smartbook

ORTHO

swiss made

ibi

Industrie Biomediche Insubri SA
Via Cantonale 67
6805 Mezzovico-Vira
Switzerland

First edition: December 2020

CAUTION: The law restricts the sales of these devices made by, or on the order of a surgeon.
Warning: Possible complications which may occur with any surgery include swelling at the surgical site, flap necrosis, bleeding, local inflammation, bone loss, infection or pain. Since SmartBone® ORTHO contains collagen, cases of allergic reactions may occur in very rare circumstances.

IBI-BOOK03 rev. 0 12/20

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IBI SA: who we are

1.1. MISSION

IBI SA - Industrie Biomediche Insubri SA - is an innovative hi-tech Swiss biomedical company focused on research, development and production of proprietary technologies and medical devices for tissue engineering, founded on 26th February 2008.

IBI SA believes that regenerative medicine and tissue engineering represent the future for reconstructive surgery.

IBI has advanced competencies and core skills in processing materials for biomedical applications, which are used to develop proprietary technologies to build new and innovative medical devices.

IBI commits to safety and quality management: IBI Quality System is compliant to ISO 13485:2016. SmartBone® ORTHO is CE marked according to 93/42/CE Directive classified as a class III Medical Device.

In July 2012 IBI introduced SmartBone® on the international market: SmartBone® is an innovative bone substitute specifically developed for bone regeneration, successfully used in oral and maxillofacial surgeries and traumatology. In the last years, following changes in references normative scenario, IBI consolidated two different certifications for SmartBone® according to the class of clinical indications of use: SmartBone® ORTHO for the orthopaedics applications and SmartBone® for the dental field.

During the 3 years IBI had been carrying on an observational study to collect clinical data obtained from patients who underwent reconstructive surgeries (from either trauma, or orthopaedic or oncology).

SmartBone® ORTHO is osteoconductive, biocompatible, biodegradable and its microstructure has a porosity that promotes a fast and effective bone regeneration, thus successfully allowing its use in orthopaedic and spine surgery.

IBI keeps the biomedical, dental and orthopaedic community, as well as all end users, updated on its website (www.ibi-sa.com) and on its YouTube channel, with sections dedicated to company history, research, clinical cases, publications and much more.

Use a scan program to discover further information about IBI SA

bsi.

By Royal Charter

Certificate of Registration

QUALITY MANAGEMENT SYSTEM - ISO 13485:2016 & EN ISO 13485:2016

This is to certify that:

Industrie Biomediche Insubri SA
Via Cantonale 67
Mezzovico-Vira
Ticino
CH-6805
Switzerland

Holds Certificate Number: **MD 652245**

and operates a Quality Management System which complies with the requirements of ISO 13485:2016 & EN ISO 13485:2016 for the following scope:

Research and development, manufacture and sale of implantable medical devices for tissue engineering, also custom-made medical devices.

For and on behalf of BSI:

Stewart Brain, Head of Compliance & Risk - Medical Devices

Original Registration Date: 2016-04-11
Latest Revision Date: 2019-02-10

Effective Date: 2018-06-05
Expiry Date: 2021-06-04

Page: 1 of 1

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bsi.

By Royal Charter

EC Design-Examination Certificate

Directive 93/42/EEC on Medical Devices, Annex II Section 4

No. CE 717465

Issued To:

Industrie Biomediche Insubri SA
Via Cantonale 67
Mezzovico-Vira
Ticino
CH-6805
Switzerland

In respect of:

SMARTBONE® ORTHO

BSI has performed a design examination on the above devices in accordance with the Council Directive 93/42/EEC Annex II Section 4 and Regulation 722/2012. The design conforms to the requirements of this directive and regulation. For marketing of these products an additional Annex II excluding Section 4 certificate is required.

For and on behalf of BSI, a Notified Body for the above Directive (Notified Body Number 2797):

Gary E Slack, Senior Vice President Medical Devices

First Issued: **2020-05-12** Date: **2020-05-12** Expiry Date: **2024-05-26**

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smartbone®

ORTHO

2. 1. INTRODUCTION

Since 1889, "modern" scientists started to focus their efforts on what can be defined as early bone tissue engineering [Senn, 1889; Gtelis, 2002]. Nowadays, hundred million surgical interventions are performed every year worldwide: current clinical gold standard for treatment of critical sized and nonunion bone defects is autograft bone.

Although autografts are advantageous for immunocompatibility, they carry a wide spectrum of risks (general anaesthesia, complex surgical maneuvers, secondary infections, fractures, pain, site morbidity, *etc*) that lead to a high percentage of failures (more than 10%) and are also followed by important cost increases [Younger, 1989; Hierholzer, 2006]. Furthermore, it is generally known that not all defects can be addressed, particularly the bigger ones, as far as few healthy sites can be harvested without a loss of function [Planell, 2009].

The need of adequate bone substitutes that promote an efficient remodeling of the native bone tissue is hence evident and it is supported by a wide spectrum of solutions proposed by academia, clinics and industry [Mistry, 2005]. In this framework, surgeons can choose among different types of substitutes that can be divided into three main categories:

- allografts, *i.e.* bone segments taken from either cadavers or living donors and duly acellularized and sterilized;
- xenografts, *i.e.* bone segments taken from animal bones (cows, horses, pigs, etc), duly acellularized and sterilized;
- synthetic scaffolds, such as *e.g.* bioceramics.

Allografts are an accepted alternative, but imply a higher risk, since disease transmission between humans is more likely than transmission between animal and human. Therefore, scientific research is progressively leading to the evaluation of other solutions [Haugen, 2019].

Xenografts and synthetic biomaterials represent an extremely valid alternative [Mistry, 2005; Winkler, 2018]. Nevertheless, to our best knowledge, only a few mixed composite substitutes are readily available on the market [Ramesh, 2017; De Grado, 2018; Ferraccini, 2018].

Finally, the hybrid approach (*e.g.* upgraded naturally derived materials) recently gains credit as of the most promising one [Rossi, 2015; Sarkar, 2015]: indeed, it enables the production of materials that can perfectly mimic healthy human bone, being rigid and elastic, compact but porous, and viable for cells and vessels [Ramesh, 2017; De Grado, 2018].

SUPPLEMENT ARTICLE

WILEY Journal of Clinical Periodontology

Bone grafts: which is the ideal biomaterial?

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Abstract

Bovine xenograft materials, followed by synthetic biomaterials, which unfortunately still lack documented predictability and clinical performance, dominate the market for the cranio-maxillofacial area. In Europe, new stringent regulations are expected to further limit the allograft market in the future.

Aim: Within this narrative review, we discuss possible future biomaterials for bone replacement.

Scientific Rationale for Study: Although the bone graft (BG) literature is overflooded, only a handful of new BG substitutes are clinically available. Laboratory studies tend to focus on advanced production methods and novel biomaterial features, which can be costly to produce.

Practical Implications: In this review, we ask why such a limited number of BGs are clinically available when compared to extensive laboratory studies. We also discuss what features are needed for an ideal BG.

Results: We have identified the key properties of current bone substitutes and have provided important information to guide clinical decision-making and generate new perspectives on bone substitutes. Our results indicated that different mechanical and biological properties are needed despite each having a broad spectrum of variations.

Conclusions: We foresee bone replacement composite materials with higher levels of bioactivity, providing an appropriate balance between bioabsorption and volume maintenance for achieving ideal bone remodelling.

KEYWORDS
bone graft, bone graft substitute, Bone replacement grafts, deal biomaterial

2.2. IBI'S APPROACH

In this sparkling context, IBI developed SmartBone® ORTHO, following an engineering approach and a bottom-up multiscale strategy: that is upgrading natural existing biomaterials, introducing advanced characteristics on a unique structural composition and architecture.

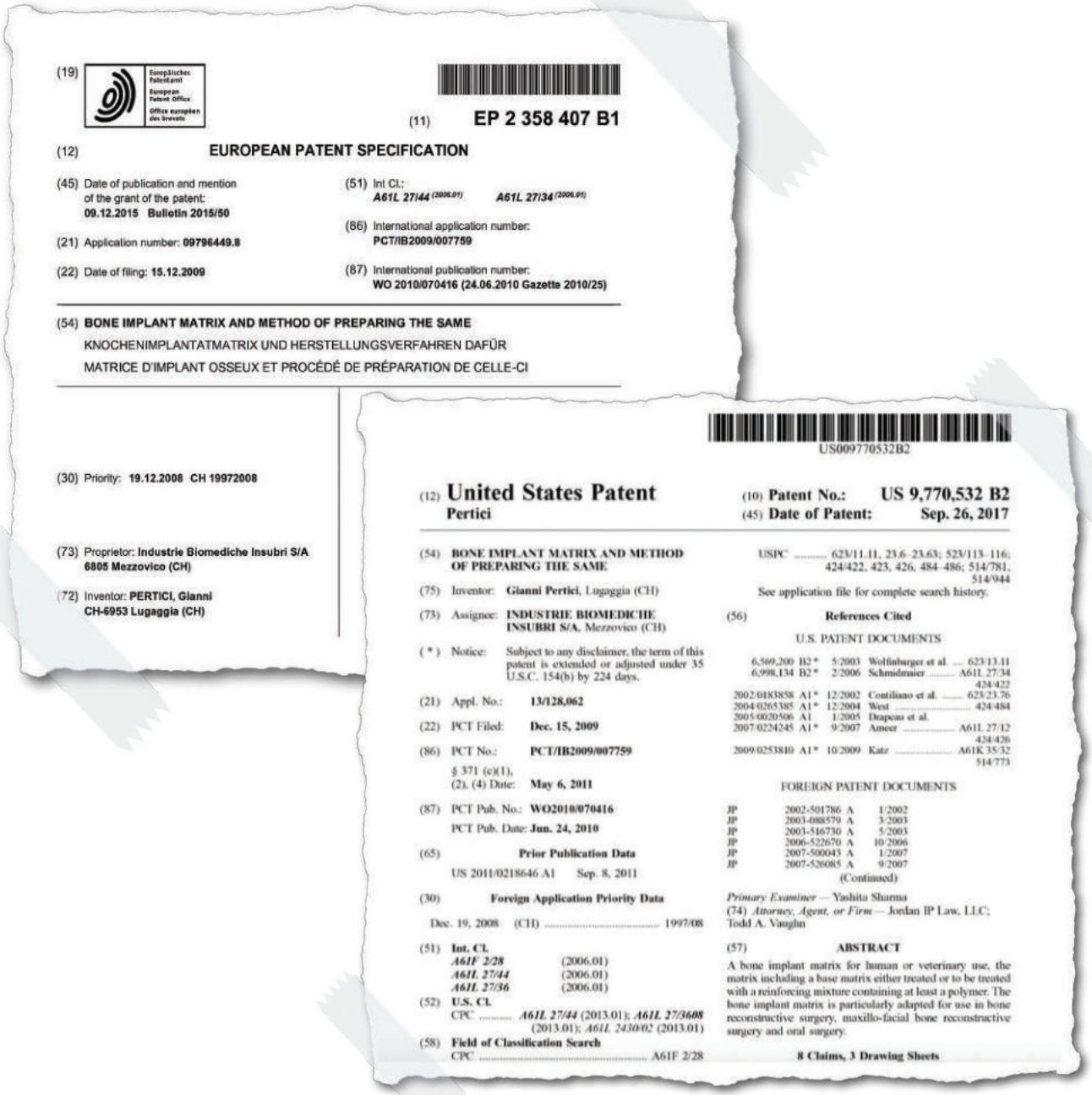
As a matter of fact, mimicking human bone's microstructure was the first point to address in order to ensure macro-scale properties: indeed, adequate-sized open porosity, combined rigid-elastic behavior and surface properties that ensure cell viability and colonization, are the key ingredients to finally obtain a remarkable and fast tissue integration and remodelling.

Giving biocompatibility as a granted request, the main features of IBI's innovative bone graft are thus the following (particularly intended with respect to other available bone grafts):

- **microstructure** comparable to the one of natural human bone (*i.e.* interconnected open porosity);
- **high mechanical performances**, close to those of a human healthy bone (*i.e.* rigid-elastic behavior, adequate elastic modulus, proper load bearing resistance, dust-free shaping, ability to be precisely modeled by all types of surgical tools, tenacity to fixation screws, hammering and heavy surgical maneuvering resistance, *etc.*);
- **high hydrophilicity** and thus high capability to absorb and retain blood (full of mesenchymal stem cells) once *in situ*;
- **high tissue integration** (*i.e.* high level of cell viability, proliferation, osteoconduction, osteoinduction).

Another key feature of SmartBone® ORTHO is the high level of homogeneity among the various samples. Many bone grafts available on the market show very high sample variability, even in the same production lot: this is due to the natural origin of the raw material, which reflects into having pieces with a different microstructure, higher/lower porosity and thus different density, as well as highly variable physical and mechanical properties.

Even if one of the initial raw materials is natural, IBI's process aims at reducing this variability in order to offer regular and homogeneous bone grafts [Cingolani (1), 2018].



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

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A61L 27/44 *(2006.01)* ***A61L 27/34*** *(2006.01)*

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PCT/IB2009/007759

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WO 2010/070416 (24.06.2010 Gazette 2010/25)

(54) **BONE IMPLANT MATRIX AND METHOD OF PREPARING THE SAME**
KNOCHENIMPLANTATMATRIX UND HERSTELLUNGSVERFAHREN DAFÜR
MATRICE D'IMPLANT OSSEUX ET PROCÉDÉ DE PRÉPARATION DE CELLE-CI

(30) Priority: **19.12.2008 CH 19972008**

(73) Proprietor: **Industrie Biomediche Insubri S/A**
6805 Mezzovico (CH)

(72) Inventor: **PERTICI, Gianni**
CH-6953 Lugaggia (CH)

US009770532B2

(12) **United States Patent**
Pertici

(10) **Patent No.: US 9,770,532 B2**
(45) **Date of Patent: Sep. 26, 2017**

(54) **BONE IMPLANT MATRIX AND METHOD OF PREPARING THE SAME**

(75) Inventor: **Gianni Pertici**, Lugaggia (CH)

(73) Assignee: **INDUSTRIE BIOMEDICHE INSUBRI S/A**, Mezzovico (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 224 days.

(21) Appl. No.: **13/128,062**

(22) PCT Filed: **Dec. 15, 2009**

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(51) **Int. Cl.**
A61F 2/28 (2006.01)
A61L 27/44 (2006.01)
A61L 27/36 (2006.01)

(52) **U.S. Cl.**
CPC ***A61L 27/44*** (2013.01); ***A61L 27/3608*** (2013.01); *A61L 2430/02* (2013.01)

(58) **Field of Classification Search**
CPC A61F 2/28
USPC 623/11.11, 23.6–23.63; 523/113–116; 424/422, 423, 426, 484–486; 514/781, 514/944
See application file for complete search history.

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(Continued)

Primary Examiner — Yashita Sharma
(74) *Attorney, Agent, or Firm* — Jordan IP Law, LLC; Todd A. Vaughn

(57) **ABSTRACT**

A bone implant matrix for human or veterinary use, the matrix including a base matrix either treated or to be treated with a reinforcing mixture containing at least a polymer. The bone implant matrix is particularly adapted for use in bone reconstructive surgery, maxillo-facial bone reconstructive surgery and oral surgery.

8 Claims, 3 Drawing Sheets

2.3. RAW MATERIALS AND PRODUCTION PROCESS

The multi-functional structure that IBI wanted for its innovative bone graft was achieved by developing a new biohybrid material composed of:

1) a bovine bone derived matrix (as starting raw material);
2) biocompatible and biodegradable biopolymers (polyesters) to reinforce the structure and to obtain an excellent biomechanical performance;
3) collagen fragments.

1) The bovine derived mineral matrix:

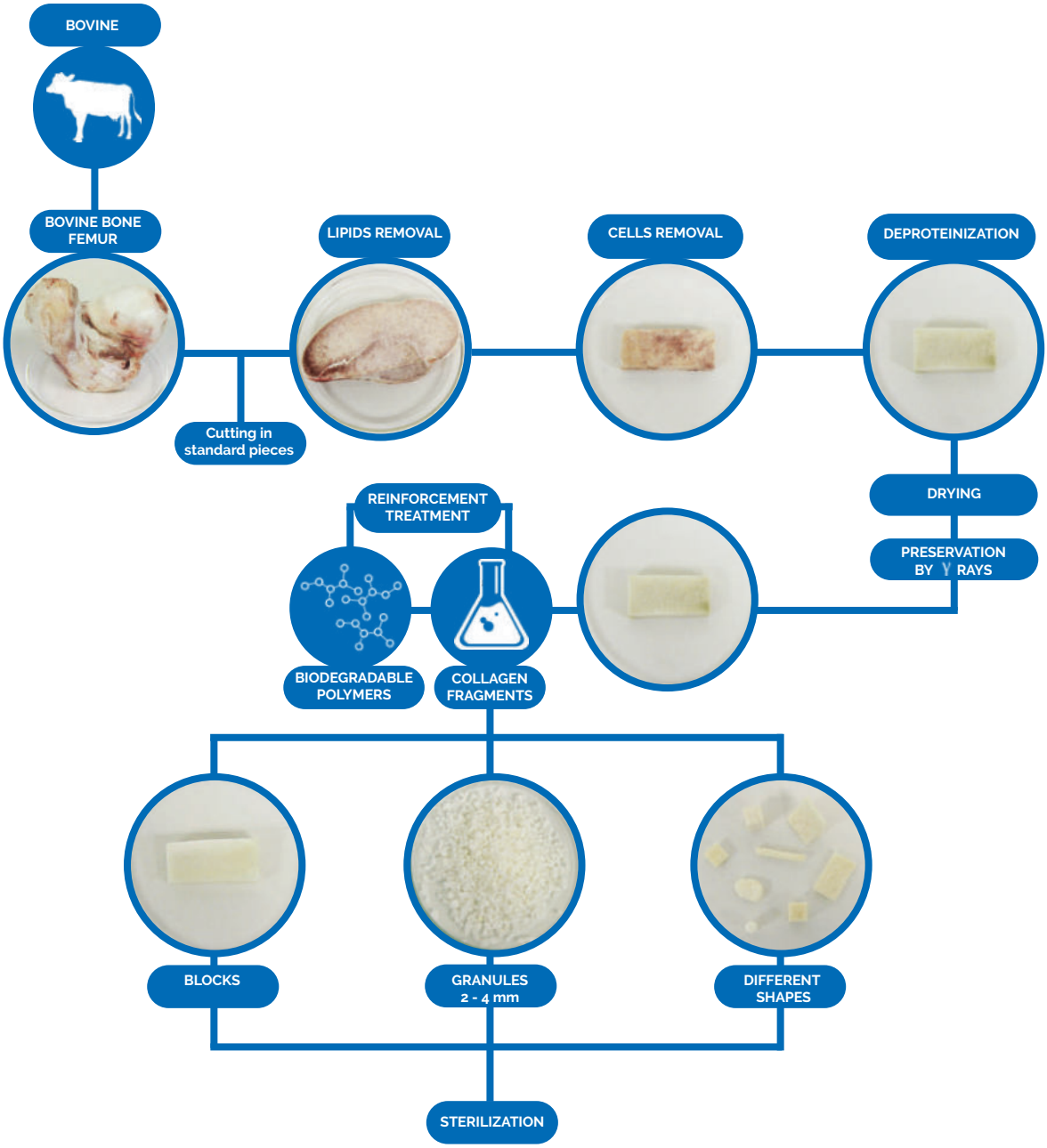
- has a chemical structure and a morphology that resemble the human bone;
- is rigid, but not elastic, and thus too fragile (since the mineral matrix loses its biomechanical properties without proteins);

2) The addition of a homogeneous polymeric coating helps to:

- reinforce the structure by adding a plastic component, thus improving resistance and reducing cracks propagation, making the graft mechanicaly performing;
- protect the graft from reabsorption during first inflammation-healing period and ensures volumetric stability.

