b.Bone™

MANAGEMENT OF BONE DEFECTS

GENERAL PRINCIPLES AND SURGICAL TECHNIQUE

GreenBone®
NATURAL BONE HEALING

The surgical technique shown is for illustrative purposes only.
The technique actually employed in each case will always depend upon the medical judgement of the surgeon who should decide on the best approach to be followed depending on their clinical experience and the patient's needs.
Please see the Instructions For Use for the complete list of indications, warnings, precautions, and other important medical information.

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INTRODUCTION

The reconstruction of large bone defects is a public health issue and a clinical challenge in several medical fields, including orthopedic, spinal, plastic, dental and maxillofacial surgery[1]. Bone defects may result from fractures, including fracture nonunion, bone tumors, osteonecrosis, or infections, among others[2, 3].
Independent of the underlying cause, bone defects pose a major source of disability and a loss of quality of life in the overall population[3].

Especially large bone defects (critical size) do not heal spontaneously and require surgical intervention, so bone grafts are often used to fill bone defects from traumatic injury or surgically created bone defects[2].

Autologous, allograft, or synthetic bone grafts are used to fill osseous defects[4, 5].

Autologous bone graft has been so far the preferred treatment, but the supply of suitable bone is limited, and its collection is associated with pain, increased infection risk, hemorrhage, disability, nerve damage and loss of function[6, 7].
Therefore, biological enhancements have evolved for better management[7].

However, synthetic bone grafts should be used following the principles of the so-called "diamond concept" to significantly improve the bone healing response and outcomes in difficult clinical situations such has long bone non-union[8, 9].

In brief, the concept involves the use of a platform/ biomaterial that serves as the scaffold (matrix) onto which bone-forming cells are added or can migrate to, under the influence of growth factors (inductive molecules) to encourage bone regeneration.

Finally, mechanical stability of the bone segments, as well as the scaffold itself, plays a crucial role in providing the necessary stability to the repair area.

b.Bone is a ceramic synthetic bone substitute, not sintered and obtained by biomorphic transformation of the rattan wood. **b.Bone** is supplied in various shapes (cylinder, block, wedge and granules). **b.Bone** is slowly resorbed in vivo and is replaced by newly formed bone during the healing process.

The rattan wood architecture incorporates xylem-transporting channels that naturally transfer fluid upward and downward, matching the way blood vessels run through bone (Fig.1a, 1b).

b.Bone is composed of hydroxyapatite and beta-tricalcium phosphate in a unique, highly interconnected and hierarchically organized porous 3D structure to reproduce the hierarchical architecture and morphology of natural human bone[10, 11].

The biomimetic and bioactive structure of **b.Bone** is a driver of new bone formation and remodelling.
b.Bone allows cellular infiltration and vascularization throughout the graft material for bone healing, with improved absorption and bio-resorption properties[12, 13, 14].

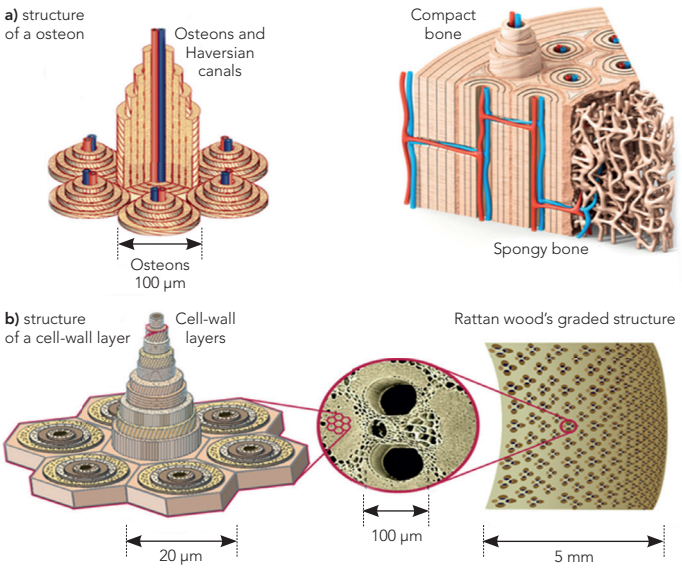


Fig. 1 a, b: Structure of human bone and rattan wood

INTRODUCTION

1.1 Instructions for Use

b.Bone is intended for use as a bone graft for voids or gaps that are not intrinsic to the stability of the bony structure.

b.Bone is indicated in the treatment of surgically created osseous defects or osseous defects resulting from traumatic injury to the bone.

b.Bone is intended to be implanted into bony voids or gaps in the extremities and pelvis.

1.2 Contraindications

b.Bone is not designed for any use except as indicated. Do not use b.Bone in the presence of any contraindication.

