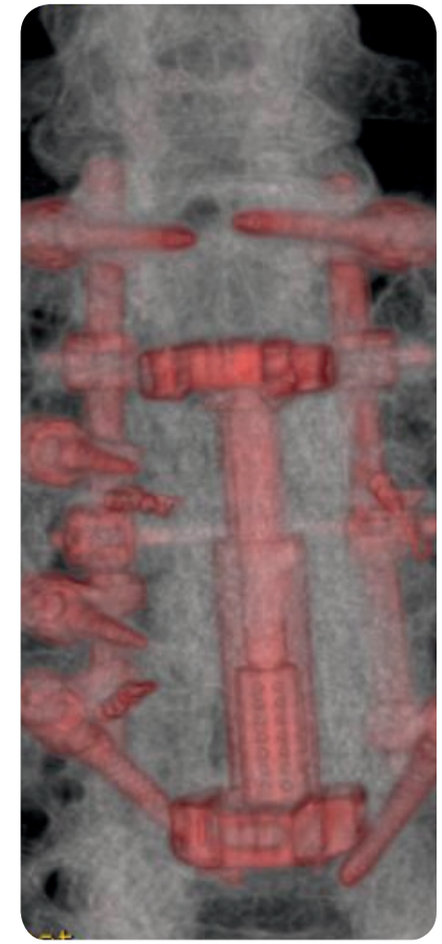
2-year post-op CT



Immediate post-op X-ray



2-year post-op CT



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**non-osteoinductive*

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BonAlive®
granules

1 cc 2.5 cc

Small applicator

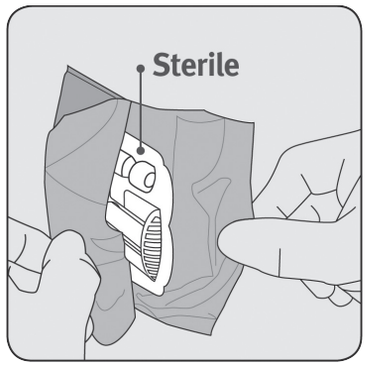
Ref. no	Granule size	Unit size
13110	0.5-0.8 mm (small)	1 cc
13120	0.5-0.8 mm (small)	2.5 cc

5 cc 10 cc

Large applicator

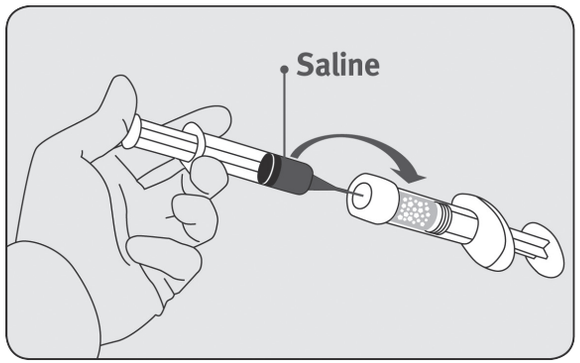
Ref. no	Granule size	Unit size
13130	0.5-0.8 mm (small)	5 cc
13140	0.5-0.8 mm (small)	10 cc
13330	1.0-2.0 mm (medium)	5 cc
13340	1.0-2.0 mm (medium)	10 cc
13430	2.0-3.15 mm (large)	5 cc
13440	2.0-3.15 mm (large)	10 cc

INSTRUCTIONS FOR USE



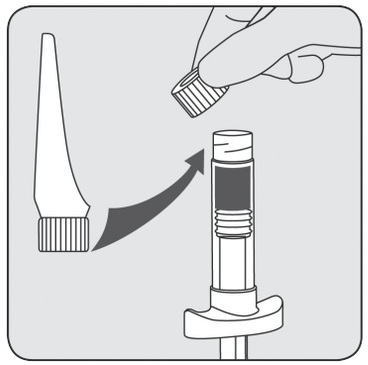
Step 1.

- Peel open the pouch (start from the corners) and aseptically remove the sterile tray (see Figure 1).
- Detach the applicator from the tray
- Note that the pouch provides a sterile barrier to the device.



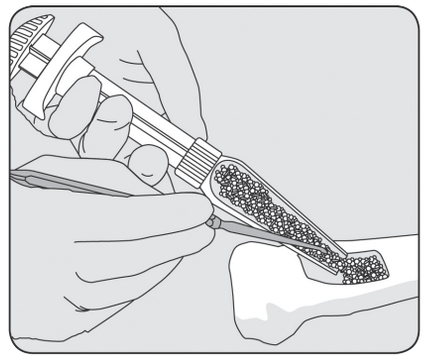
Step 2.