3) Finally, the presence of collagen fragments, even if in extremely low quantities:

- make the surface very viable for cells and thus enhances tissue remodeling and integration;
- promote cell adhesion;
- increase the graft wettability, making it highly hydrophilic.


BOVINE
BOVINE BONE FEMUR
Cutting in standard pieces
LIPIDS REMOVAL
CELLS REMOVAL
DEPROTEINIZATION
DRYING
PRESERVATION BY γ RAYS
REINFORCEMENT TREATMENT
BIODEGRADABLE POLYMERS
COLLAGEN FRAGMENTS
BLOCKS
GRANULES 2 - 4 mm
DIFFERENT SHAPES
STERILIZATION

2.4. MICRO AND MACRO-STRUCTURE

SmartBone® ORTHO's major characteristic resides in its microstructure. In this sense, decellularized and deproteinized trabecular bovine bone already naturally presents a perfectly wide-opened, interconnected porosity, which is optimal for cell migration and colonization.

Nevertheless, in the frame of using it as base material for the development of implantable devices, a technique not only improving but also homogenizing the mechanical properties, making them independent on the raw, untreated material characteristics, is required. In this respect, IBI's proprietary process of adding resorbable polymeric components and collagen fragments improves material's mechanical and biological performances.

The combination of these two concepts is of utmost importance: on one hand, homogenous mechanical response is ensured; on the other one, cells proliferation is not only favoured by changes in the porous structure, but even further enhanced by the presence of collagen fragments. This way, full substitution by patient living healthy bone is recorded after complete remodeling.

The final geometrical characteristics of SmartBone® ORTHO were further investigated using computer tomography and are reported in figure 1, where an exemplificative image of a 3D render of a SmartBone® ORTHO 8x8x8 mm^3 cube is presented: it resulted that the tested sample had an equivalent volume of about 512 mm^3, a free volume of about 375 mm^3 and a free surface of about 2.300 mm^2.

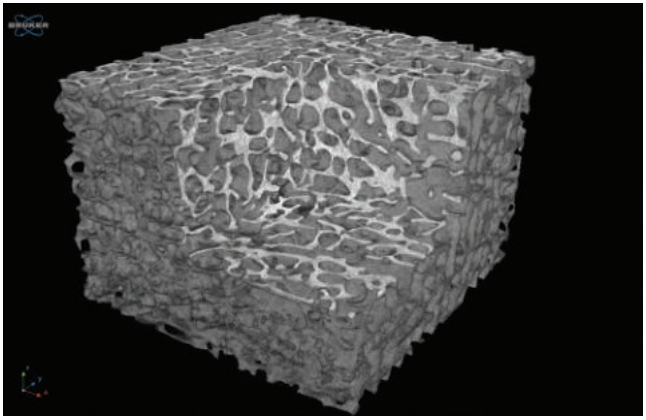


Figure 1. 3D render of an IBI's SmartBone® ORTHO obtained via reconstruction from a microCT scan.

Annals of Oral & Maxillofacial Surgery 2014 Feb 14;2(1):4.

Emerging Technologies

Research study

Composite polymer-coated mineral grafts for bone regeneration: material characterisation and model study

G Pertici[1,2], F Rossi[3], T Casalini[3], G Perale[1,2,4*]

Abstract

Introduction

This study discusses composite polymer-coated mineral grafts for bone regeneration.

Materials and Methods

Bone xenografts are coated with degradable synthetic [poly(L-lactide-co-ε-caprolactone)] and natural(polysaccharides) polymers in order to increase their mechanical properties, on one side, and to improve cell adhesion, on the other, with the purpose of developing a novel composite material for bone tissue engineering. In vitro assayshelp examine the microstructure of the scaffold by Fourier transform infrared and environmental scan-ning electron microscopy analyses and the porosity of the material by micro-computed tomography. The good adhesion property of polymer coated on to the mineral scaffold is deeply analysed and proved. The in vitro polymerdegradation, in terms of time evolution of polymer-coating thickness, was rationalised with a mathematical model. The purpose of such modelling activity is to provide a simple but powerful-tool to understand the influence of design parameters on coating behaviour.

Results

The fabricated bone graft exhibited regular microstructure similar to healthy iliac bones with an average of 27% open porosity and an adequately rigid structure, which ensures a better osteointegration once implanted.

Conclusion

This approach avoids the use of trial -and-error methods and consents a better a priori material design.

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[2] Department of Innovative Technologies, University for Applied Science and Art of Southern Switzerland, Switzerland
[3] Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Milan, Italy
[4] Swiss Institute for Regenerative Medicine, Taverne, Switzerland

2.5. POLYMER DEGRADATION

When dealing with implantable medical device, product formulation and manufacturing need to follow specific procedures. In this respect, accurate selection of the base material has to be done. This has to take into consideration not only the characteristics of pristine, base polymers, but also the way they will be affected by all manufacturing and post-processing steps (including terminal sterilization).

Biodegradable polymers have the great advantage of naturally diseappear from patient body in a reasonable and controllable time after implantation, leaving minimal traces and small impact.

SmartBone® ORTHO polymeric fraction is subject to a complete degradation which occurs in an average of 18 weeks. This represents an optimal result because it degrades and fades away approximately in four months, matching the new bone ingrowth and tissue integration.

As visible in Figure 2 in the first two months, the degradation occurs with the thinning of the polymer film. From the end of the third month, it drops dramatically, reaching a complete dissolution between the fourth and the sixth month, independently on the initial thickness, in the range of 2 - 10 µm.

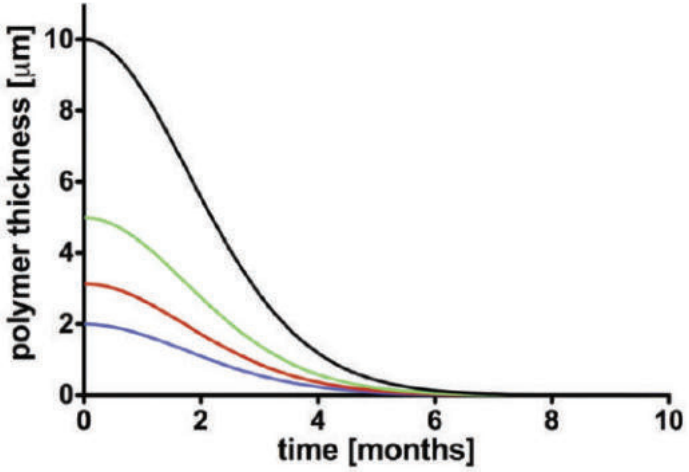

Figure 2. Polymeric film thinning during time as degradation proceeds almost independently from starting thicknesses (2, 3, 5, 10 (µm)).

polymers

MDPI

Article

A Methodologic Approach for the Selection of Bio-Resorbable Polymers in the Development of Medical Devices: The Case of Poly(L-lactide-*co*-"-caprolactone)

Alberto Cingolani [1,2], Tommaso Casalini [1,3], Stefano Caimi [1], Antoine Klaue [1], Mattia Sponchioni [4], Filippo Rossi [4,*] and Giuseppe Perale [2,3,*]

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Abstract: In the last decades bioresorbable and biodegradable polymers have gained a very good reputation both in research and in industry thanks to their unique characteristics. They are able to ensure high performance and biocompatibility, at the same time avoiding post-healing surgical interventions for device removal. In the medical device industry, it is widely known that product formulation and manufacturing need to follow specific procedures in order to ensure both the proper mechanical properties and desired degradation profile. Moreover, the sterilization method is crucial and its impact on physical properties is generally underestimated. In this work we focused our attention on the effect of different terminal sterilization methods on two commercially available poly(L-lactide-*co*-"-caprolactone) with equivalent chemical composition (70% PLA and 30% PCL) and relatively similar initial molecular weights, but different chain arrangements and crystallinity. Results obtained show that crystallinity plays a key role in helping preserve the narrow distribution of chains and, as a consequence, defined physical properties. These statements can be used as guidelines for a better choice of the most adequate biodegradable polymers in the production of resorbable medical devices.

Keywords: electron beam; ethylene oxide; medical devices; polymers; sterilization

Polymers 2018, 10, 851; doi:10.3390/polym10080851

2.6. MECHANICAL PROPERTIES

Mechanical handling and performances of bone grafts during surgical maneuvering is tremendously essential. Grafts are expected to undergo heavy stresses and loads, as far as they need to be shaped and cut before being placed. Furthermore, they need to withstand drilling and fixing of osteosynthesis screws and must remain firmly in place, offering a strong mechanical bond to the host tissue: the better the mechanical stability and the higher the surface contact with the host tissue, the higher and better the integration is achieved. A major point in this sense, is also represented by the necessity of having homogenous mechanical performance, even when the graft is shaped in complex geometries. IBI's treatement, not only reinforces the mechanical characteristics of pristine bone, but also ensures good homogeneity,

Full characterization from a torsional, flexural and compression point of view, have been run on SmartBone® ORTHO, showing excellent mechanical response under each of these texts. Results are reported in the following Table 1.

Torsion	Max Torque [Nmm]	Max Stress [MPa]	Max Strain %	Torsional Elastic Modulus [MPa]	Kg/cm²
Medium Value	1'505.4	25.5	5.8	490.6	259.8
Standard Dev.	294.9	4.4	0.9	103.7	44.9
Bending	**Max Force [N]**	**Max Stress [MPa]**	**Max Strain %**	**Flexural Modulus [MPa]**	**Kg/cm²**
Medium Value	100.3	23.8	7.6	340.6	242.4
Standard Dev.	17.4	4.2	0.9	63.1	42.4
Compression	**Max Force [N]**	**Max Stress [MPa]**	**Max Strain %**	**Elasticity Modulus [MPa]**	**Kg/cm²**
Medium Value	1'914.2	25.8	2.2	1'245.7	262.9
Standard Dev.	590.6	7.8	0.4	225.9	80.1

Table 1. SmartBone® ORTHO mechanical properties adapted from (Cingolani, 2018).

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Current Pharmaceutical Biotechnology, 2018, *19*, 1005-1013

RESEARCH ARTICLE

Improving Bovine Bone Mechanical Characteristics for the Development of Xenohybrid Bone Grafts

Alberto Cingolani[1,2], Carlo Francesco Grottoli[2], Raffaella Esposito[3], Tomaso Villa[3], Filippo Rossi[4] and Giuseppe Perale[2,5,6*]

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ARTICLEHISTORY

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Abstract: ***Background***: The further functionalization of natural existing biomaterials is a very efficient method to introduce additional advanced characteristics on a unique structural composition and architecture.

Objective: As an example, different animal sources, if properly treated, can be used to develop bone xenograft active in hard tissues regeneration. In this sense, it is also important to consider that the selected process has to take into consideration the intrinsic variability of the base material itself and possibly being able to compensate for it.

Methods: In this work we characterize cancellous bovine bone treated by deposition of polymer and collagen and we show that the added components not only lead to a more resistant and more hydrophilic material, but also reduce the conventional correlation between apparent density and elastic modulus, which, in general, is a major source of uncertainty and risk in xenografts usage.

Results: Moreover, though intrinsically reinforcing the material, the deposition process leaves the specific open-porous structure, that allows cells proliferation and vessels ingrowth, basically unaltered.

Conclusion: The final material combines in a single piece and at the same time, mechanical resistance, homogeneous mechanical response and proper structural characteristics that allow further integration within the patient autochthonous tissues.

Keywords: Hard tissues regeneration, xenografts, tissue engineering, biomaterials, bovine bone, biopolymers.

2.7. ISO BIOCOMPATIBILITY TESTS

Wide preclinical investigations have been carried out on SmartBone® ORTHO during the development phase, both *in vitro* with different cell populations and *in vivo* on reference animal models.

Standard compulsory ISO 10993 investigations on biocompatibility were carried out under GLP conditions, specifically: Intracutaneous Reactivity Test, Systemic Toxicity Test and Delayed Hypersensitivity Test were performed, all resulting completely negative, thus confirming SmartBone® ORTHO full biocompatibility.

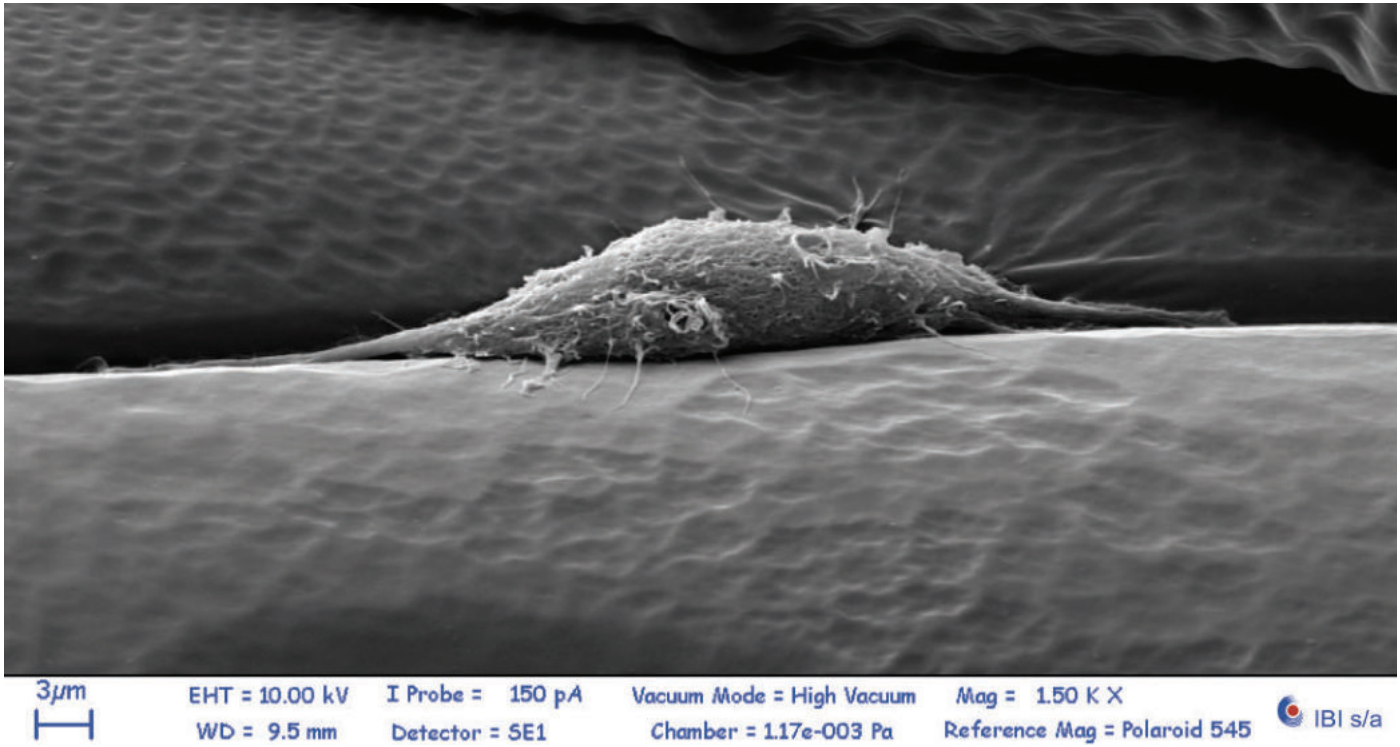

Figure 3. Exemplificative E/SEM zoomed-in image of a cell spreading onto a SmartBone® ORTHO internal surface, well evidencing the high cell conductivity of SmartBone® ORTHO surfaces.

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COMPOSITE POLYMER-COATED MINERAL SCAFFOLDS FOR BONE REGENERATION: FROM MATERIAL CHARACTERIZATION TO HUMAN STUDIES

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Bovine bone xenografts, made of hydroxyapatite (HA), were coated with poly(L-lactide-co-ε-caprolactone) (PLCL) and RGD-containing collagen fragments in order to increase mechanical properties, hydrophilicity, cell adhesion and osteogenicity. *In vitro* the scaffold microstructure was investigated with Environmental Scanning Electronic Microscopy (ESEM) analysis and micro tomography, while mechanical properties were investigated by means compression tests. In addition, cell attachment and growth within the three-dimensional scaffold inner structure were validated using human osteosarcoma cell lines (SAOS-2 and MG-63). Standard ISO *in vivo* biocompatibility studies were carried out on model animals, while bone regenerations in humans were performed to assess the efficacy of the product. All results from *in vitro* to *in vivo* investigations are here reported, underlining that this scaffold promotes bone regeneration and has good clinical outcome.

Orthopaedic Proceedings

Abstract

ADIPOSE-DERIVED STROMAL VASCULAR FRACTION SHOWS MARKED BONE-REGENERATIVE POTENTIAL ON A XENOHYBRID BONE SCAFFOLD

G. Perale, I. Roato, D.C. Belisario, M. Compagno, F. Mussano, T. Genova, F. Veneziano, G. Pertici, R. Ferracini

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Intra-articular infusions of adipose tissue-derived stem cells (ASCs) are a promising tool for bone regenerative medicine, thanks to their multilineage differentiating ability. One major limitation of ASCs is represented by the necessity to be isolated and expanded through in vitro culture, thus a strong interest was generated by the adipose stromal vascular fraction (SVF), the non-cultured fraction of ASCs. Besides the easiness of retrieval, handling and good availability, SVF is a heterogeneous population able to differentiate in vitro into osteoblasts, chondrocytes and adipocytes, according to the different stimuli received. We investigated and compared the bone regenerative potential of SVF and ASCs, through their ability to grow on SmartBone®, a composite xenohybrid bone scaffold. SVF plated on SmartBone® showed better osteoinductive capabilities than ASCs. Collagen I, osteocalcin and TGF markedly stained the new tissue on SmartBone®; microCT analysis indicated a progressive increase in mineralised tissue apposition by quantification of newly formed trabeculae (3391 ± 270,5 vs 1825 ± 133,4, p± 0,001); an increased secretion of soluble factors stimulating osteoblasts, as VEGF (153,5 to 1278,1 pg/ml) and endothelin 1 (0,43 to 1,47 pg/ml), was detected over time. In conclusion, the usage of SVF, whose handling doesn't require manipulation in an in vitro culture, could definitively represent a benefit for a larger use in clinical applications. Our data strongly support an innovative idea for a bone regenerative medicine based on resorbable scaffold seeded with SVF, which will improve the precision of stem cells implant and the quality of new bone formation.

3

Mechanism of Action

3. 1. REMODELLING OF SMARTBONE® ORTHO

SmartBone® ORTHO integration into the natural bone, and hence its resorption, is driven by its being progressively substituted with healthy living bone from host: it is, indeed, important to underline the key role of remodeling, hence the capability of SmartBone® ORTHO to be substituted by healthy living bone.

This is a key feature of SmartBone® ORTHO and one of its major innovative claims, also with respect to competing grafts. Here, moreover, lies one of the keys to understanding the mechanism of action of SmartBone® ORTHO [Pertici, 2010; Grecchi, 2014; Pertici, 2014; Pertici, 2015; Zollino, 2015; Secondo, 2017; D'Alessandro, 2017; Roato (1), 2018; Cingolani (1), 2018;Cingolani (2), 2018 Mandelli, 2018; Facciuto, 2019; Grottoli, 2019; Ferracini, 2019; Boffano, 2020; Ferracini, 2020]. SmartBone® ORTHO graft soaks up blood, thus starting microcoagulation to occur inside the graft itself and hence enhancing graft integration [D'Alessandro, 2017; Mandelli, 2018; Stacchi, 2018].