Use of the b.Bone IS NOT INDICATED in the following situations:

- Acute and chronic infections in the operation area, involving the bone or the soft tissues
- Bone malignant tumor(s)
- Concomitant infectious systemic diseases
- Inflammatory systemic diseases
- Concomitant myeloproliferative disorders
- Treatment with systemic immunosuppressive agents
- Active autoimmune disease
- Known or suspected allergy or hypersensitivity to the b.Bone device components
- Calcium metabolism disorder (i.e. hypercalcemia)
- Known hyperthyroidism or autonomous thyroid adenoma
- Severe, poorly controlled diabetes (diabetes mellitus) with impaired wound healing tendencies
- Known severe osteoporosis.

b.Bone is intended to be used as a bone substitute in adults. Its effect in pediatric patients and in pregnant or breast-feeding women has not been established.

2. PRODUCT OVERVIEW

2.1 Specifications

b.Bone is composed of hydroxyapatite and beta-tricalcium phosphate in a unique, highly interconnected and porous 3D structure which mimics the hierarchical architecture and morphology of natural human bone.

Phase and chemical composition

Hydroxyapatite (HA) = 85 %

Beta-Tricalcium Phosphate (ß-TCP) = 15%

Ca/P= 1,60

Presence of magnesium (Mg^{2+}), strontium (Sr^{2+}), and carbonate (CO_3^{2-}) ions

Porosity

b.Bone is highly porous and exhibits a total porosity ≥ 45 vol %.
The porosity evaluation confirmed the presence of micro and macro porosity.
Pore distribution: Macropores (>10 micron) > 30%
Micropores (<10 micron) > 30%.

2. PRODUCT OVERVIEW

2.2. b.Bone structure

A novel multi-step process transforms the native vegetable structures into **b.Bone**, which mimics the original 3D morphology and hierarchical architecture of the rattan wood.

Thanks to this patented technology, a process, in water and at low temperatures, **b.Bone** crystal structure has submicrometric dimensions, very similar to those present in natural bone, which make the hydroxyapatite crystals more bioactive and resorbable[13, 15] (Fig.2a, 2b).

When compared to other synthetic materials on the market, **b.Bone** presents also a different porosity, in terms of pores' shape and organization[16] (Fig.3a, 3b).

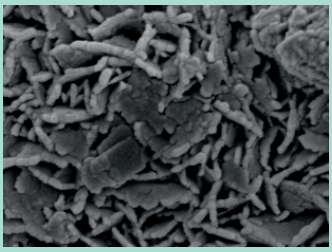


Fig. 2a: HA crystals dimentions of b.Bone 100 – 300 nm

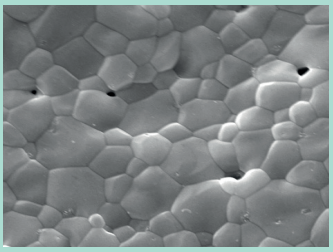


Fig. 2b: HA crystals of a synthered competitor

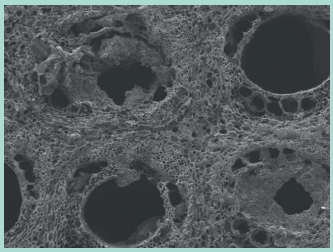


Fig. 3a: Hierarchical porosity of b.Bone

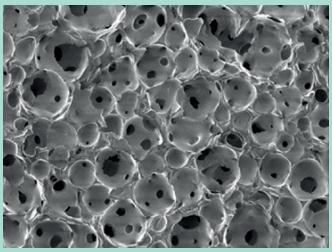
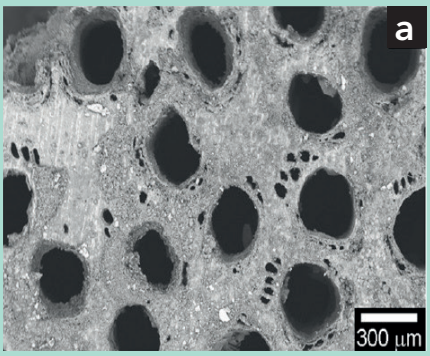


Fig. 3b: Porosity of a competitor bone substitute

b.Bone is highly porous and exhibits a totol porosity ≥ 45 vol %. The porosity evaluation confirmed the presence of micro and macro porosity[13] (Fig.4, 5).



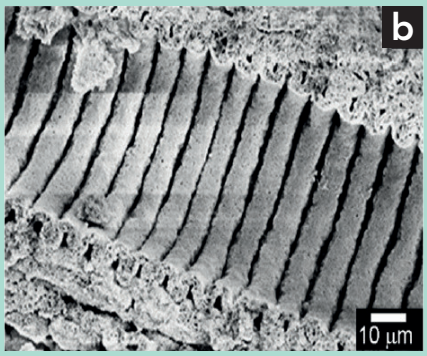


Fig. 4: **a)** view from the top of the b.Bone showing macroscopic longitudinal channels. **b)** view of the transversal section showing interconnected smaller channels.