- Moisten the granules by injecting sterile physiological saline slowly through the cap membrane (see Figure 2).
- Make sure the granules are evenly moistened. The applicator can be turned upside down or tapped to allow the saline to moisten all granules.
- Note: saline injection can cause increase in pressure inside the applicator unless the excess pressure is released e.g. with the injection needle.



Step 3.

- In order to prevent spilling of the moistened granules from the applicator keep the cap facing upwards.
- Unscrew the cap (remove the stopper) and screw the shovel tightly onto the applicator body (see Figure 3).



Step 4.

- Turn the applicator to a horizontal position, and push the plunger rod to slide the moistened granules onto the shovel. Move the applicator to the defect site and implant the moistened granules from the shovel into the defect with the aid of a sterile instrument (see Figure 4).
- (Alternatively, if the shovel is not used, turn the applicator over a sterile cup, push the plunger rod to slide the moistened granules into the cup and subsequently perform the implantation with a sterile instrument.)
- Avoid dropping the granules outside the bone defect. Misplaced granules must be removed.

For complete instructions for use, see package insert.

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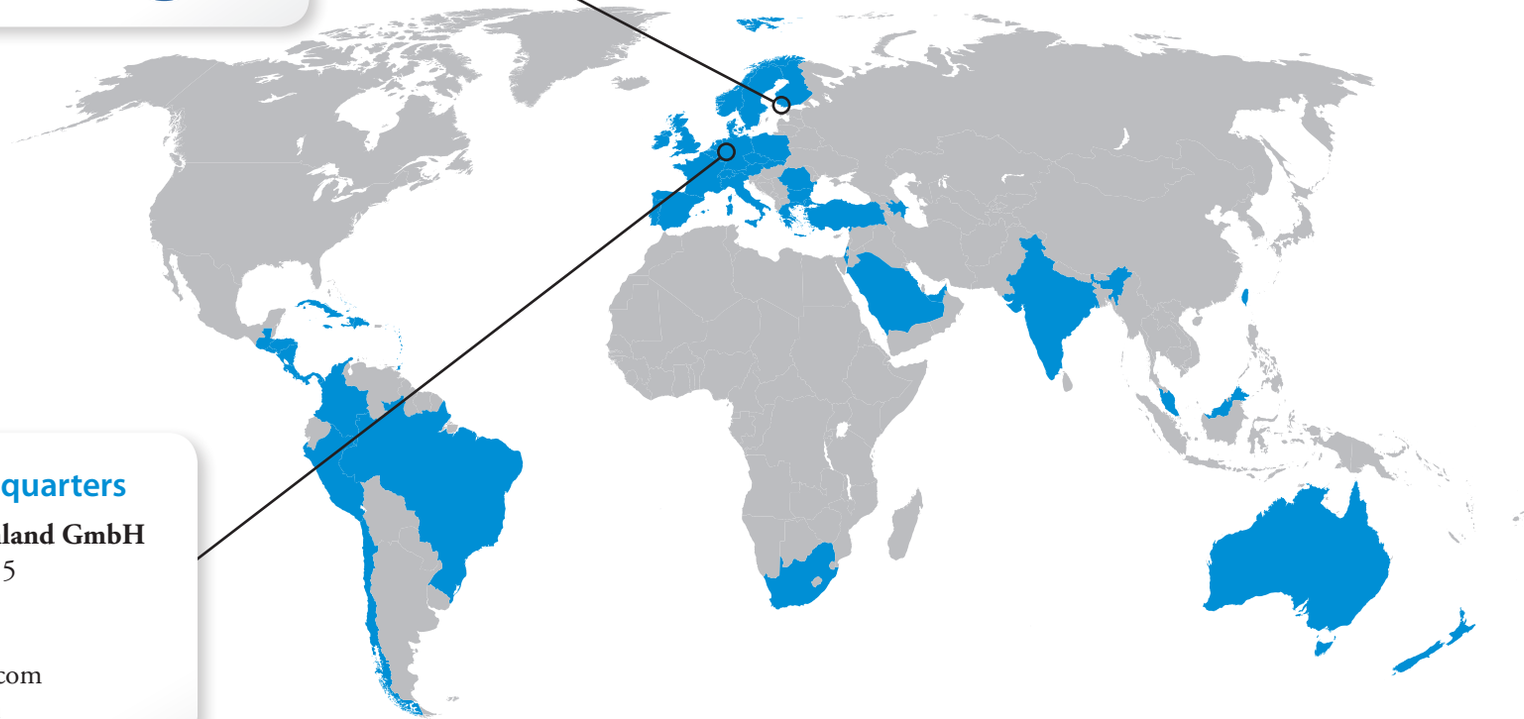

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