The first weeks are then needed for cellular colonization of the graft, which is also enhanced by the presence of gelatine that offers a viable environment for cells to spread onto; meanwhile, this time lag is also necessary for the degradation of the thin polymeric film, which progressively fades away leaving mineral structure for cells to consolidate and promote the formation of new living bone (also by means of formation of new vessels); the following couple of months are needed for the integration of the graft with the native patient bone, thanks also to vascularization and new bone formation inside the graft.

Human histological and radiological studies provided very robust confirmation, with clinical evidences, on this action mechanism, offering a greatly detailed insight also on new bone formation supported by SmartBone® ORTHO [Pertici, 2010 ; Grecchi, 2014; Pertici, 2014, Pertici, 2015; Zollino, 2015; Secondo, 2016; D'Alessandro, 2017; Mandelli, 2018; Roato(1), 2018; Stacchi, 2018; Facciuto, 2019; Grottoli, 2019; Ferracini, 2019; Boffano, 2020; Ferracini, 2020].

The choice of a bovine-derived mineral matrix is driven by the very high similarity with the human one [Datta, 2006; Haugen, 2019]. The adding of resorbable polymers serves not only to increase the mechanical performances but also to protect the mineral fraction from the very initial post-surgical inflammation and finally to sustain bone formation.

The adding of gelatine to the polymeric thin film serves to provide immobilized biomolecules containing the RGD (Arg-Gly-Asp) sequence, which promotes cell adhesion and hence sparks the formation of new bone.

SmartBone® ORTHO undergoes complete substitution via remodelling process: it shows about 1/3 substitution at about 6 months (averaged considering key factors *e.g.* graft volume, surgical site, patient sex and age, *etc.*) which proceeds till about 2/3 substitution in *ca*. 1 year, up to complete substitution with no evidences of residuals in the following years.

This evidences have been averaged from different districts, with different metholdogies, as described in the following paragraphs.

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Bovine bone matrix/poly(L-lactic-co-ε-caprolactone)/gelatin hybrid scaffold (SmartBone®) for maxillary sinus augmentation: A histologic study on bone regeneration

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ABSTRACT

The ideal scaffold for bone regeneration is required to be highly porous, non-immunogenic, biostable until the new tissue formation, bioresorbable and osteoconductive. This study aimed at investigating the process of new bone formation in patients treated with granular SmartBone® for sinus augmentation, providing an extensive histologic analysis. Five biopsies were collected at 4–9 months post SmartBone® implantation and processed for histochemistry and immunohistochemistry. Histomorphometric analysis was performed. Bone-particle conductivity index (BPCi) was used to assess SmartBone® osteoconductivity.

At 4 months, SmartBone® (12%) and new bone (43.9%) were both present and surrounded by vascularized connective tissue (37.2%). New bone was grown on SmartBone® (BPCi = 0.22). At 6 months, SmartBone® was almost completely resorbed (0.5%) and new bone was massively present (80.8%). At 7 and 9 months, new bone accounted for a large volume fraction (79.3% and 67.4%, respectively) and SmartBone® was resorbed (0.5% and 0%, respectively). Well-oriented lamellae and bone scars, typical of mature bone, were observed. In all the biopsies, bone matrix biomolecules and active osteoblasts were visible. The absence of inflammatory cells confirmed SmartBone® biocompatibility and non-immunogenicity. These data indicate that SmartBone® is osteoconductive, promotes fast bone regeneration, leading to mature bone formation in about 7 months.

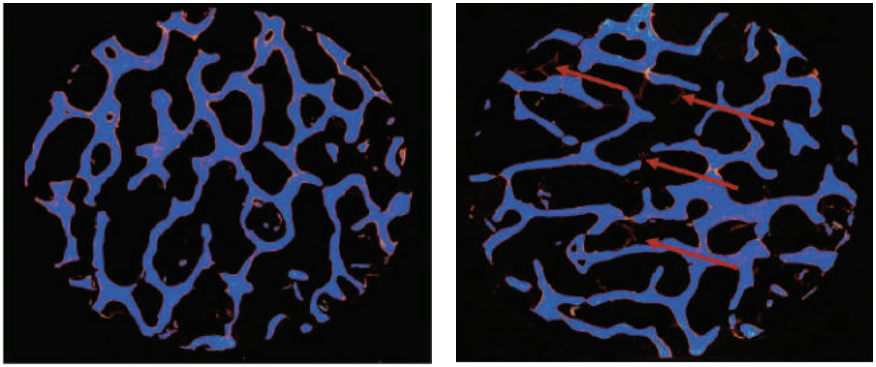
3.2. CELLULAR EXPLANATION OF SmartBone® ORTHO REMODELING MECHANISM

IBI devoted important resources into the detailed investigation of SmartBone® ORTHO integration mechanism. Driven by human histological results, IBI committed to deeply investigate the very initial phases of SmartBone® ORTHO integration and had, hence, developed a reliable *in vitro* model reproducing the first 60 days post-grafting. Essential issue in model development was the choice of the cell population to be used, aiming at best reproducing the natural *in vivo* environment faced by grafted SmartBone® ORTHO. Literature suggested the use of non-cultured fraction of adipose tissue-derived stem cells [Roato (1), 2018].

Adipose tissue-derived stem cells (ASCs) are a promising tool for the treatment of bone diseases or skeletal lesions, thanks to their ability to potentially repair damaged tissue. One of the major limitations of ASCs is represented by the necessity to be isolated and expanded through *in vitro* culture; thus, a strong interest was generated by the adipose stromal vascular fraction (SVF), the non-cultured fraction of ASCs. SVF is a heterogeneous cell population, directly obtained after collagenase treatment of adipose tissue.

SVF has hence a high potential as model cell type in assessing bone graft performances in vitro assays. We demonstrated [Roato (1), 2018] that SVF cells plated on SmartBone® ORTHO expressed their osteoinductive potential. Moreover, we observed an increasing area of new tissue over time, with and also without osteointegration media!

These data proved the dynamics of bone remodeling supported by SmartBone® ORTHO during the very early phase post-surgical grafting. Furthermore, these results strongly support an innovative idea for the use of adipose SVF and SmartBone® ORTHO to promote tissue regeneration and repair, also thanks to an easier cell management preparation that allows a potentially larger use in clinical applications [Roato (2), 2018].



SmartBone® ORTHO Stromal Vascular Fraction (SVF)

Figure 5. Adipose-derived Stromal Vascular Fraction (SVF) cultured on SmartBone® ORTHO promoted the formation of new trabeculae also in in vitro model. Images taken from [Roato(1), 2018].

Hindawi
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Research Article

Adipose-Derived Stromal Vascular Fraction/Xenohybrid Bone Scaffold: An Alternative Source for Bone Regeneration

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Academic Editor: Huseyin Sumer

Adipose tissue-derived stem cells (ASCs) are a promising tool for the treatment of bone diseases or skeletal lesions, thanks to their ability to potentially repair damaged tissue. One of the major limitations of ASCs is represented by the necessity to be isolated and expanded through *in vitro* culture; thus, a strong interest was generated by the adipose stromal vascular fraction (SVF), the noncultured fraction of ASCs. SVF is a heterogeneous cell population, directly obtained after collagenase treatment of adipose tissue. In order to investigate and compare the bone-regenerative potential of SVF and ASCs, they were plated on SmartBone®, a xenohybrid bone scaffold, already used in clinical practice with successful results. We showed that SVF plated on SmartBone, in the presence of osteogenic factors, had better osteoinductive capabilities than ASCs, in terms of differentiation into bone cells, mineralization, and secretion of soluble factors stimulating osteoblasts. Indeed, we observed an increasing area of new tissue over time, with and without OM. These data strongly support an innovative idea for the use of adipose SVF and bone scaffolds to promote tissue regeneration and repair, also thanks to an easier cell management preparation that allows a potentially larger use in clinical applications.

3.3. RADIOLOGICAL ASSESSMENT OF SMARTBONE® ORTHO INTEGRATION AND REMODELING OVER TIME

Assessing remodeling of SmartBone® ORTHO, and above all ITS integration, is an essential surgical need as it helps the surgeon to evaluate the best timing to further proceed with the treatment.
Typically, histological sampling is a non-commonly available tool in daily practice, where on the other hand radiographic imaging is routinely performed.
The rule of a thumb in assessing bone remodelling is density, evaluated by means of radiographic opacity. Briefly, one of major causes of opacity is the mineral fraction: the denser is the more opaque.

Importantly, opacity of grafted SmartBone® ORTHO changes with time: it is a real indicator of bone regeneration and a measurable parameter to monitor remodeling!

Other mineral biomaterials, both of natural origin and artificial are very opaque because they are dense. However, it must be pointed out that the counter-effect of this high density is the very low resorption and the poor capability to sustain remodeling: using these materials bone, indeed, heals by simply "growing around" mineral granules. Moreover, standard xenograft treatment foresees the use of high temperature processes that also change the material mineral crystal structure, making them denser, hence more opaque, but also less resorbable [Piattelli, 1999; Sartori, 2003]. Last, but not least, these types of grafts are usually very weak from a mechanical point of view and hence can easily be "compacted" (since they are in small granules which behave as powder-like). The more you compact them, the more opaque they become, the more they become stable and the less they resorb [Carusi, 2016].

As seen before, IBI philosophy underneath SmartBone® ORTHO design is exactly the opposite: a bone graft that is not too dense, not too compact as it must conduct cells within it and support an effective remodeling. SmartBone® ORTHO mineral fraction is designed to be as similar as possible to human bone, particularly to young human bone [Kuhn, 2008], which is less dense and hence less opaque: this allows blood, cells and micro vessels to colonize it, growing on the polymeric film attaching to RGD-fragments from gelatin, progressively degrade the polymeric film, find the mineral matrix and start remodeling it into new healthy bone that can become mature and robust healthy bone in due time.

To obtain this, SmartBone® ORTHO has the adequate open and interconnected porosity, that leads to a not-too-dense material, hence poorly opaque immediately after grafting. Moreover, given the most important claim of complete remodeling, the mineral crystal matrix comes from bovine bones (*i.e.* most similar to human one) but not high temperature treated because it must not be changed into a stable mineral structure that the body cannot remodel! This essential feature means that the material is initially poorly opaque. Microgranules size is important too: the overall performances of granules are ensured exactly thanks to their structure: they are tough and can hence not be compressed too much, again resulting in poor opacity but in a very supportive micro-environment for regeneration!

3.4. CONCLUSION

Osteoinduction is the process by which osteogenesis is induced. It is a phenomenon regularly seen in any type of bone healing process. Osteoinduction implies the recruitment of immature cells and the stimulation of these cells to develop into pre-osteoblasts. Osteoinduction is a part of the so-called remodeling process over a bone graft, *i.e.* the replacement of graft by new bone tissue. This is supported by health bone physiologic processes which occur in the adult skeleton to maintain bone mass.

Overall, all levels of investigations on SmartBone® ORTHO have recorded the occurrence of this sequence of phenomena. Indeed, from a clinical point of view SmartBone® ORTHO integration can be briefly described as follows: the graft very easily soaks up large amounts of blood, thus starting micro coagulation to occur inside the graft itself and hence strongly enhancing graft integration (as far as the local micro coagulation sparkles a chemical cascade that is essential for patient native cells ingrowth into the graft); the first weeks are then needed for cellular colonization of the graft, which is also enhanced by the presence of gelatine (offering RGD-end as site-specific terminals for adhesion via linking with integrins from cells, as widely known from literature back from the '90s [Yamamoto, 1995; Ruoslahti, 1996; Duong, 1998; Rodan, 1998] that offers a viable environment for cells to spread onto; meanwhile, this time lag is also necessary for the degradation of the thin polymeric film, which progressively fades away leaving mineral structure for cells to consolidate and promoting the formation of new living bone (also by means of formation of new vessel); following months are needed for the integration of the graft with the native patient bone, due also to vascularization and new bone formation inside the graft.

Studies have also proven that SmartBone® ORTHO sustains the anatomically selective remodeling: even if SmartBone® ORTHO is an homogeneous dense spongy bone graft, it undergoes progressive remodeling supporting the formation of either cancellous or cortical new bone according to the site specific anatomical selective recruitment.

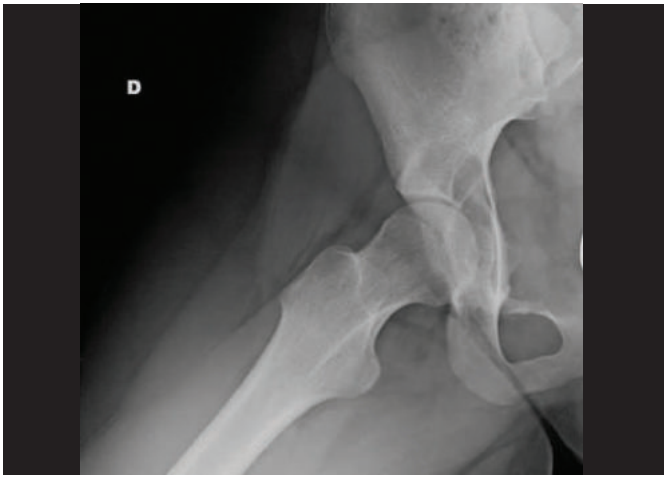

Figure 6. Pre Operation.

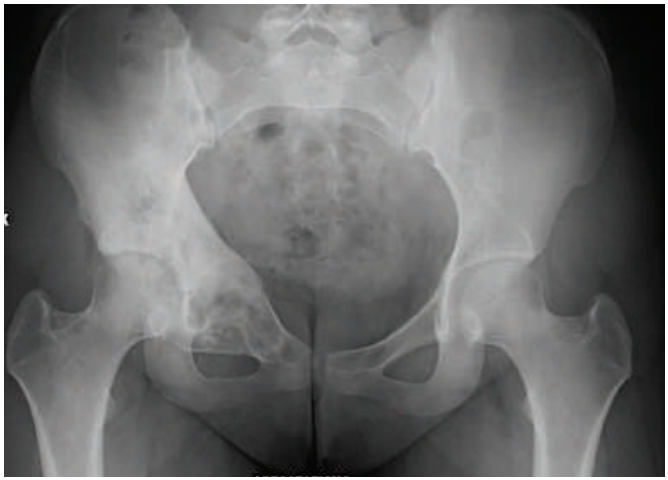

Figure 7. Post Operation.

Both figures adapted from Boffano (2020). See also Case 1 at next page 50.

applied sciences

MDPI

Article

A Radiological Approach to Evaluate Bone Graft Integration in Reconstructive Surgeries

Carlo F. Grottoli [1], Riccardo Ferracini [2,*], Mara Compagno [3], Alessandro Tombolesi [4], Osvaldo Rampado [4], Lucrezia Pilone [1,5], Alessandro Bistolfi [6], Alda Borrè [4], Alberto Cingolani [1] and Giuseppe Perale [1,2,7,*]

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check for updates

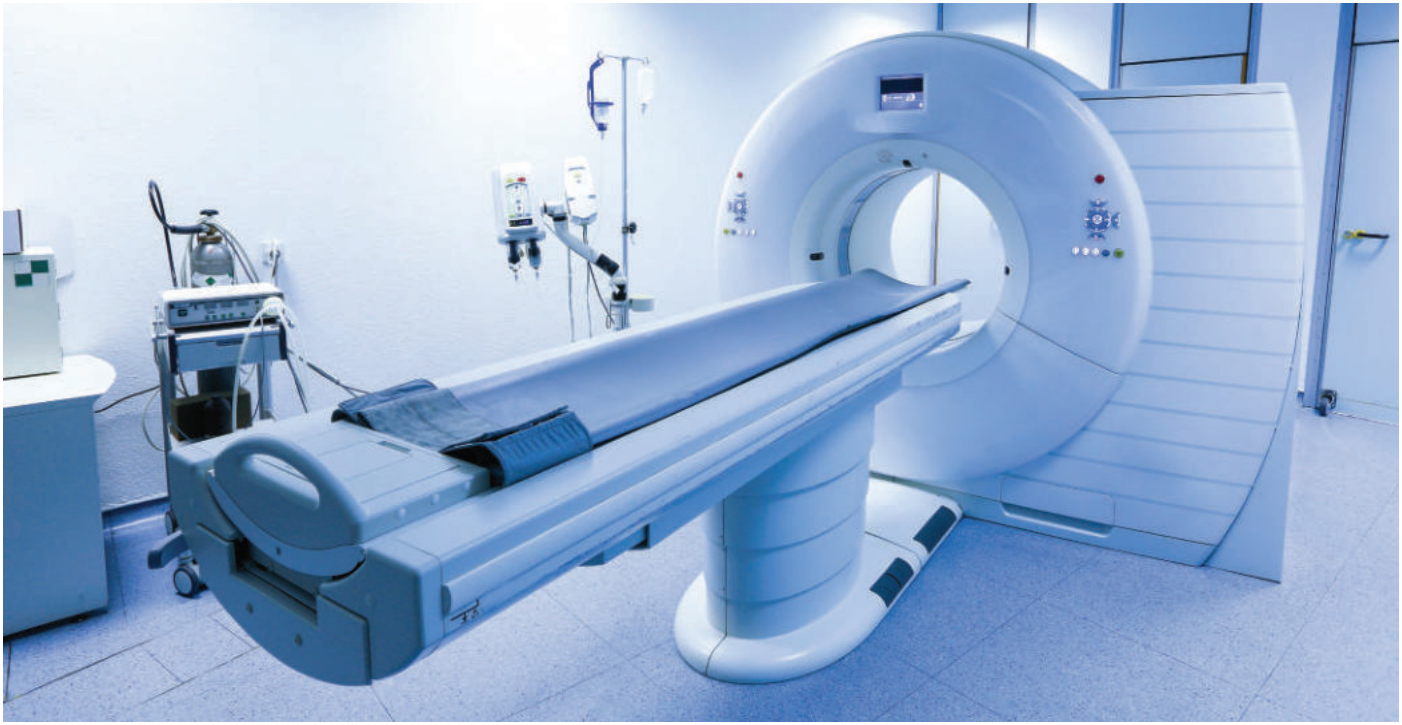
Featured Application: This protocol allows tracking new bone formation after implantation of a xenohybrid bone graft (SmartBone®), without invasive histological samples.

Abstract: (1) Background: Bone tissue engineering is a promising tool to develop new smart solutions for regeneration of complex bone districts, from orthopedic to oral and maxillo-facial fields. In this respect, a crucial characteristic for biomaterials is the ability to fully integrate within the patient body. In this work, we developed a novel radiological approach, in substitution to invasive histology, for evaluating the level of osteointegration and osteogenesis, in both qualitative and quantitative manners. (2) SmartBone ®, a composite xeno-hybrid bone graft, was selected as the base material because ofits remarkable effectiveness in clinical practice. Using pre- and post-surgery computed tomography (CT), we built 3D models that faithfully represented the patient's anatomy, with special attention to the bone defects. (3) Results: This way, it was possible to assess whether the new bone formation respected the natural geometry of the healthy bone. In all cases of the study (four dental, one maxillo-facial, and one orthopedic) we evaluated the presence of new bone formation and volumetric increase. (4) Conclusion: The newly established radiological protocol allowed the tracking of SmartBone ® effective integration and bone regeneration. Moreover, the patient's anatomy was completely restored in the defect area and functionality completely rehabilitated without foreign body reaction or inflammation.