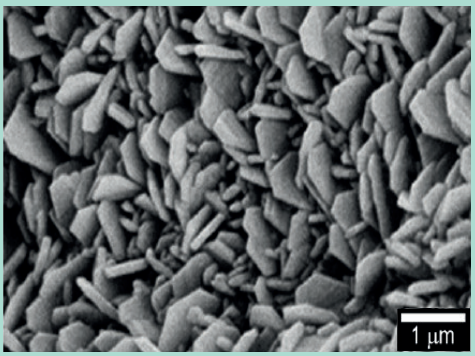


Fig. 5: high magnification image showing the lamellar structure of the b.Bone HA.

2. PRODUCT OVERVIEW

The b.Bone structure closely mimics the structural hierarchy typical of the osteonic system of compact bone, and the major channels are characterized by an intricate tubular morphology.

Analysis at larger magnification reveals prismatic nanocrystals with a hexagonal-like shape, forming a textured structure featuring strong inter-particle interaction, and mimicking the organization of mineral crystals in natural bones.
b.Bone shows open pores, uniformly distributed from the macro to the nanoscale[16] (Fig.6, 7).

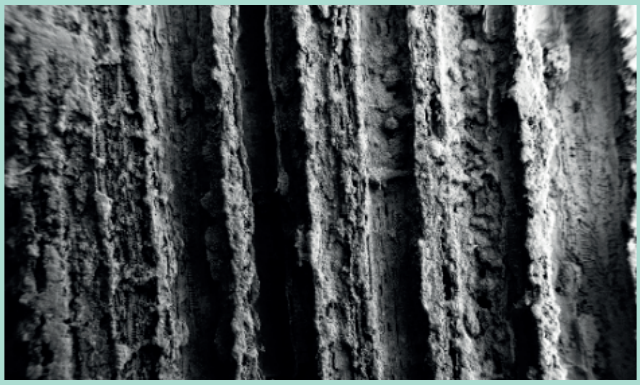
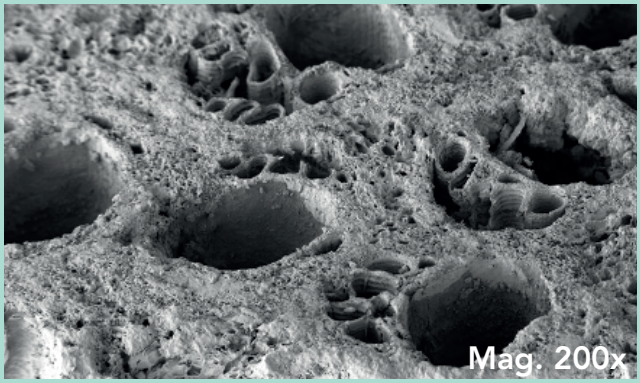


Fig. 6: Interconnected smaller channels



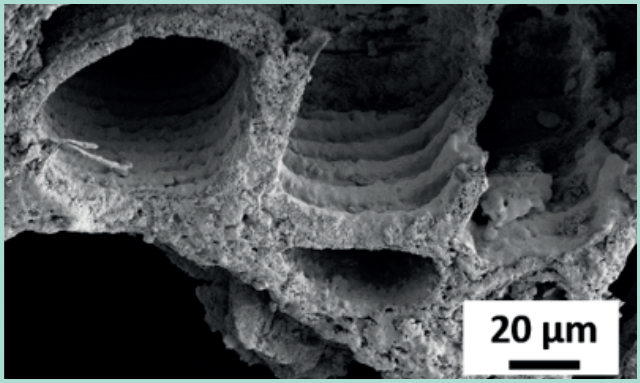


Fig. 7: Channel like structure mimicking the osteonic structure of natural bone.

Micro-CT imaging confirms that the open channels in b.Bone run along the entire length of the scaffold without interruptions[13] (Fig.8).

In addition, these channels are extensively interconnected at the multi-scale. Those characteristics are beneficial to ensure new bone formation and vascularization in the whole scaffold.

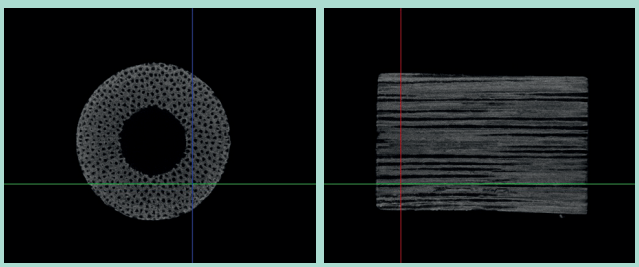


Fig. 8: Micro CT scan of a cylinder and a block of b.Bone.

2. PRODUCT OVERVIEW

Although it is not load-bearing without the appropriate fixation systems, due to its specific architecture, b.Bone possesses a certain mechanical resistance to compression, superior to other ceramic competitors. It has a damage-tolerant behaviour, like natural bone[17].