Keywords: bone tissue regeneration; computed tomography; Xenografts

Appl. Sci. 2019, 9, 1469; doi:10.3390/app9071469 www.mdpi.com/journal/applsci

3.5. CT SCAN PROTOCOL



CT suggested protocol in the evaluation of SmartBone® ORTHO's properties.
Please read it carefully before scanning.

GENERAL SCAN REQUIREMENTS:

Take off any non-fixed metal prosthesis, jewellery, zippers or other metal objects that might tamper with the region to be scanned.
Talk about the procedure with the patient. The patient must not move any body part during the scanning sequence.
Position the patient to maximize comfort and minimize motion.

Imaging modality	CT
Scanner type	A common CT machine can be used. Please make sure that images fulfil the minimum requirements stated below.
Patient Centering	Set the table height so that the area to be scanned is centered in the field of view, [0- +5 cm]
Field of View (FOV)	FULL FOV (FOV 40) - Scan all slices with the same FOV, reconstruction center and table height (coordinate system)
ASIR	ASIR 30%
Algorithm	A STANDARD algorithm
	A BONE algorithm
	For scans where metal implants are present: A metal Artefact Reduction Method
kVp	140 kV
mAs	30 mA for small joint
	[30 mA - 300 mA] As given by the automatic system for axial skeleton - modulation current system
Reconstructions	STANDARD - FULL FOV 40 cm - MAR BONE - FULL FOV 40 cm STANDARD - FOV 20 cm BONE - FOV 20 cm STANDARD - FOV 20 CM - MAR

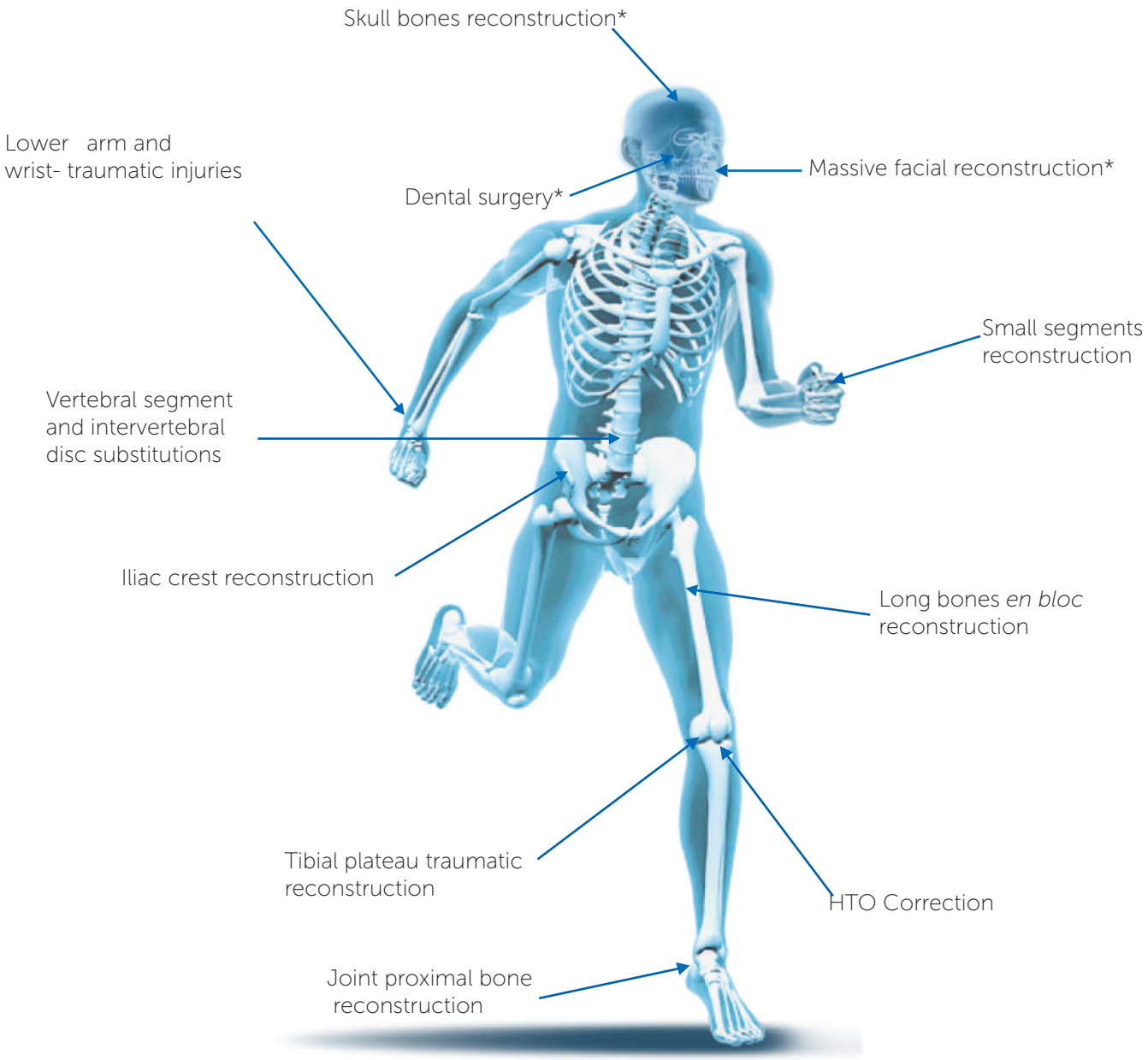
Table 2. Scan data.

Use a scan program in order to discover further information about IBI SA

4

Clinical indications

4.1. WHERE SmartBone® ORTHO CAN BE USED



* Indications out of scope of present document.

SmartBone® ORTHO is a bone substitute, intended to be used for reconstruction surgeries and for bone regeneration/augmentation: it is intended for filling bone defect and for bone augmentation. SmartBone® ORTHO is intended for professional use only. It should be used by trained surgeon, *e.g*. orthopaedic surgeons, neurosurgeons, plastic surgeons, oral and maxillofacial surgeons and trained dentists.

The patient population consist of adults (skeletally mature subjects) with bone defects.

General principles of surgical use must be observed, while using SmartBone® ORTHO. The product is to be used in a sterile environment (surgical theatre). The general principles of sterile handling, using sterile surgical instruments and patient medication must be followed when using SmartBone® ORTHO.

The duration of use SmartBone® ORTHO is of long term: SmartBone® ORTHO integration into the natural bone and, hence, its resorption is driven by its being progressively substituted with healthy living bone from host (remodelling process of resorbable bone graft). The device is a sterile and single use.

In ortophaedic surgery SmartBone® ORTHO is used:

- During arthroplasty and revision arthroplasty to fill or reconstruct the acetabular bone or for replenishment of the femur in impaction allografting;
- After wedge osteotomy;
- After curettage of benign bone tumors and tumor-like lesions for structural scaffolding of curetted lesions or filling;
- For reconstruction after geometric osteotomies for benign aggressive tumor resections;
- For *en bloc* customized bone reconstructions in malignant tumor resection.

4.2. CONTRAINDICATONS

- Do not use SmartBone® ORTHO in case of acute and chronic infections at the site of the implant.
- Do not use SmartBone® ORTHO in patients with known allergies to collagen and its derivatives.

As a matter of experience from clinical practice and similarly to any bone grafting procedures, surgeons should be restrained in using SmartBone® ORTHO in the following cases, due to higher risks for complications and side-effects:

- Uncontrolled metabolic diseases, such as diabetes, thyroid dysfunctions;
- Severe kidney or liver diseases;
- Bone metabolic diseases, osteomalacia;
- On-going treatment with gluco- and mineralcorticoids and with agents affecting calcium metabolism e.g. calcitonin);
- Autoimmune diseases;
- Immunosuppressive therapy;
- Sclerodermia;
- Local radiotherapy;
- High LDL or low HDL cholesterol level;
- Low blood levels of Vitamin D.

4.3. PATIENT POPULATION

Adult male and female patients that have reached skeletal maturity with traumatic trabecular bone loss or with orthopedic reconstructions after tumor surgery. Do not treat patients who have not reached skeletal maturity with SmartBone® ORTHO. Do not treat pregnant or lactating women with SmartBone® ORTHO.

Patient medical history should be properly investigated prior to SmartBone® ORTHO grafting.

Patient should be excluded if they present with a medical condition that would contraindicate orthopaedics surgery or interfere with the wound healing process:

- Uncontrolled diabetes;
- Uncontrolled hypertension;
- Active chemotherapy.

4.4. SHAPES AND SIZES

SmartBone® ORTHO is available in a wide variety of shapes and dimensions, to best and most easily meet surgeons common needs. Shapes are available in different sizes which were specifically designed to allow simpler, easier and faster surgical procedures and, hence, guaranteeing better results and a higher safety for patients!

smartbone® Block ORTHO

ITEM	SIZE	Q.TY
SBO101010	10x10x10 mm	1
SBO101020	10x10x20 mm	1
SBO102020	10x20x20 mm	1
SBO141208	14x12x8 mm	1
SBO141224	14x12x24 mm	1
SBO153020	15x30x20 mm	1
SBO153060	15x30x60 mm	1

smartbone® Wedge ORTHO

ITEM	SIZE	Q.TY
SBO352510	35x25x10 mm	1
SBO402514	40x25x14 mm	1

smartbone® Rod ORTHO

ITEM	SIZE	Q.TY
SBO350403	35x4x3 mm	1

smartbone® Granules ORTHO

ITEM	SIZE	Q.TY
SBOG20405	2-4 mm	5 cc
SBOG20410	2-4 mm	10 cc
SBOG20420	2-4 mm	20 cc
SBOG20430	2-4 mm	30 cc

smartbone® Block
ORTHO

ITEM	SIZE	Q.TY
SBO070707	7x7x7 mm	1
SBO141206	14x12x6 mm	1
SBO141207	14x12x7 mm	1
SBO141209	14x12x9 mm	1
SBO141210	14x12x10 mm	1
SBO141212	14x12x12 mm	1
SBO141216	14x12x16 mm	1
SBO141220	14x12x20 mm	1
SBO153030	15x30x30 mm	1
SBO153040	15x30x40 mm	1
SBO153050	15x30x50 mm	1
SBO161406	16x14x6 mm	1
SBO161407	16x14x7 mm	1
SBO161408	16x14x8 mm	1
SBO161409	16x14x9 mm	1

smartbone® Plate
ORTHO

ITEM	SIZE	Q.TY
SBO041010	4x10x10 mm	1
SBO031010	3x10x10 mm	1
SBO032515	3x25x15 mm	1
SBO201502	20x15x2 mm	1

smartbone® Wedge
ORTHO

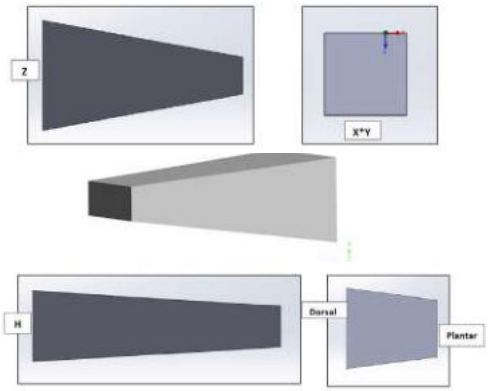
ITEM	SIZE	Q.TY
SBO352205	35x22x5 mm	1
SBO352208	35x22x8 mm	1
SBO352512	35x25x12 mm	1
SBO402512	40x25x12 mm	1

smartbone® Block
ORTHO

ITEM	SIZE	Q.TY
SBO101005	10x10x5 mm	1
SBO152325	15x23x25 mm	1

smartbone® Special Wedge
ORTHO

ITEM	SIZE	Q.TY
SBO181808	18x18x08 mm	1
SBO181810	18x18x10 mm	1
SBO181812	18x18x12 mm	1
SBO222208	22x22x08 mm	1
SBO222210	22x22x10 mm	1
SBO222212	22x22x12 mm	1
SBO161045	16x14x10x4.5 mm	1
SBO161055	16x14x10x5.5 mm	1
SBO161065	16x14x10x6.5 mm	1
SBO201045	20x14x10x4.5 mm	1
SBO201055	20x14x10x5.5 mm	1
SBO201065	20x14x10x6.5 mm	1

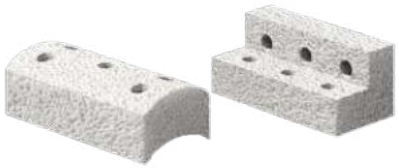


smartbone® Cylinder
ORTHO

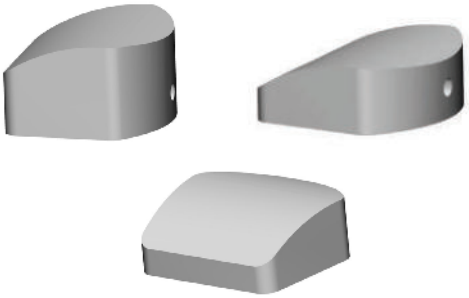
ITEM	SIZE	Q.TY
SBO112000	ø11xh20 mm	1
SBO122000	ø12xh20 mm	1
SBO142000	ø14xh20 mm	1
SBO162000	ø16xh20 mm	1
SBO111000	ø11xh10 mm	1
SBO141400	ø14xh14 mm	1
SBO083000	ø8xh30 mm	1
SBO083500	ø8xh35 mm	1
SBO103000	ø10xh30 mm	1
SBO103500	ø10xh35 mm	1
SBO123000	ø12xh30 mm	1
SBO123500	ø12xh35 mm	1
SBO65400M	ø6.5xh40 mm M	1
SBO65400F	ø6.5xh40 mm F	1

smartbone® Special Shape
ORTHO

ITEM	SIZE	Q.TY
SBO150604	15x6x4 mm	1
SBO150735	15x7x3.5 mm	1
SBO081201	ø8xh12 mm	1
SBO150706	15x7x6 mm	1
SBO157504	15x7.5x4 mm	1
SBO14114C	14x11x4 mm	1
SBO14115C	14x11x5 mm	1
SBO14116C	14x11x6 mm	1
SBO14117C	14x11x7 mm	1
SBO14118C	14x11x8 mm	1
SBO14119C	14x11x9 mm	1
SBO16144C	16x14x4 mm	1
SBO16145C	16x14x5 mm	1
SBO16146C	16x14x6 mm	1
SBO16147C	16x14x7 mm	1
SBO18164C	18x16x4 mm	1
SBO18165C	18x16x5 mm	1
SBO18166C	18x16x6 mm	1
SBO18167C	18x16x7 mm	1
SBO200800	20x8 mm 0°	1
SBO200700	20x7 mm 0°	1
SBO206595	20x6.5x9.5 mm	1
SBO156595	15x6.5x9.5 mm	1
SBO106595	10x6.5x9.5 mm	1
SBO082505	ø8x25 mm 5°	1
SBO083005	ø8x30 mm 5°	1
SBO083505	ø8x35 mm 5°	1
SBO092505	ø9x25 mm 5°	1
SBO093005	ø9x30 mm 5°	1
SBO093505	ø9x35 mm 5°	1
SBO102505	ø10x25 mm 5°	1
SBO103005	ø10x30 mm 5°	1
SBO103505	ø10x35 mm 5°	1



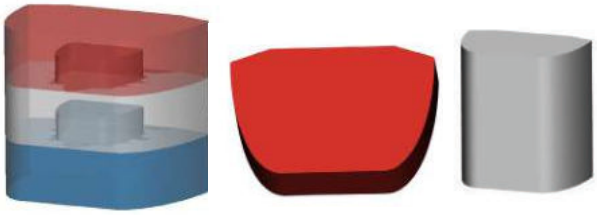
ON REQUEST



smartbone® Special Shape
ORTHO

ITEM	SIZE	Q.TY
SBO605425	60x54 mm 2.5°	1
SBO202727	20x2.7x2.7 mm	1
SBO202222	20x2.2x2.2 mm	1
SCT152310	C Top 15 x 23 x 10	1
SCM152310	C Middle 15 x 23 x 10	1
SCB152310	C Bottom 15 x 23 x 10	1
SLT452310	L Top 45 x 23 x 10	1
SLM452310	L Middle 45 x 23 x 10	1
SLB452310	L Bottom 45 x 23 x 10	1
STT352310	T Top 35 x 23 x 10	1
STM352310	T Middle 35 x 23 x 10	1
STB352310	T Bottom 35 x 23 x 10	1

ON REQUEST



5

Use of smartbone® ORTHO

5.1. ORTHOPAEDIC INDICATIONS

Orthopaedic surgery, among all surgical fields, is the one who took advantage of the most of technological advancements in instruments and materials in the last 50 years. It has been the first medical arena where bone metal substitutes had been introduced to restore loss of functions, starting with hip arthroplasty in the late '50s, and the first one to employ video assisted surgery in the early '80s. From there, everything evolved rapidly in all fields of orthopaedics. Both trauma surgery and elective surgery benefited from the evolution of bone substitute materials in the last decades.

In trauma, and especially in post-traumatic complications, such as bone loss and delayed or non-union, morselized bone filling, bone struts, and other solid components such as blocks of various sizes are invaluable.

In elective orthopaedics surgeries such as osteotomies, the use of bony wedges was implemented; in prosthetic re-implant surgery morselized bone, bone cups or domes are now widely used.

In spinal surgery, the need for bone augments to promote arthrodesis guarantees the rapid stabilization of the metal construct, either in the cases of disk cages or paravertebral synthesis. Bone struts are often required for that purpose.

In the late 70s, mostly due to outstanding advances in oncological treatments, which increased dramatically the life expectancy of the affected patients, orthopaedic oncology came of age. This relatively new field is a surgical challenge for bone reconstruction after wide resections. This type of operations needs large amounts of new bone, often requiring custom made constructs. These special fittings can be easily obtained from 3D pre-operative studies using bone substitutes of new generation.

Often times, the availability of bone substitutes is paramount in all orthopaedic surgical scenarios. The surgeon requires bone substitutes for filling, stabilization and for biological stimulation of bone healing. Bone substitutes must be readily available in the operating room and must respond to biocompatibility and mechanical issues. Ideally, autologous bone is the way to go, but its harvest can be harmful, and the amount can be insufficient. Bone banks of frozen bone from homologous donors' present various problems. The freezing and thawing together with the sterilization process can damage the structure of the bone graft and the use of this material must be planned well in advance, considering that most orthopaedic hospitals do not have a resident tissue bank. The off the shelf bone substitutes can answer most of these needs, provided the quality of the material. The recent diffusion of these substitutes has been documented and quantified. (Coherent Market Insight on "Bone Graft, Substitutes And Membrane Market"; Jan 2019).

Journal of *Functional Biomaterials*

MDPI

Article

Simulated Performance of a Xenohybrid Bone Graft (SmartBone®) in the Treatment of Acetabular Prosthetic Reconstruction

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Abstract: Total hip arthroplasty (THA) is a surgical procedure for the replacement of hip joints with artificial prostheses. Several approaches are currently employed in the treatment of this kind of defect. Overall, the most common method involves using a quite invasive metallic support (a Burch–Schneider ring). Moreover, valid alternatives and less invasive techniques still need to be supported by novel material development. In this work, we evaluated the performance of SmartBone®, a xenohybrid bone graft composed of a bovine bone matrix reinforced with biodegradable polymers and collagen, as an effective support in acetabular prosthesis reconstruction. Specifically, the material's mechanical properties were experimentally determined (E_c = ~1.25 GPa, E_f = ~0.34 GPa, and E_t = ~0.49 GPa) and used for simulation of the hip joint system with a SmartBone® insert. Moreover, a comparison with a similar case treated with a Burch–Schneider ring was also conducted. It was found that it is possible to perform THA revision surgeries without the insertion of an invasive metal support and it can be nicely combined with SmartBone®'s osteointegration characteristics. The material can withstand the loads independently (σ_{max} = ~12 MPa) or be supported by a thinner titanium plate in contact with the bone in the worst cases. This way, improved bone regeneration can be achieved.