The scaffold does not undergo abrupt fracturing as expected for porous ceramics, it seems to retain memory of some properties of the original wood, and is able to adapt its structure, absorbing mechanical energy and adapting to traumas (Fig.9).

These mechanical properties make b.Bone easy to use, thus allowing the surgeon to customize its shape to resemble the bone defect and achieve a better fit. Furthermore, b.Bone can be easily drilled without crumbling like other traditional ceramics.

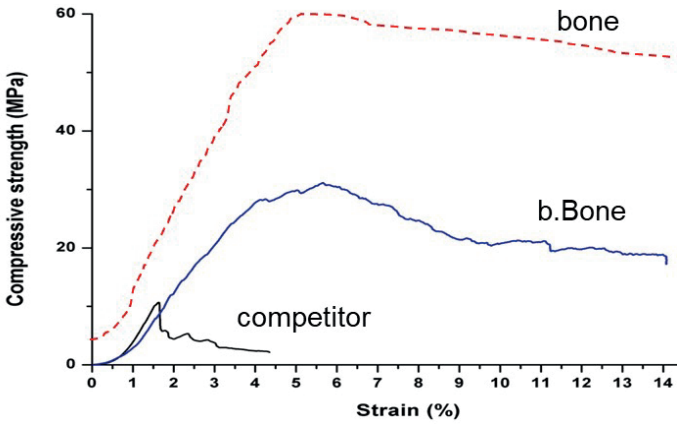


Fig. 9: Compressive strength graphic.

2.3 In-vitro and in-vivo results

In-vitro experiments were performed on mesenchymal stem cells to evaluate the behaviour of **b.Bone**[13] in bioreactor.

The biomimetic characteristics of **b.Bone** show that after 14 days of incubation in a bioreactor, the cells colonize, populate and proliferate in the entire scaffold.

Cell morphology is well spread which is a sign of good viability[13] (Fig.10).

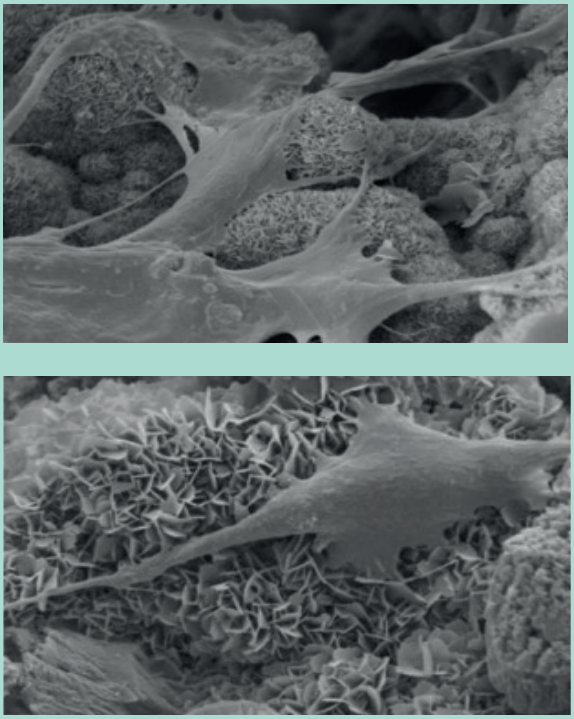


Fig. 10: Mesenchymal cells which lay upon b.Bone.

b.Bone was implanted subcutaneously in animal models (rabbits)[13] (Fig.11).

After 12 weeks from implantation, the histological analysis showed well-developed bone tissue, also at an ectopic site.

The histology revealed copious trabecular bone structures, with the presence of a neovascular network penetrating through the scaffold, copious osteoid tissue covered by numerous osteoblasts and osteocytes embedded in the dense matrix, and also some osteoclasts.

These results show the presence of some new blood vessels formation, the first indication of **b.Bone** angiogenesis activity[13] (Fig.12).

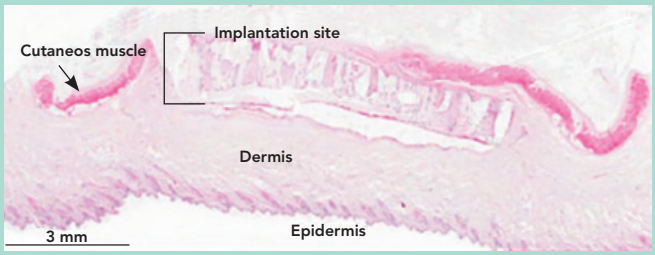


Fig. 11: Ectopic implantation site in rabbit.

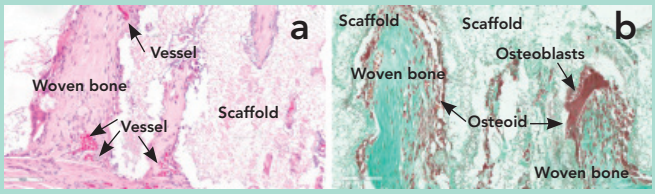


Fig. 12 a and b: Histological analysis of explanted b.Bone after 12 weeks showing the presence of osteoid, woven bone and new blood vessels.

2. PRODUCT OVERVIEW

An in-vivo study was conducted on sheep[14]. **b.Bone** was implanted in a critical cortical defect of 30 mm length.

In comparison to allograft, after 6 months **b.Bone** showed higher new bone formation and quality of regenerated bone (Fig.13).

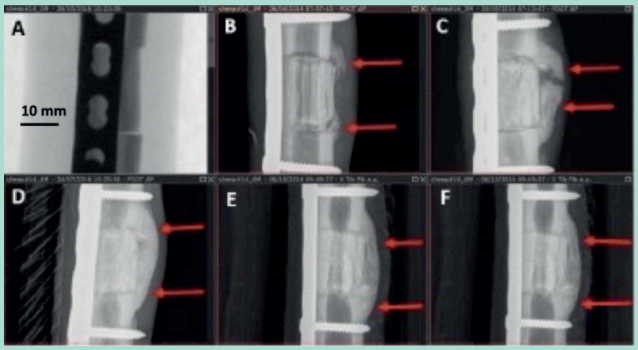


Fig. 13: Different stages of callus formation. Serial radiographs on the same sheep. (A): immediate post implant radiograph, (B): month 1, non-bridging callus, (C): month 2, partially bridging callus, (D): month 4, complete bridging callus, (E,F): months 5,6, complete bridging unchanged.

In addition, higher osteoid surface, osteoid thickness, osteoblast surface,number of vessels/microvessels, were observed (Fig.14).

The scaffold was largely reabsorbed.
From a mechanical analysis, it was proved that the newly formed bone is mechanically stable and resistant in a manner comparable to natural bone.

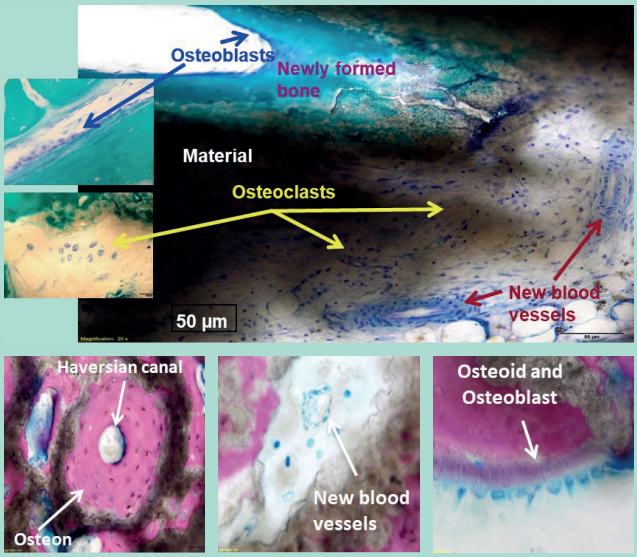


Fig. 14: Histological analysis of explanted b.Bone after 6 months showing the presence of osteoid and osteon, new blood vessels and newly formed bone.

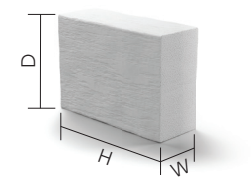
2.4 Clinical Evidence

Clinical Evidence, collected through clinical studies and other post-market surveillance activities[18, 19], demonstrates the product's safety and performance, and supports the benefits it provides, namely its regenerative and mechanical capabilities, previously demonstrated in vitro and in vivo.

3. CONFIGURATIONS AND SIZES

b.Bone is available in four different configurations: hollow cylinder, block, granules and wedge.

The available dimensions for each configuration are reported in Figure 15.

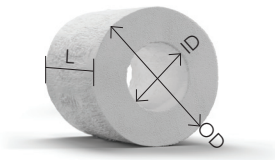


BLOCK
Available size

PRODUCT CODE	WIDTH (W)	DEPTH (D)	HEIGHT (H)
HP401020PS	10 mm	20 mm	40 mm

BLOCK
Upon request

WIDTH (W) - RANGES	DEPTH (D) - RANGES	HEIGHT (H) - RANGES
5 mm - 10 mm - 15 mm	10 mm - 20mm - 30 mm	20 mm - 30 mm - 40 mm - 50 mm

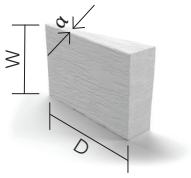


CYLINDER
Available sizes

PRODUCT CODE	OUTER DIAMETER (OD)	INNER DIAMETER (ID)	LENGTH (L)
HC100030PS	10 mm	0 mm	30 mm
HC150630PS	15 mm	6 mm	30 mm
HC201030PS	20 mm	10 mm	30 mm
HC251330PS	25 mm	13 mm	30 mm
HC301530PS	30 mm	15 mm	30 mm
HC100060PS	10 mm	0 mm	60 mm
HC150660PS	15 mm	6 mm	60 mm
HC201060PS	20 mm	10 mm	60 mm
HC251360PS	25 mm	13 mm	60 mm
HC301560PS	30 mm	15 mm	60 mm