Keywords: total hip arthroplasty; bone substitute; computational model; 3D reconstruction

5.2. ONCOLOGICAL CASES

CASE 1 - Aneurysmal bone cysts treated without osteosynthesis devices adapted from (Boffano,2020)

Patient: female, 16 years old, skeletally mature.

Surgical procedure: This *de novo* aneurysmal bone cysts has been carefully removed and the surrounding tissue cleaned and prepared (curettage and borettage), saving the external cortical laminas. The void space has been filled with SmartBone® ORTHO blocks, tightly positioned in place along major bone stress lines.

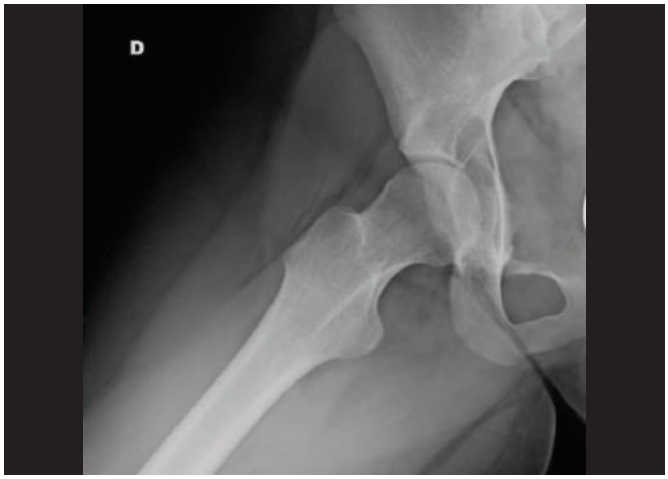

Figure 8. Pre Operation: Pre-op situation with ABC in posterior acetabular and iliac right region.

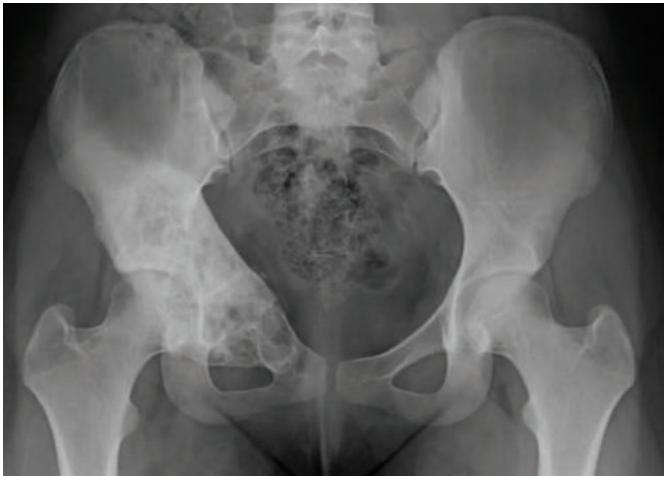

Figure 9. Follow-up 1 Year: Evidence of a good bone regeneration.

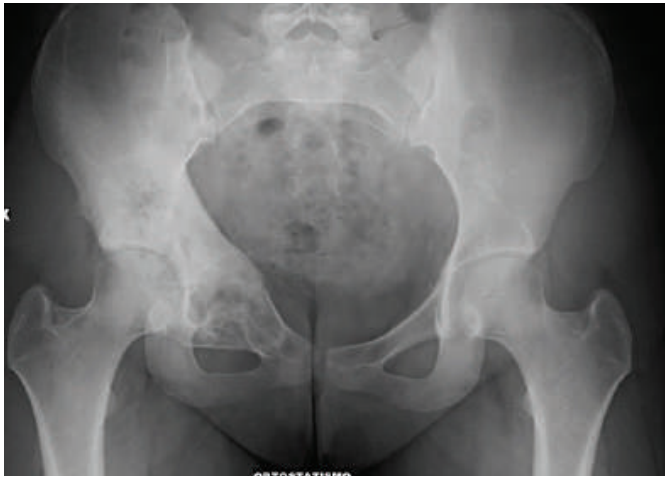

Figure 10. Follow-up 2 Years: Good regeneration and high quality bone.

CASE 2 - Aneurismal bone cist – NO fixation devices – loading after 30 days adapted from (Boffano,2020)

Patient: male, 53 years old.
Surgical procedure: The bone cist has been carefully removed and the surrounding tissue cleaned and prepared (curettage and borettage), saving the external cortical laminas. The void space has been filled with SmartBone® ORTHO blocks, tightly positioned in place along major bone stress lines.

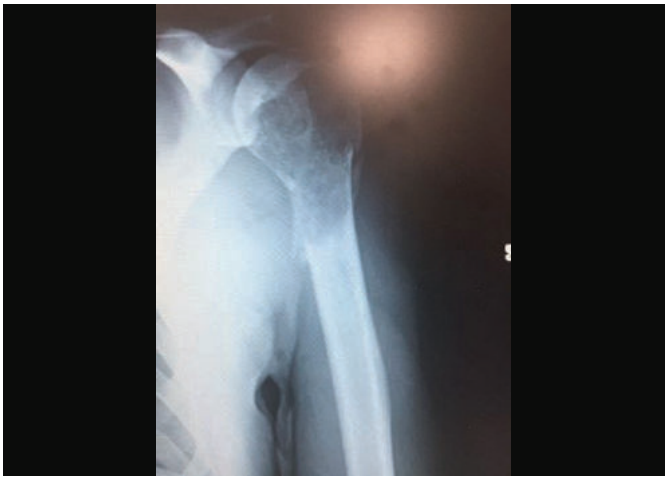

Figure 11. Initial condition.

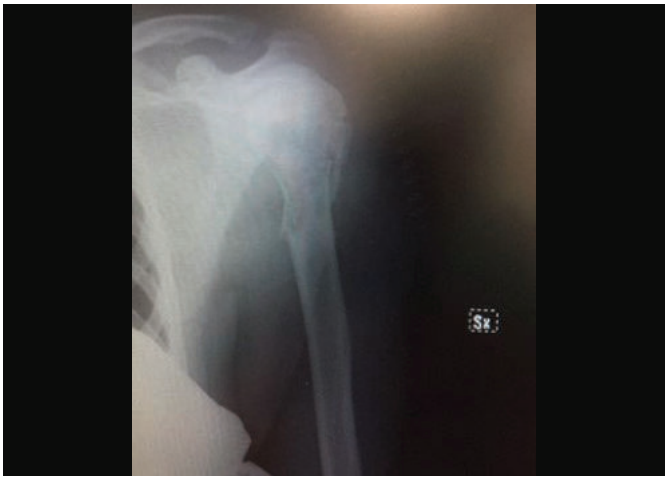

Figure 12. Follow-up 4 Months.

This mild level oncologic case allowed the surgeon to take the best advances from the use of SmartBone® ORTHO thanks to its high biomechanical and biological performances.
The bone cist has been carefully removed and the surrounding tissue cleaned and prepared (curettage and borettage), saving the external cortical laminas. The void space has been filled with SmartBone® ORTHO blocks, tightly positioned in place along major bone stress lines.
High mechanical performances of SmartBone® ORTHO allowed the avoidance of metal fixation devices. This, together with its high biological properties, allowed a fast recovery and a mobilization already after 30 days post-surgery. Robust bone remodeling has been observed in the following months, with a bone callus well evident at the 4 months control.

CASE 3 - Chondrosarcoma left proximal femur adapted from (Boffano,2020)

Patient: female, 42 years old.

Surgical procedure: A window made with the intact cortical lamina, opened as a flap, was used to access tumor, where a deep lesion curettage was performed. The accurately cleaned cavity was then filled with SmartBone® ORTHO blocks, tightly positioned in place along major bone stress lines and finally the cortical lamina was closed back in position.

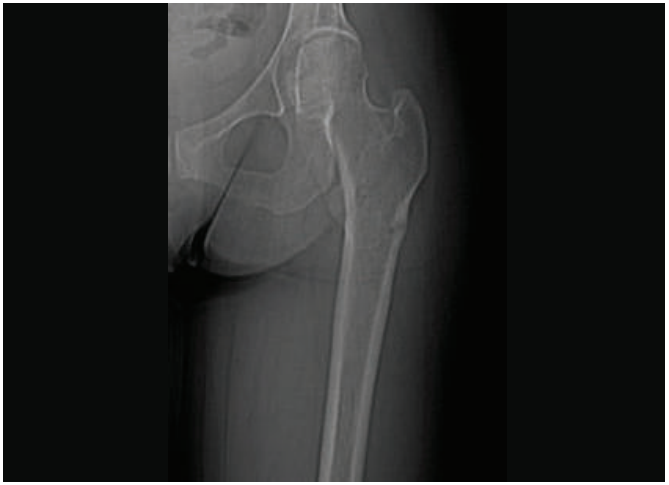

Figure 13. Pre operation: Evidence of metaphyseal mass with erosion of the cortical bone.

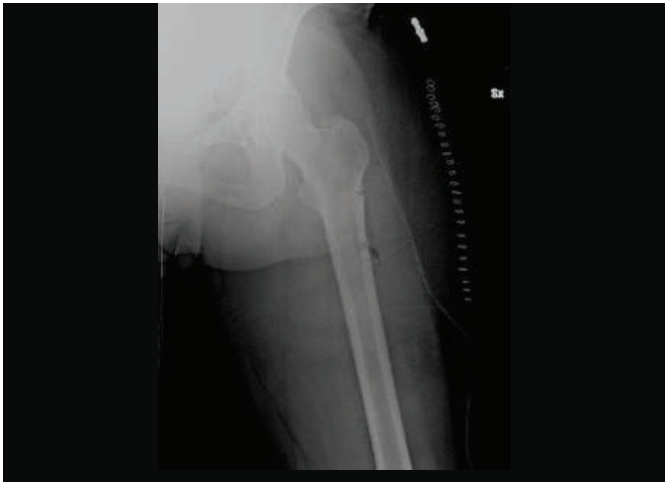

Figure 14. Post operation: Cortical bone window curettage, lesion filling with SmartBone® ORTHO Blocks, No fixation device, immediate load bering.

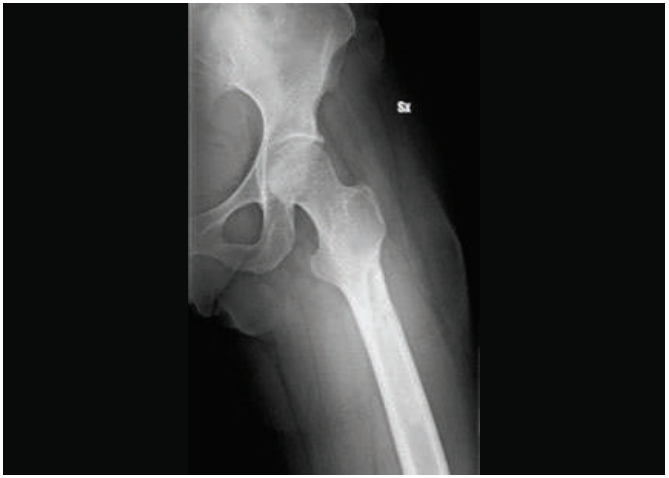

Figure 15. Follow-up 2 Months.

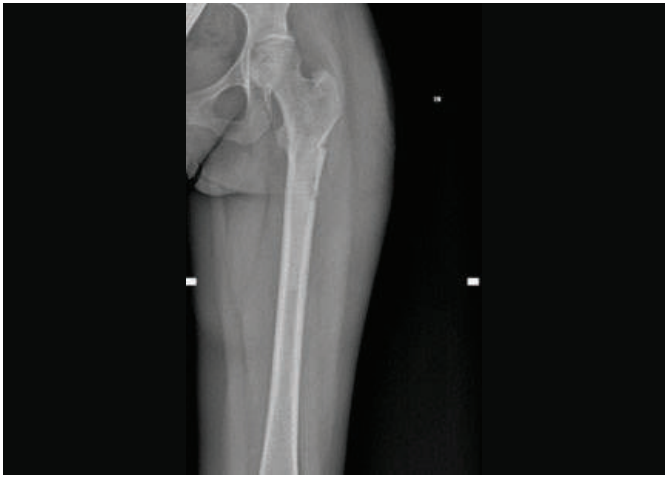

Figure 16. Follow-up 3 Months.

Complete recovery, full load bearing high stability, increasing bone density, good mineralization, new bone formation, comparable to contralateral.

Journal of Clinical Medicine

MDPI

Article

A Preliminary Study on the Mechanical Reliability and Regeneration Capability of Artificial Bone Grafts in Oncologic Cases, With and Without Osteosynthesis

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Abstract: Several bone grafts are available for clinical use, each with their own peculiar biological and mechanical properties. A new bone graft was obtained by combining mineral structures from natural bovine bones with bioresorbable polymers and cellular nutrients. The study aims to evaluate the clinical, biological and structural properties of this bone graft and its reliability in orthopedic oncology. 23 adult patients (age range 18–85 years) were treated between October 2016 and December 2018; the oncologicdiagnoses were heterogeneous. After surgical curettage and bone grafting, a clinical-radiological follow up was conducted. Radiographs were used to evaluate graft integration according to the usual bone healing and oncologic follow up. Local complications (infection, local recurrence, wound dehiscence, fracture or early reabsorption) were evaluated. The mean followup was of 18.34 ± 4.83 months. No fracture or infection occurred. One case of patellar Giant Cell Tumor (GCT) and one of proximal tibia low-grade chondrosarcoma recurred after about one year. Two wound dehiscences occurred (one required a local flap). Follow-up X-rays showed good to excellent graft integration in most patients (20 out of 21). The investigated graft has a mechanical and structural function that can allow early weight-bearing and avoid a preventive bone fixation (only needed in four patients in this series). The graft blocks are different for shapes and dimensions, but they can be customized by the producer or sawcut by the surgeon in the operating theatre to fit the residual bone cavity. The complication rate was low, and a rapid integration was observed with no inflammatory reaction in the surrounding tissues. Further studies are mandatory to confirm these promising results.

Keywords: bone grafting; bone regeneration; bone tumor; osteointegration

CASE 4 - Removal of a calcaneous cist

Patient: male, 50 years old.

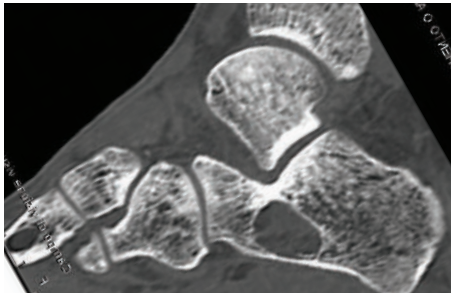


Figure 17. CT Scan of the initial situation.

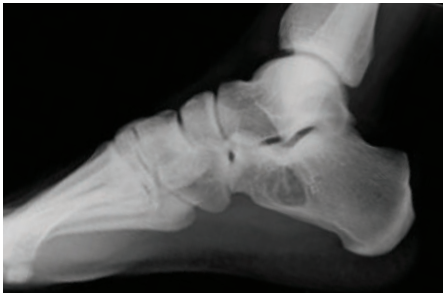


Figure 18. Follow-up 0 Months: post operative X-Ray.

FOLLOW-UP FROM 5 TO 6 MONTHS

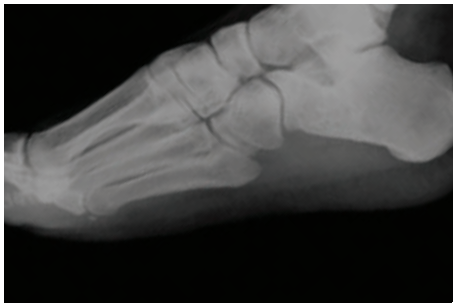


Figure 19. Follow-up 5 Months: good bone regeneration.

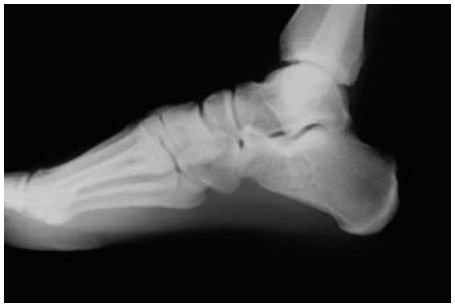


Figure 20. Follow-up 5 1/2 Months: good bone regeneration.

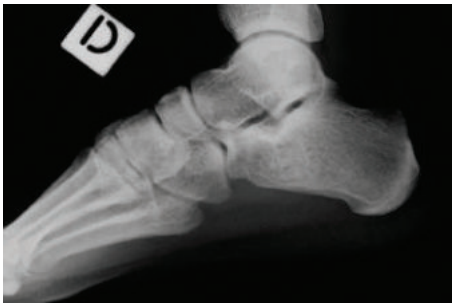


Figure 21. Follow-up 6 Months: excellenct good bone remodelling.

CASE 5 - Comminuted olecranon and capitulum humeri fracture reduced with internal fixation

Patient: male, 32 years old.
Surgical procedure: Positioning of two omeral and two ulnar fiches, bone gap filling with SmartBone® ORTHO block adapted to shape and finally fixed with 3 K-wires.

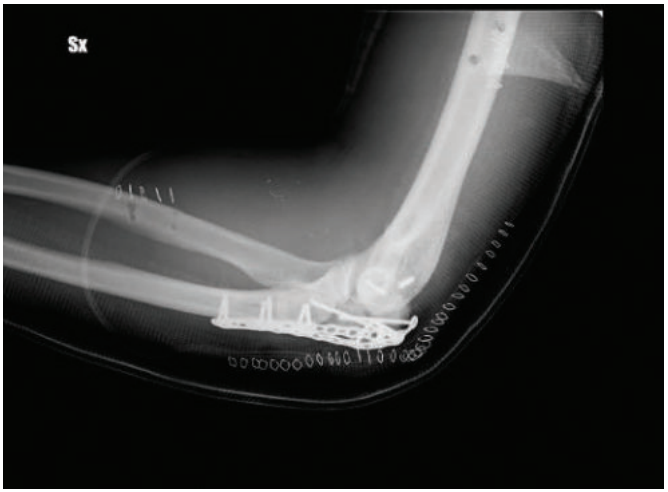


Figure 22. Post surgical control with fixation device in place (plates, screws, figure of 8 cercalge wire with pints.

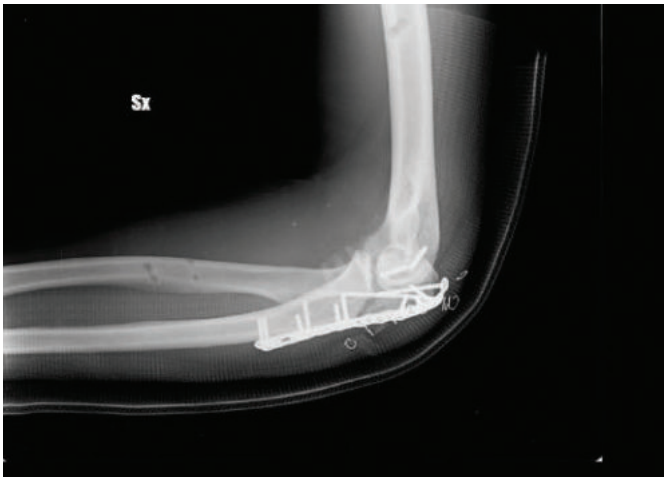


Figure 23. Follow-up 1 Month: The osteosinthesis is stable and patient begins physioterapy.