CYLINDER
Upon request

LENGTH (L)
10 mm - 20 mm - 40 mm - 50 mm for each outer diameter



WEDGE
Available sizes

PRODUCT CODE	ANGLE (α)	DEPTH (D)	WIDTH (W)
WE093015PS	9°	30 mm	15 mm
WE113015PS	11°	30 mm	15 mm
WE133015PS	13°	30 mm	15 mm
WE094030PS	9°	40 mm	30 mm
WE114030PS	11°	40 mm	30 mm
WE134030PS	13°	40 mm	30 mm

GRANULES
Available sizes

PRODUCT CODE	RANGE	QUANTITY
GR051005PS	0.5 - 1 mm	5 g
GR102005PS	1 - 2 mm	5 g
GR204005PS	2 - 4 mm	5 g
GR407105PS	4 - 7.1 mm	5 g

Fig. 15: Confirgurations and sizes

4. SURGICAL PROCEDURE

4.1 General Prerequisites

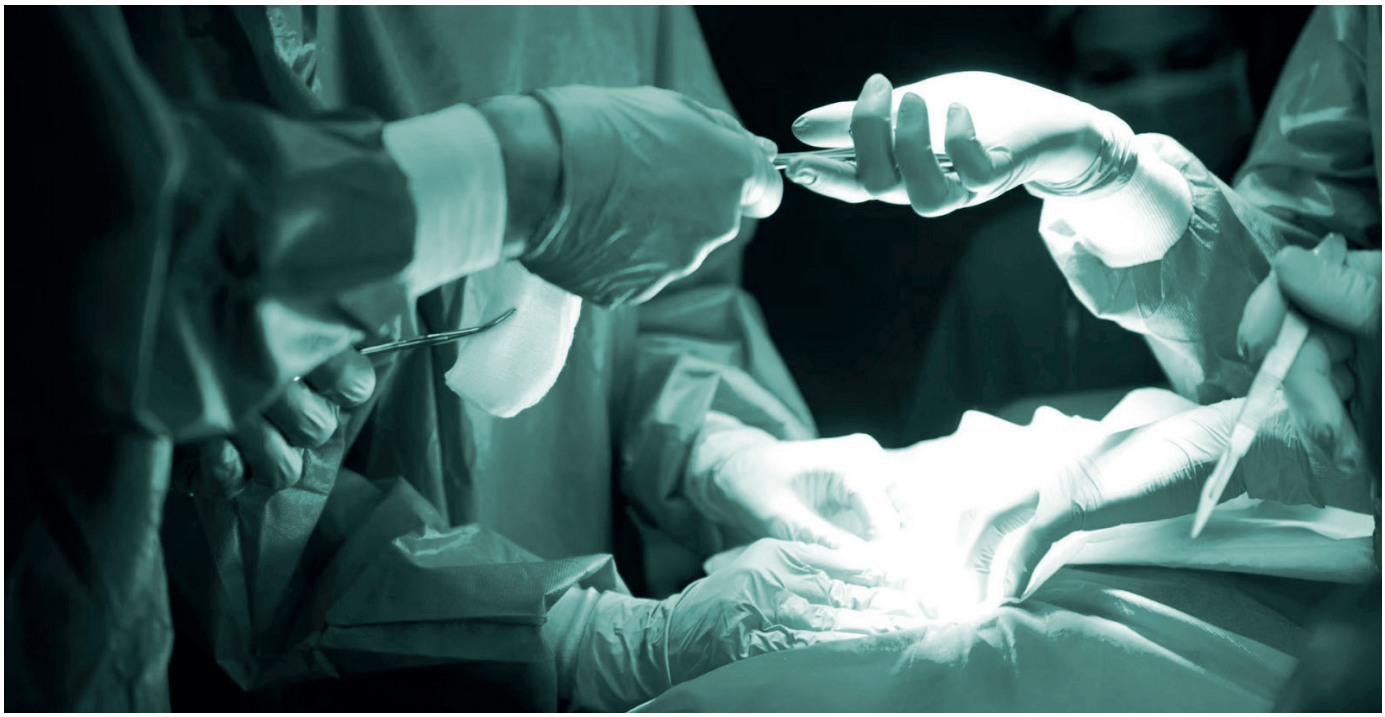
1. For details on the device handling and preparation please read carefully the IFU code n. LI0004.

2. The use of **b.Bone** is the same as the routine application of a bone substitute in bone defect reconstructive surgery.

3. The local bone environment MUST be clear of infection.
   b.Bone can be used in bone defects after control of the infection, e.g. for bone reconstruction in a 2-stage Masquelet procedure with no signs of ongoing infection at stage 2.