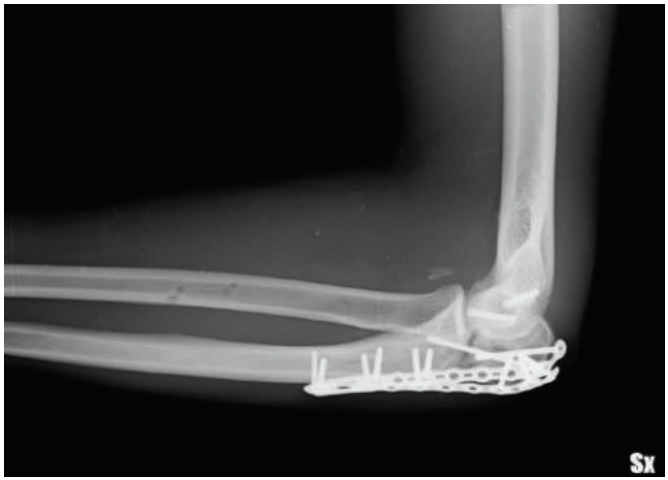


Figure 24. Follow-up 2 Months: Regular evolution of the fracture site with evidence of a good bone regeneration.

CASE 6 - A displaced comminuted fracture of the distal diaphysis region of the fibula and a displaced comminuted joint fracture of the distal diaphise-epiphyseal region of the tibia

Patient: female, 60 years old.

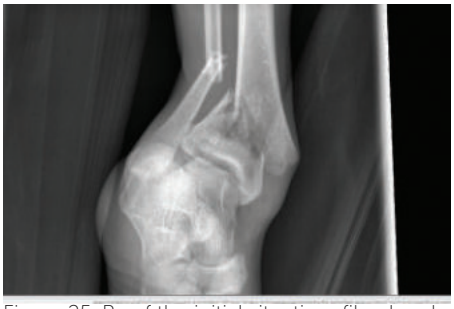


Figure 25. Rx of the initial situation: fibual and tibial fractures.

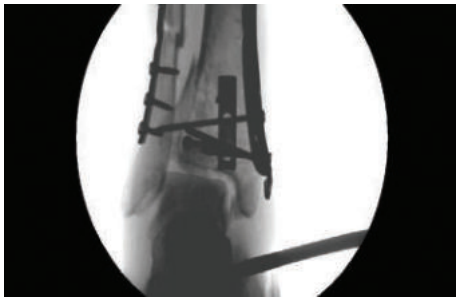


Figure 26. Follow-up 1 1/2 Months: Follow-up post operative with hardware and external fixation

FOLLOW-UP FROM 2 1/2 to 5 MONTHS

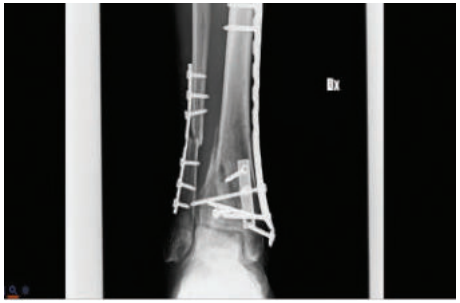


Figure 27. Follow-up 2 1/2 Months: The fixation was removed and presents calcific bone callus signs.

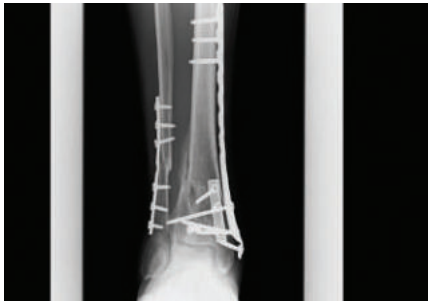


Figure 28. Follow-up 3 1/2 Months: Callus on the lateral tibial side on peripheral side is observed.

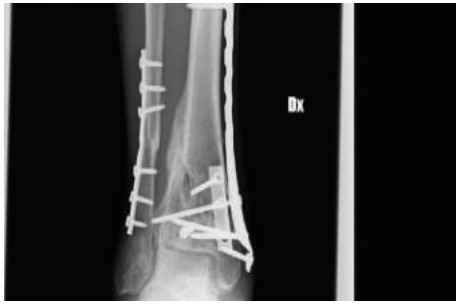


Figure 29. Follow-up 5 Months: Increase of the calcified bone callus at the level of the fracture sites.

CASE 7 - Left ankle displaced multifragmentary fracture of the distal third of the tibia and fibula

Patient: female, 60 years old.

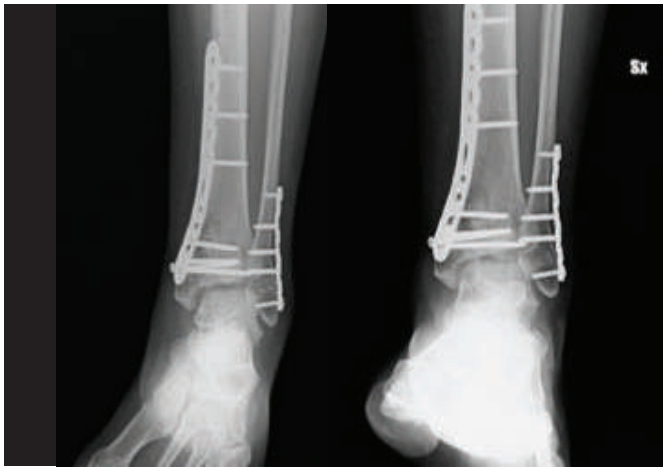


Figure 30. Follow 2 Months: Good positioning of the fixation devices; and good fracture reduction, good pain control.

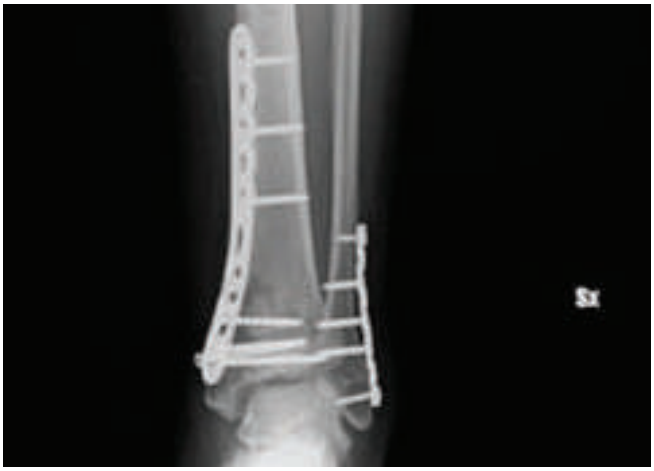


Figure 31. Follow 3 Months: Good clinical course.

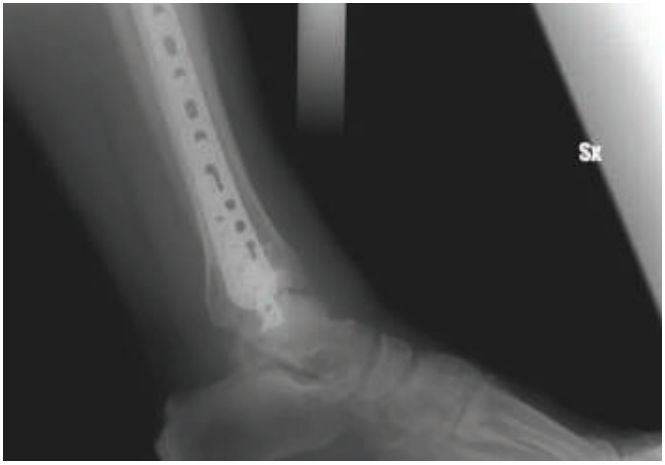


Figure 32. Follow 6 Months: Improvement of the clinical condition and good range of motion.

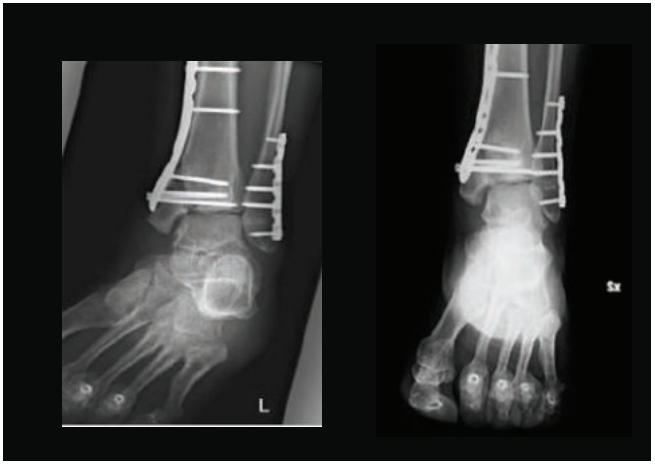


Figure 33. Follow 6 Months: Good fracture consolidation.

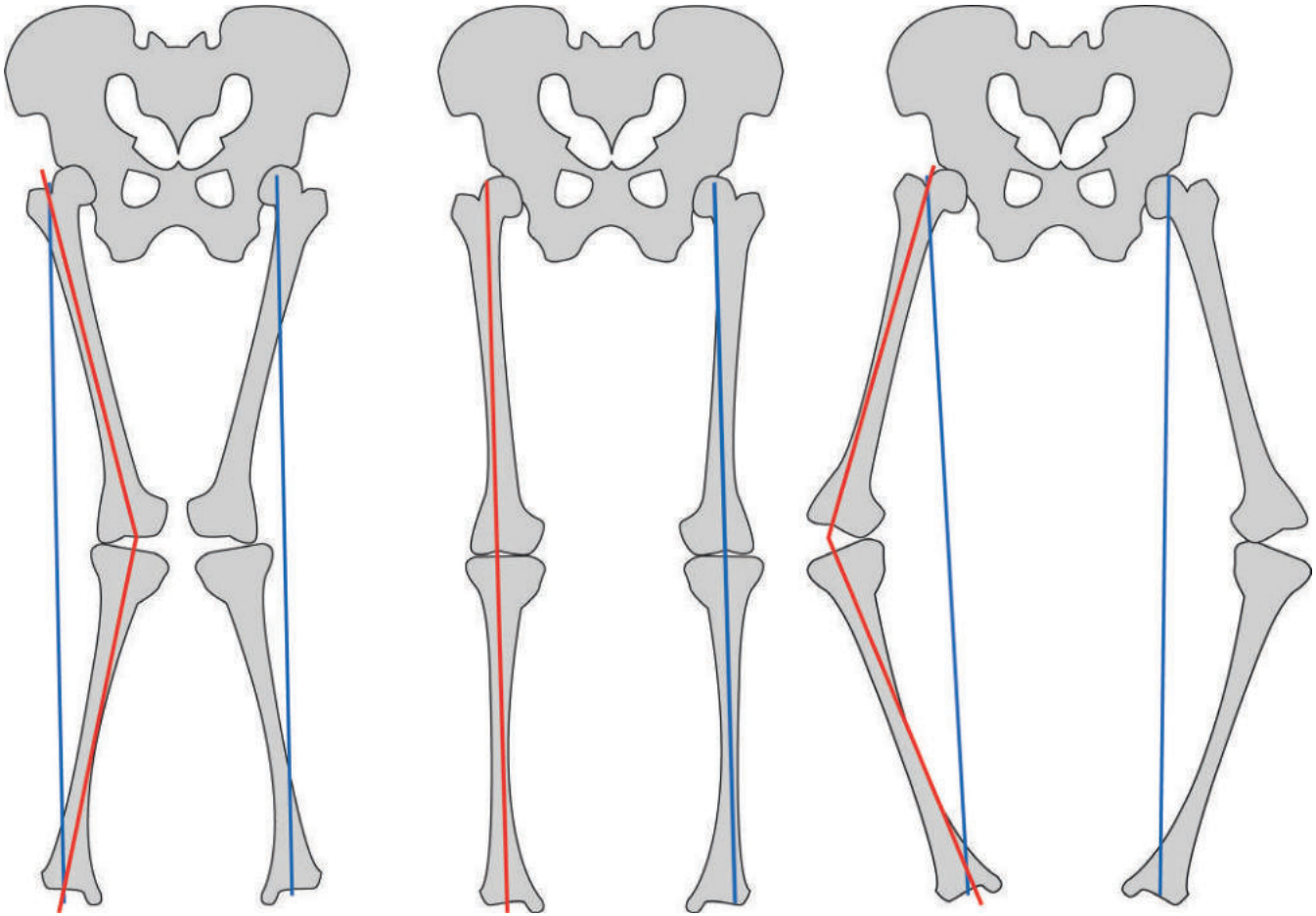
5.3. OSTEOTOMY

An orthopedic osteotomy is a surgical operation whereby a bone is cut to shorten or lengthen it in order to restore the physiological alignment. In orthopedic surgery 3 different anatomic sites can be involved in the osteotomies:

- Osteotomy of the hip
  Two main types of osteotomies are used in the correction of hip dysplasias and deformities to improve alignment/ interaction of acetabulum – (socket) – and femoral head (femur head). Those are known as femur osteotomies. The bones are cut, reshaped or partially removed to realign the load-bearing surfaces of the joint.

- Osteotomy of the knee
  The procedure of knee osteotomy involves removing or adding a wedge of bone to your shinbone (tibia) or thighbone (femur) to help shift your body weight off the damaged portion of your knee joint. During a high tibial osteotomy, surgeons remove a wedge of bone from the outside of the knee, which causes the leg to bend slightly inward. This resembles the realigning of a bowlegged knee to a knock-kneed position. The patient's weight is transferred to the outside (lateral) portion of the knee, where the cartilage is still healthy.

- Osteotomy of the ankle
  Supramalleolar osteotomy is an alternative surgical procedure for the management of asymmetric early arthritis of the ankle.


VALGUS
NORMAL
VARUS

5.3.1 CLINICAL CASES

CASE 8 - Corrective proximal tibial osteotomy in a varus knee

Patient: male, 40 years old.

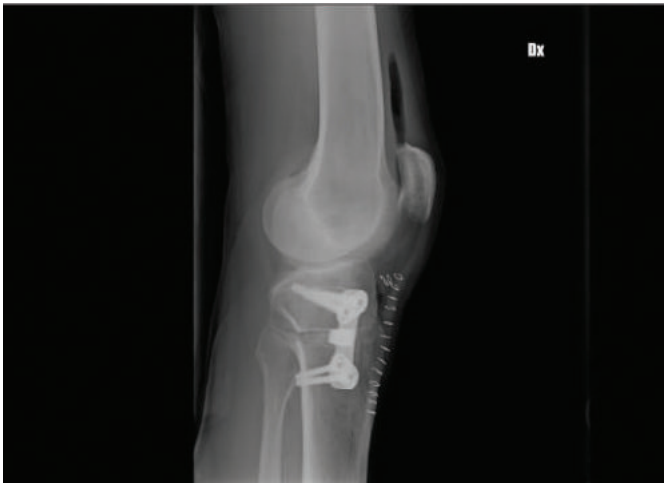


Figure 34. Post surgery: Post operative X-Ray tibial osteotomy.

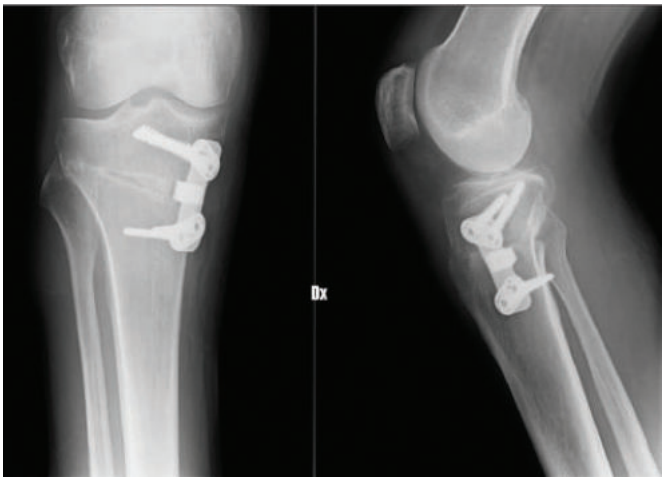


Figure 35. Follow-up 1 Month: The osteotomy site appears stable.

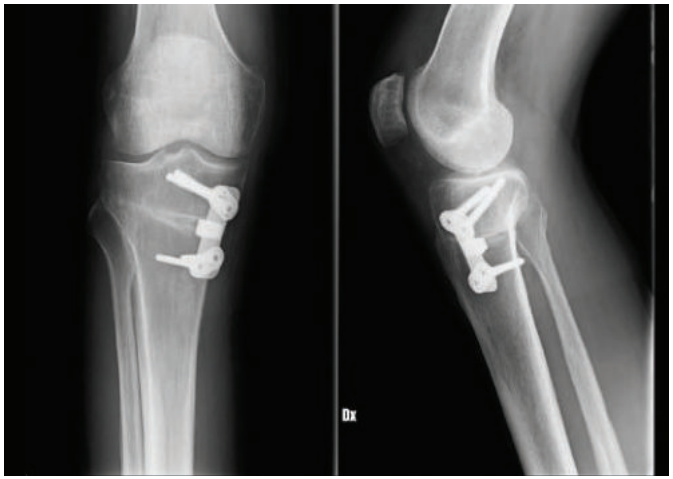


Figure 36. Follow-up 4 Months: Good bone regeneration.

CASE 9 - Valgus proximal tibial osteotomy using Puddu plate in left knee

Patient: male, 62 years old.

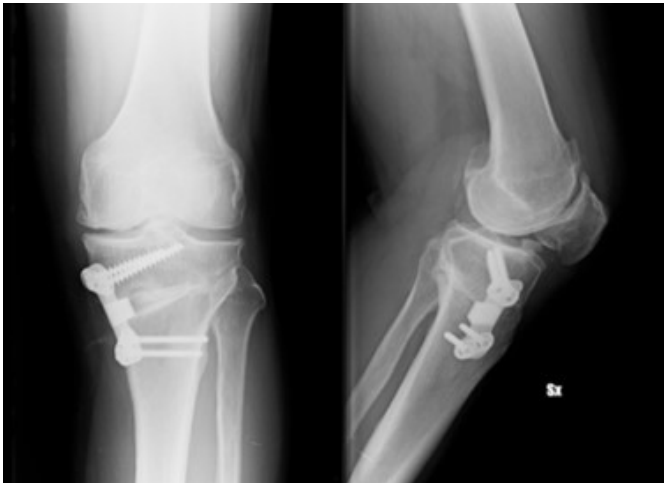


Figure 37. Follow-up 6 Months: Good stability of the fixation device and regular clinical course.

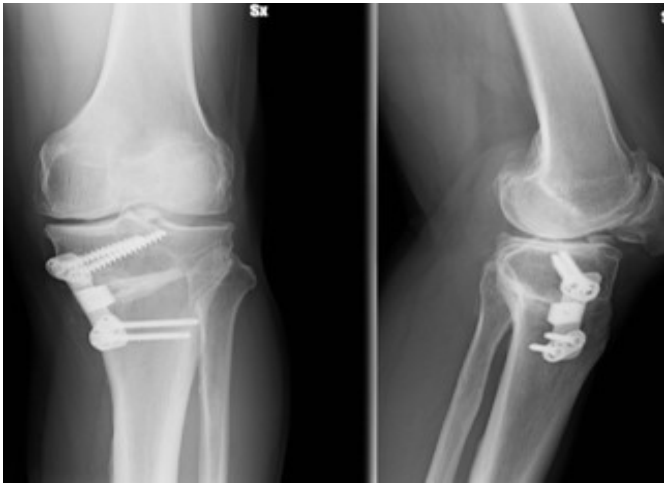


Figure 38. Follow-up 1 Year: Good stability of the fixation device and regular clinical course.