4. **b.Bone** must always be in direct contact with the edges of the void. Both the bone edges and the surrounding soft tissue should be healthy and well vascularized.

5. In general, adequate mechanical stability and fracture alignment should be achieved for the reconstruction of the affected extremity prior to the implantation of **b.Bone**.



4. SURGICAL PROCEDURE

4.2 Preparation of b. Bone

1. Measure the bone defect (Fig.16) and choose the appropriate **b.Bone** configuration and size. If needed, **b.Bone** can be shaped gently with an orthopedic saw in order to better fit in the bone gap.

2. When selecting a cylinder, if the size corresponding to the bone diameter is not available, choose a **b.Bone** cylinder with a smaller diameter to facilitate callus formation around the **b.Bone**.

3. It is recommended to soak **b.Bone** with blood or bone marrow aspirate (BMA) either before implantation (Fig.17) or once implanted. (Fig.18). The surgeon should also consider soaking of **b.Bone** in PRP preparations.

4. **b.Bone** granules configuration could be used to expand the volume of autologous bone graft (i.e. pelvic, RIA graft). It is recommended to use enough material to fill the bone cavity appropriately.

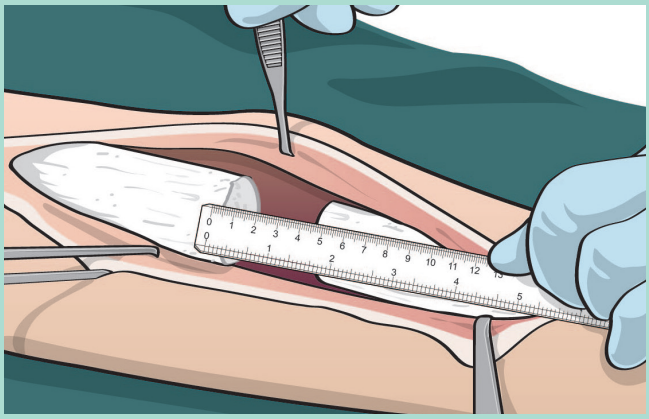


Fig. 16

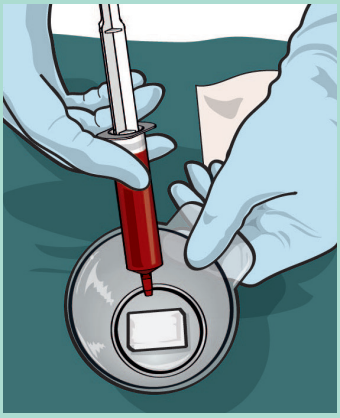


Fig. 17

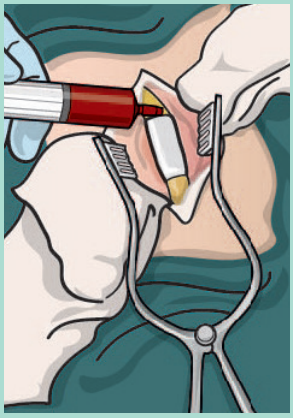


Fig. 18

4.3 Implantation of b. Bone

1. b.Bone must be implanted securely within the bone void or defect area in direct contact with the bone edges (Fig.19a).

   a. In case of iliac crest reconstruction: a press fit technique is recommended.
   Shape and cut b.Bone to fit the defect, and gently advance it while press fitting (Fig.19b).

   b. In case of other applications, reduce and stabilize the bone of the affected extremity with the appropriate fixation device.
   The basic principles of fixation of the selected stabilization device must be adhered.

   c. When using granules, it is recommended to use enough material to fill the bone cavity appropriately and achieve good impaction to prevent secondary fracture collapse.