5.4. TIBIAL PLATEAU FRACTURES

Tibial plateau fractures represent a common orthopaedic care problem accounting for 1–2% of all human fractures and are particularly frequent in patients over 50 years old, most commonly due to high-energy traumas. The most common mechanism of injury involves axial loading. In younger patients, the most common pattern of fracture is splitting, while older, more osteoporotic patients, depression fractures typically are sustained.

Several surgical and non-surgical approaches for the management of tibial plateau fractures have been described, but open reduction and plating still remain the treatment of choice in most centres. In some cases, due to comminuted fractures or excessive bone substance loss, it may be necessary to integrate surgery with bone grafting [Ferracini et all.,2019].

Fractures of the lateral plateau are much more common than the medial plateau. To injure the medial plateau, a large amount of force is required; fractures of the medial plateau are usually seen in conjunction with fractures of the lateral plateau and other bones around the knee joint.

Tibial plateau fractures are complex injuries that require adequate imaging procedures in order to proceed with the fixation. Plain radiography often underestimates the severity of the injury. CT accurately defines the extent of the bony injury and facilitates orthopedic intervention instead MRI is very helpful in the assessment of soft tissue injury around the joint.

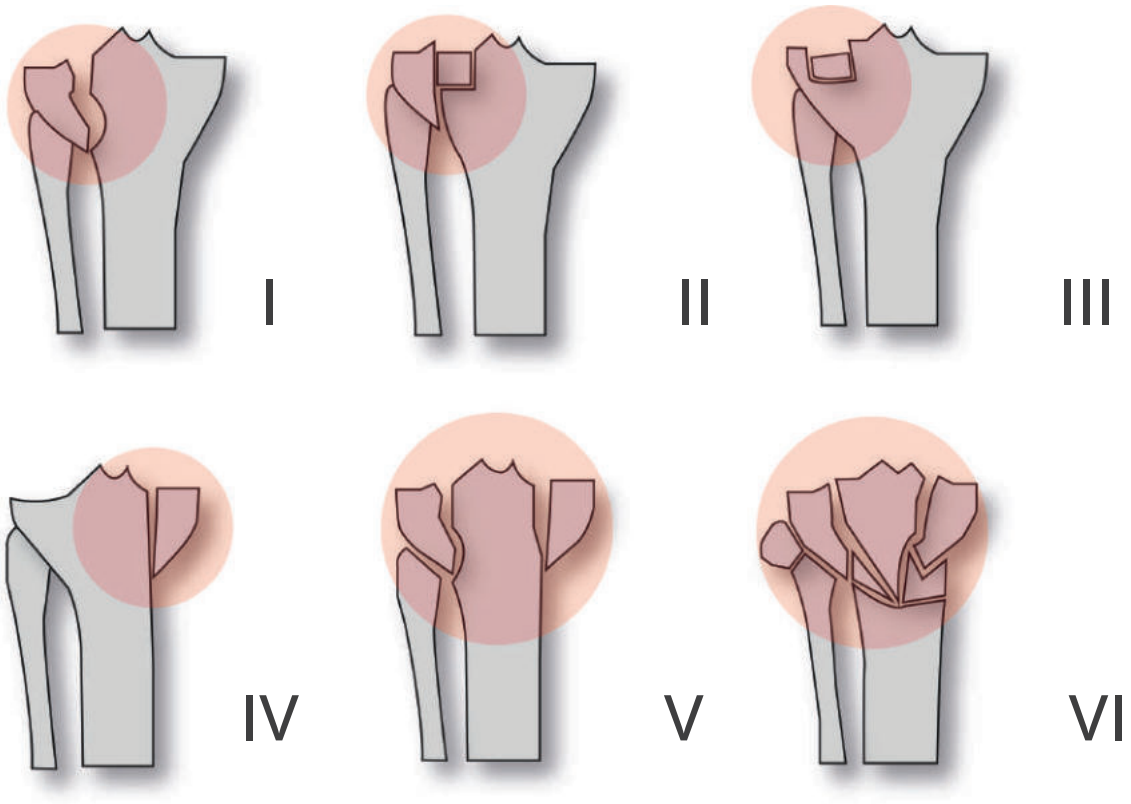
The Schatzker classification is used in tibial plateau fractures to determinate the lesions degree and it was first published by Joseph Schatzker et al. in 1979. Increase in type number denotes increasing severity, reflecting an increase in energy imparted to the bone at the time of injury and also an increasingly worse prognosis. The most common fracture of the tibial plateau is type II.

SCHATZKER CLASSIFICATION

Schatzker classification system is one method of classifying tibial plateau fractures here below reported.
This system divides tibial plateau fractures into six types:

- **Schatzker I**: wedge-shaped pure cleavage fracture of the lateral tibial plateau, originally defined as having less than 4 mm of depression or displacement
- **Schatzker II**: splitting and depression of the lateral tibial plateau; namely, type I fracture with a depressed component
- **Schatzker III**: pure depression of the lateral tibial plateau; divided into two subtypes:
  - **Schatzker IIIa**: with lateral depression
  - **Schatzker IIIb**: with central depression
- **Schatzker IV**: medial tibial plateau fracture with a split or depressed component
- **Schatzker V**: wedge fracture of both lateral and medial tibial plateau
- **Schatzker VI**: transverse tibial metadiaphyseal fracture, along with any type of tibial plateau fracture (metaphyseal-diaphyseal discontinuity)

Schatzker classification system:



5.4.1 CLINICAL CASES

CASE 10 - A displaced multifragmentary tibial plateau fracture (Schatzker VI)

Patient: female, 74 years old.
Surgical procedure: medial tibial plateau fixation using screws for cancellous bone and plates (1/3 LCP and T LCP, SmartBone® ORTHO is inserted in the defect area.

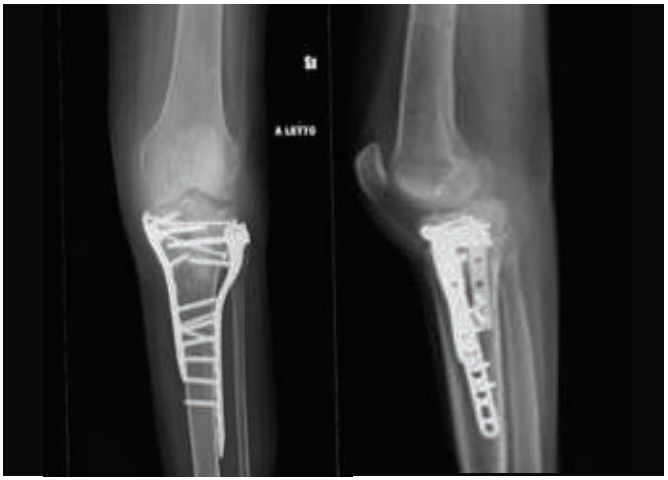


Figure 39. Follow-up 1 Month: Multifragmentary fracture check up, reduction of bone density but no signs of inflammation nor sepsis.

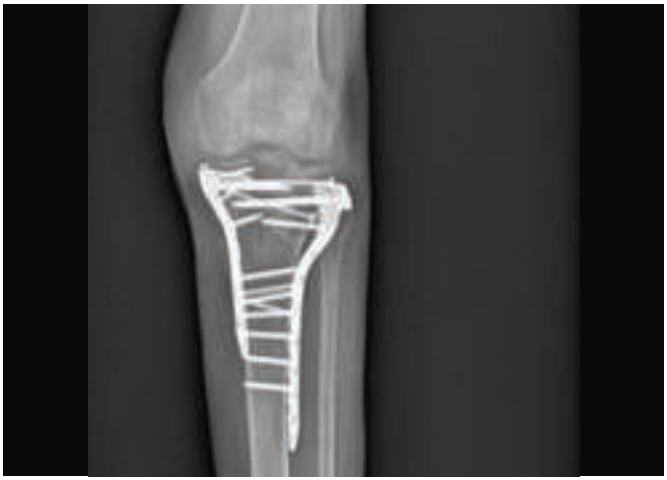


Figure 40. Follow-up 2 Months: Reduction of bone density but no significative issues.

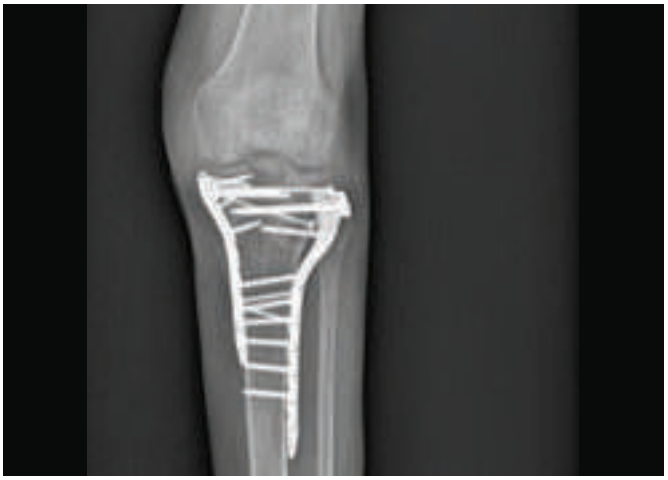


Figure 41. Follow-up 3 Months: Good healing and without further complications.

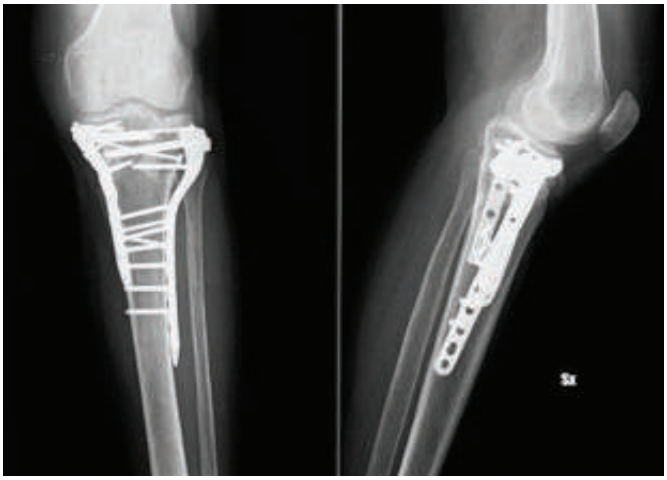


Figure 42. Follow-up 1 Year: Good stability and integration of the grafted material and fixation devices.

CASE 11 - External left (Schatzker II) tibial plateau fracture

Patient: male, 65 years old.
Surgical procedure: reduction of the fracture under fluoroscopic imaging, the defect is filled with SmartBone® ORTHO.

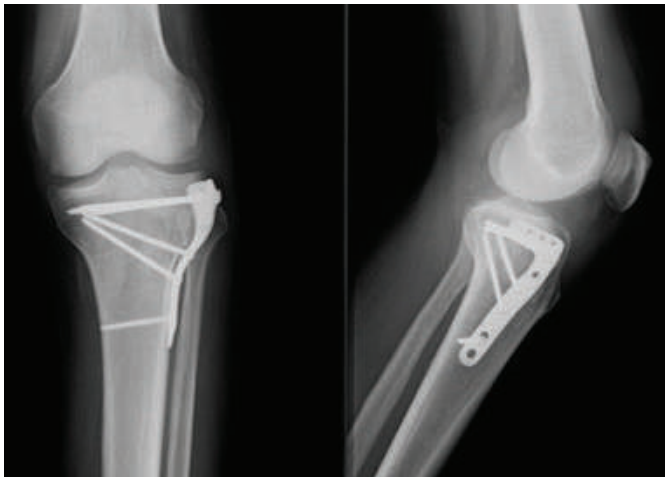


Figure 43. Follow-up 1 Month: Evidence of good stability and bone density.

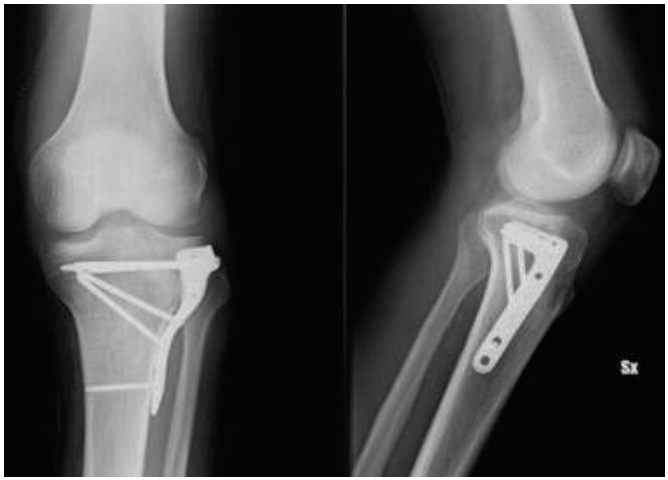


Figure 44. Follow-up 2 Months: Good clinical outcome.

CASE 12 - Lateral left tibial plateau fracture (Schatzker III)

Patient: male, 69 years old.
Surgical procedure: arthroscopic fracture reduction of the tibial plateau 3 Asnis screws, defect stabilized with SmartBone® ORTHO.

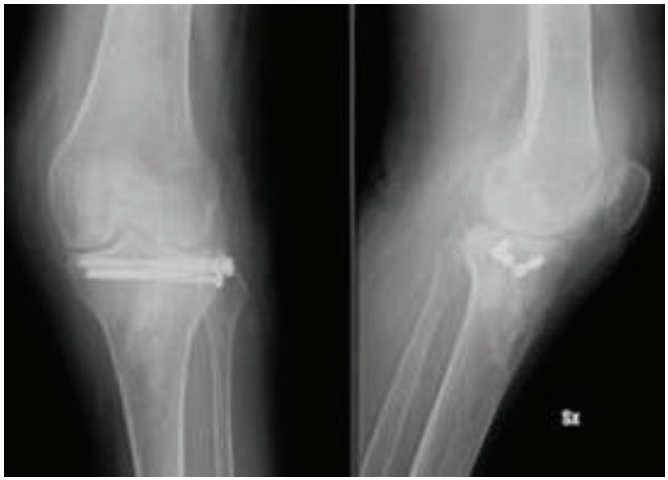


Figure 45. Follow-up 1 Month: Good healing and stabilization.

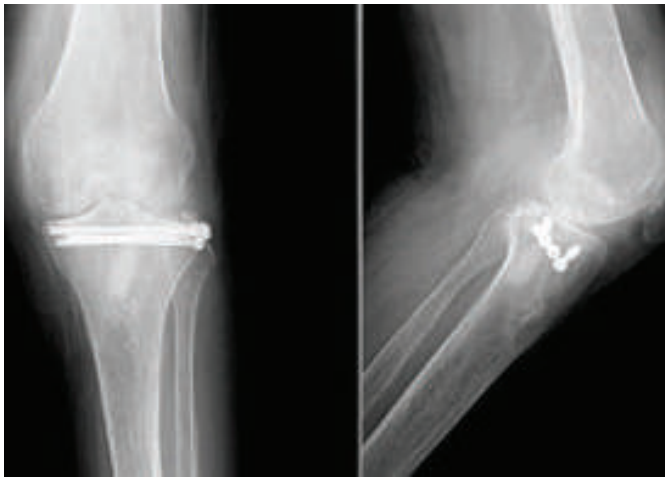


Figure 46. Follow-up 2 Months: Improving of the clinical course, slightly knee tumefaction, no signs of phrogosis, no particular issues observed.

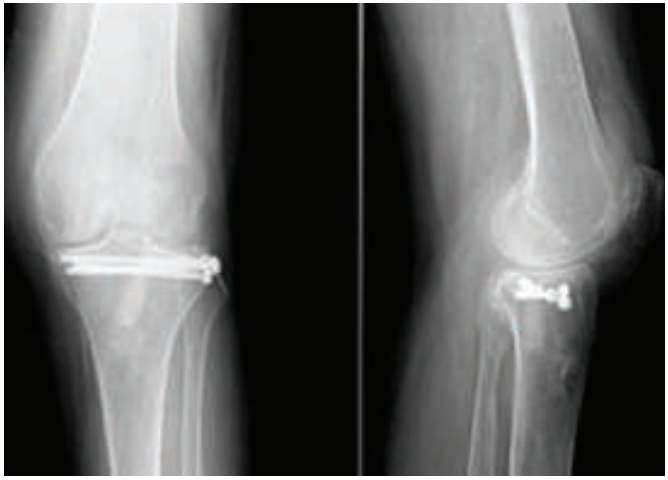


Figure 47. Follow-up 3 Months: No pain, good healing process of the tibial plateau, muscular reinforcement and good articular recovery.

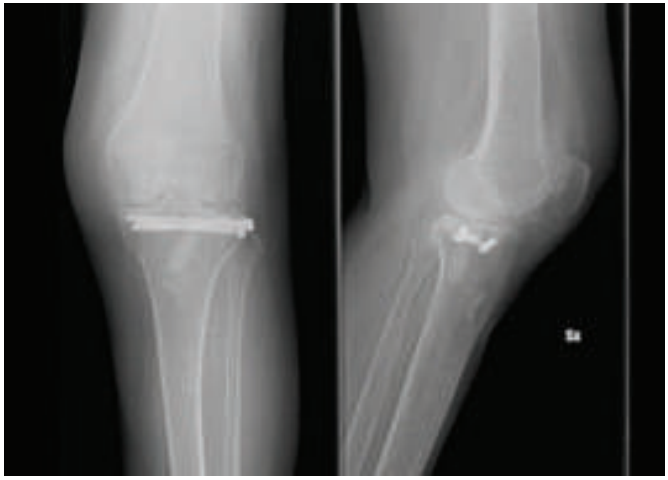


Figure 48. Follow-up 5 Months: Unrestricted load and painless walking.

CASE 13 - Multifragmentary lateral tibial plateau fracture and medial tibial plateau fracture of the right knee (Schatzker II-VI)

Patient: male, 32 years old.
Surgical procedure: fractures reduction with LCP and screws and defect filled with SmartBone® ORTHO.

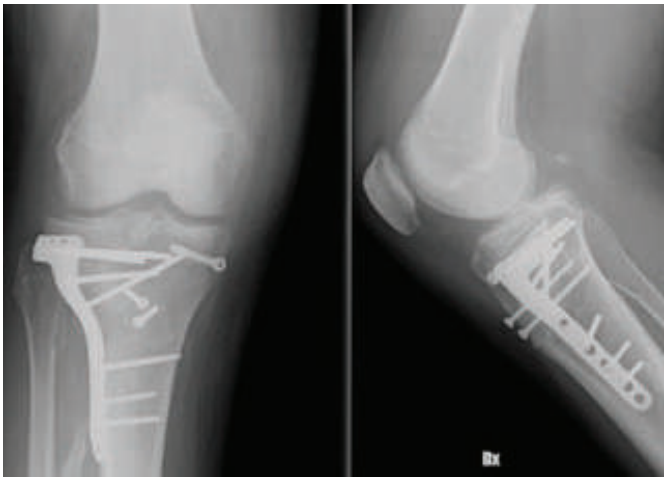


Figure 49. Follow-up 2 Months: Good clinical course and stability.