2. The accurate positioning of b.Bone should be checked with fluoroscopy.

3. Augmentation of b.Bone with either BMA or PRP must be done prior to wound closure if not done previously.

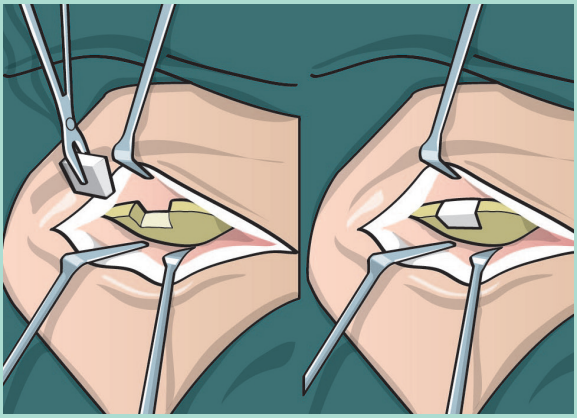


Fig. 19 a

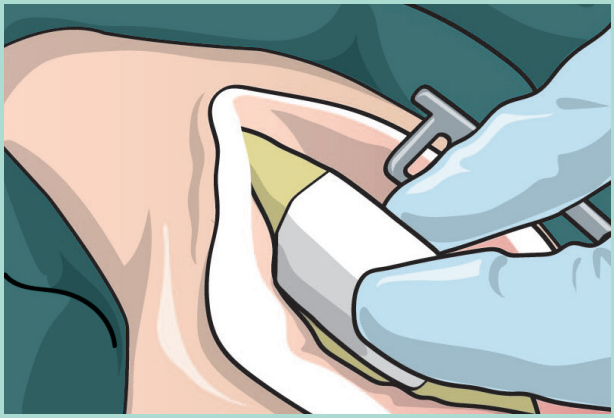


Fig. 19 b

4.4 Considerations when using fixation devices

4.4.1 Intramedullary Nailing

1. When choosing a b.Bone cylinder, the internal diameter should be at least 2 mm bigger than the selected nail diameter.
   The curvature of the nail should also be considered (Fig.20).

2. Provide adequate stability and good alignment (maintaining reduction) to the proximal and the distal segment of the bone during nail insertion.
   This is essential to preserve the integrity of b.Bone.

   Note: b.Bone cannot be reamed.

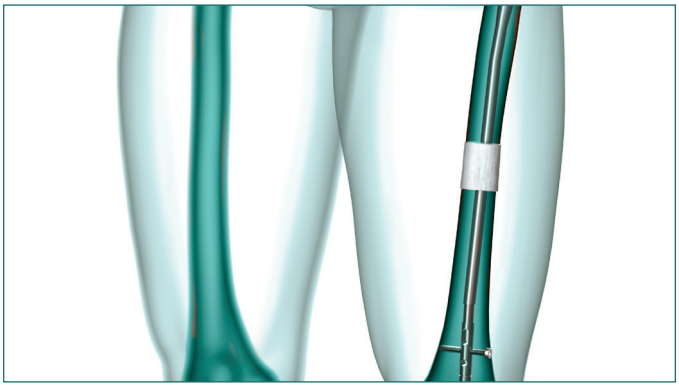


Fig. 20

4.4.2 Compression Plating

1. Position the plate and insert the screws with no compression mode.

2. Insert b.Bone gently in the void, making sure that it is in contact with the vital bone.

3. Check accurate positioning of the plate and screws under fluoroscopy.

4. Proceed with insertion of compression screws in the plate to facilitate good stability of the scaffold.

5. Complete the insertion of the screws according to the preoperative planning (Fig.21).

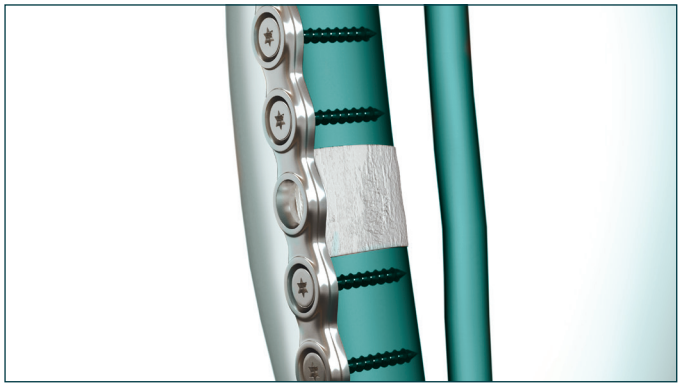


Fig. 21

4.4.3 External Fixation

It is important to apply the external fixator before inserting **b.Bone** (Fig.22).

Optimum mechanical stability and alignment should be achieved for the reconstruction of the affected extremity prior to the implantation of **b.Bone**.

Good contact and compression between **b.Bone** and the bone segments is desirable to support evolution of bone healing.

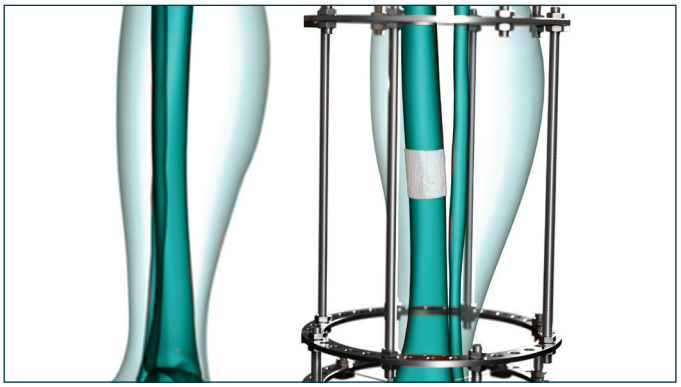


Fig. 22

4.5 Post-operative management

The surgeon should dictate the most appropriate postoperative rehabilitation protocol taking into account the fixation method, the anatomical site and the patient profile.

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GREENBONE ORTHO S.p.A.

FAENZA - Registered Office
Via Albert Einstein, 8
48018 Faenza (RA) Italy

RONCADELLE
Trav. di Via Martiri della Libertà, 7
25030 Roncadelle (BS) Italy

www.greenbone.it