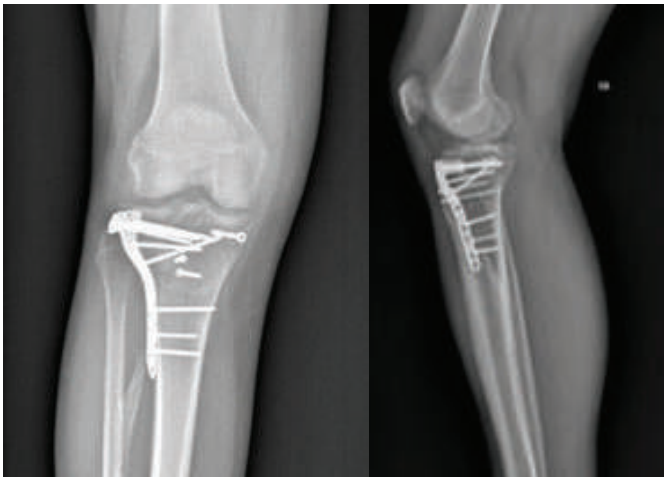


Figure 50. Follow-up 3 Months: Good bone consolidation.

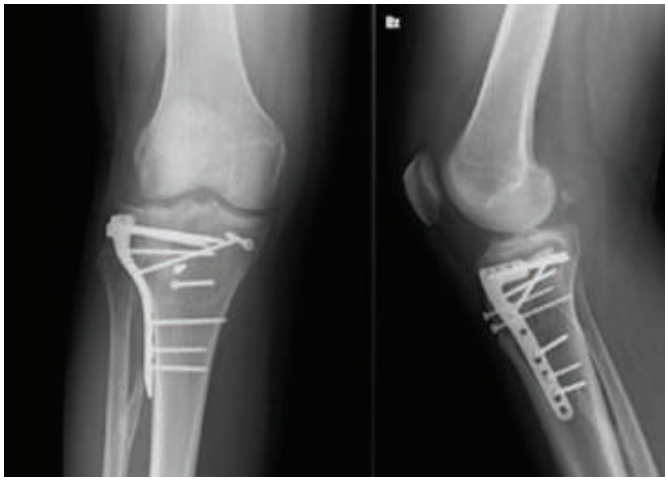


Figure 51. Follow-up 5 Months: No deficit in knee range of motion, good osteointegration, no inflmmation or other issues observed.

CASE 14 - Multifragmentary right tibial plateau fracture (Schatzker VI)

Patient: male, 51 years old.
Surgical procedure: sinthesis reduction using T plate and L plate as fixation devices, SmartBone® ORTHO was inserted in the defect.

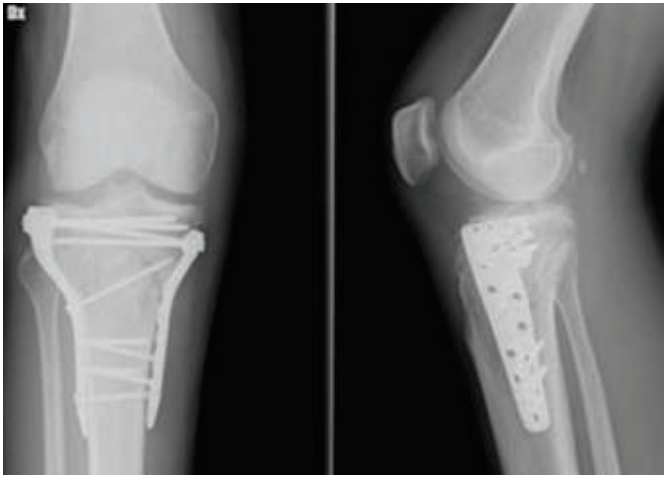


Figure 52. Follow-up 1 Month: Good stabilization of the fractured site, no pain and good clinical outcome.

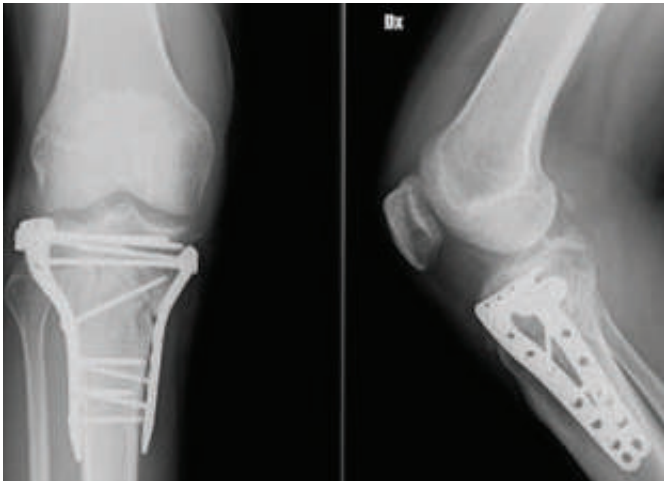


Figure 53. Follow-up 3 Months: Free range of motion, no pain and good healing process.

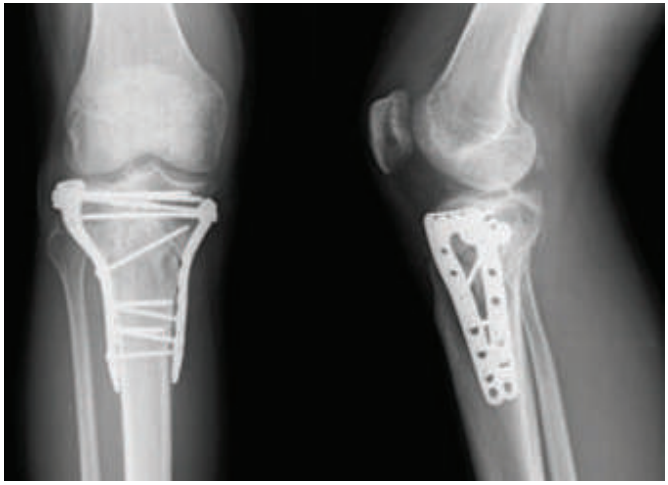


Figure 54. Follow-up 4 Months:Good consolidation and good fracture reduction, and painless unrestricted walking.

CASE 15 - Multifragmentary proximal left metaphyseal tibial plateau fracture (Schatzker VI).

Patient: male, 52 years old.
Surgical procedure: reduction using internal fixation with LCP plate and screws and SmartBone® ORTHO Wedge and Granules applied in defect area.

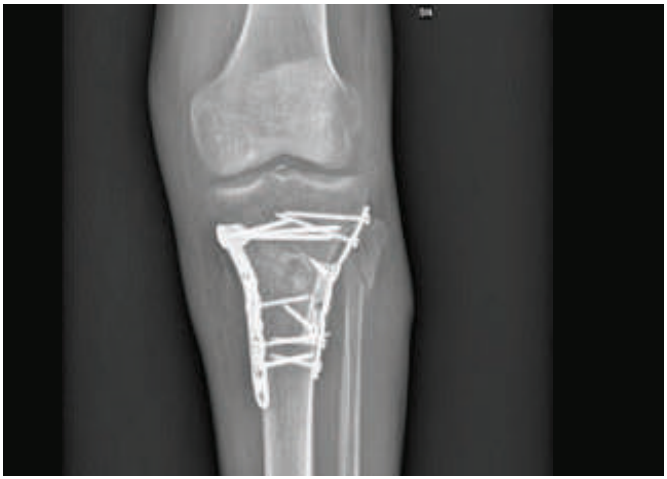


Figure 55. Follow-up 1 Month: Presence of pain (3-4).

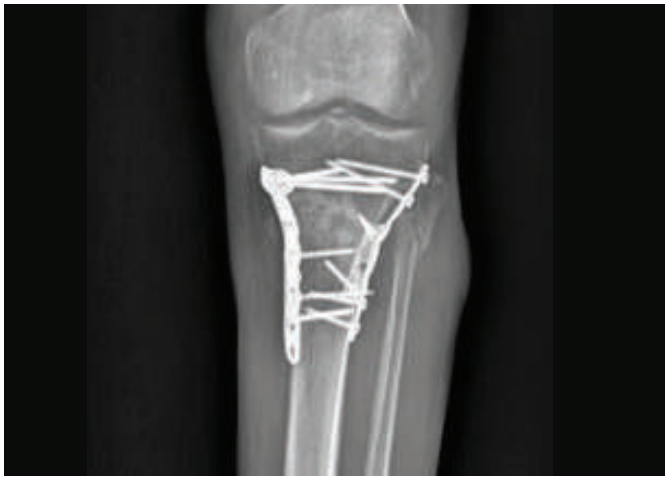


Figure 56. Follow-up 2 Months: Good range of motion.

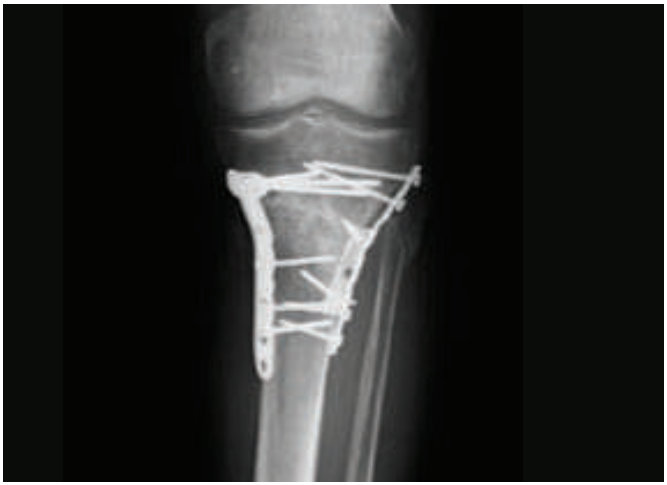


Figure 57. Follow-up 3 Months: Bone integration has to be detected.

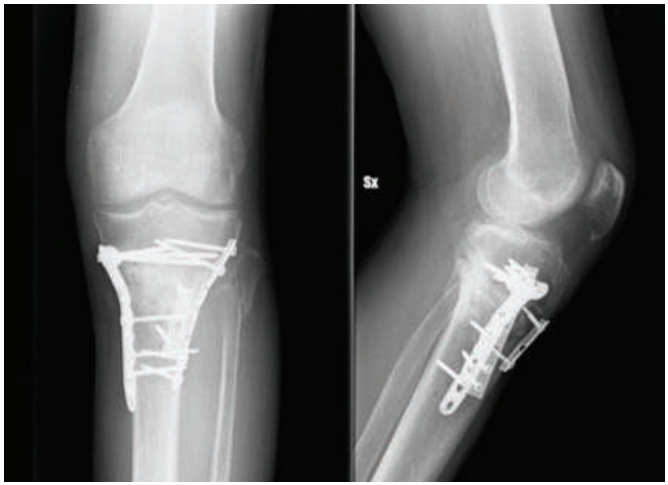


Figure 58. Follow-up 4 Months: Good clinical course, no issues observed, completed recovery.

CASE 16 - Tibial plateau lateral fracture w/o meniscal or legament involvement (Schatzker II)

Patient: female, 53 years old.
Surgical procedure: synthesis reduction using LCP with SmartBone® ORTHO.

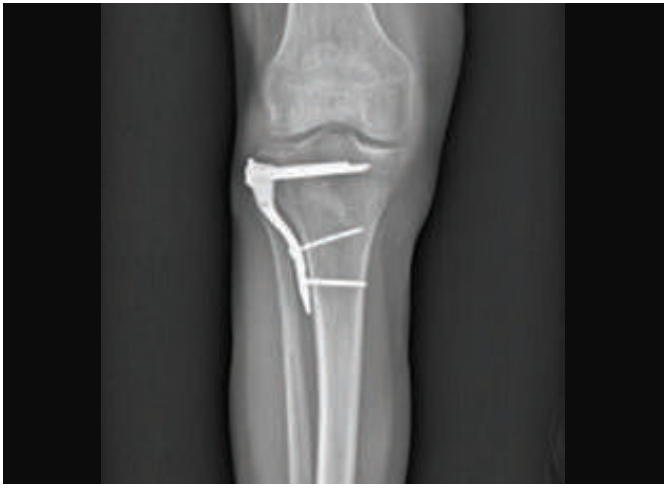


Figure 59. Follow-up 2 Months: Good stabilization and good clinical course.

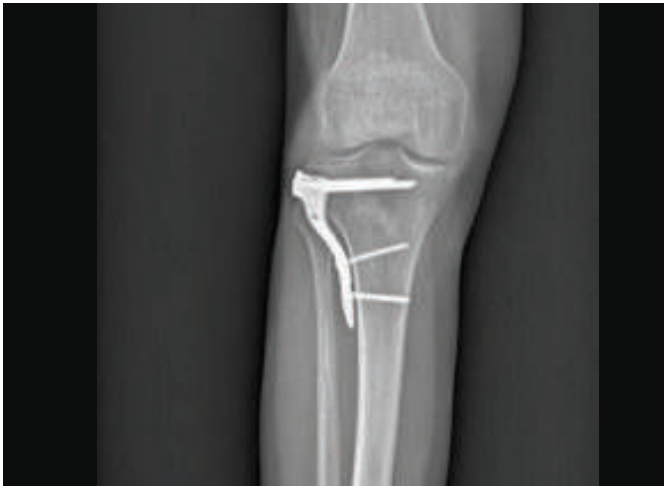


Figure 60. Follow-up 3 Months: Evidence of bone integration, pain free, good range of motion with small flection deficit.

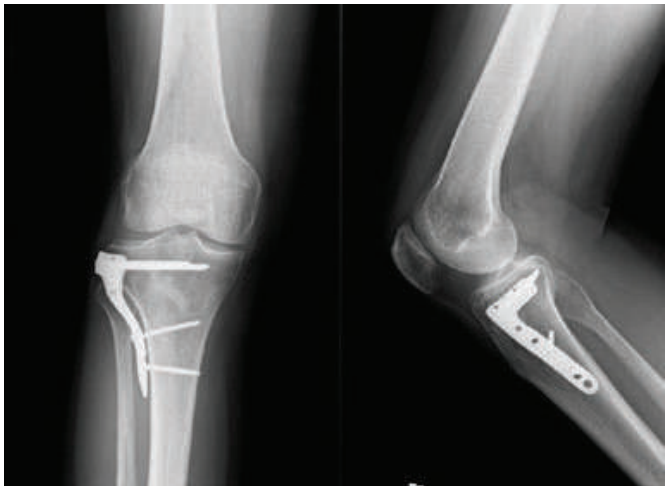


Figure 61. Follow-up 6 Months: Gains complete flection with a pain free and stable knee. Good bone integration.

CASE 17 - Multifragmentary lateral right tibial plateau fracture

Patient: female, 59 years old.
Surgical procedure: synthesis reduction using lateral LCP with SmartBone® ORTHO.

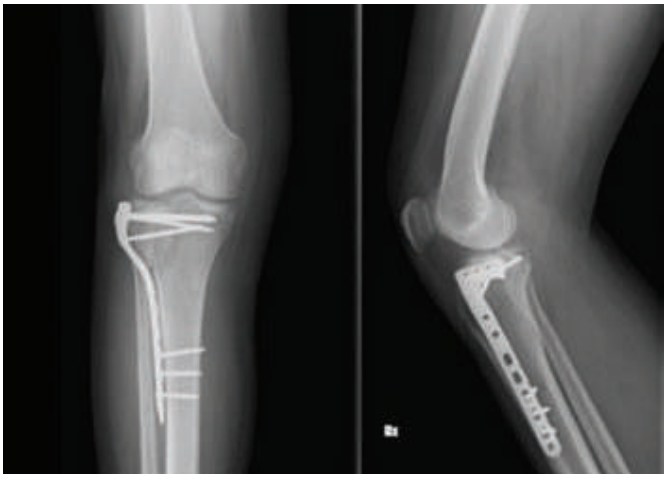


Figure 62. Follow-up 3 Months: Good bone consolidation and good stability of the fixation devices.

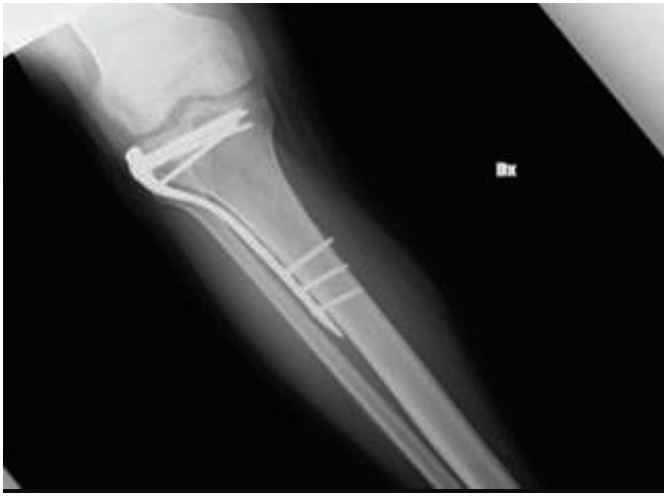


Figure 63. Follow-up 6 Months: No particulary issues, regular clinical course.

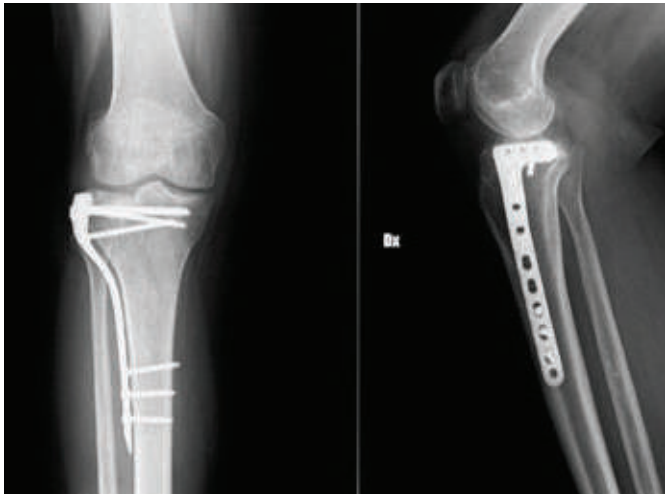


Figure 64. Follow-up 1 Year: Good bone integration and complete recovery.

CASE 18 - Left tibial plateau fracture

Patient: male, 65 years old.
Surgical procedure: synthesis reduction using lateral LCP with SmartBone® ORTHO.

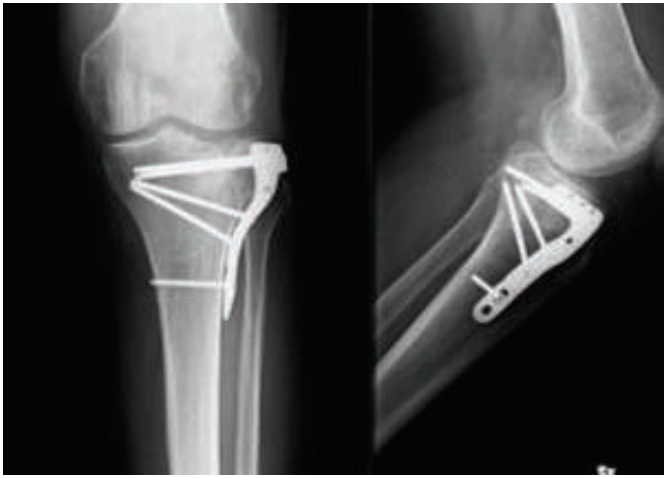


Figure 65. Follow-up 2 Months: Regular clinical course with slight depression of the articular plate laterally.

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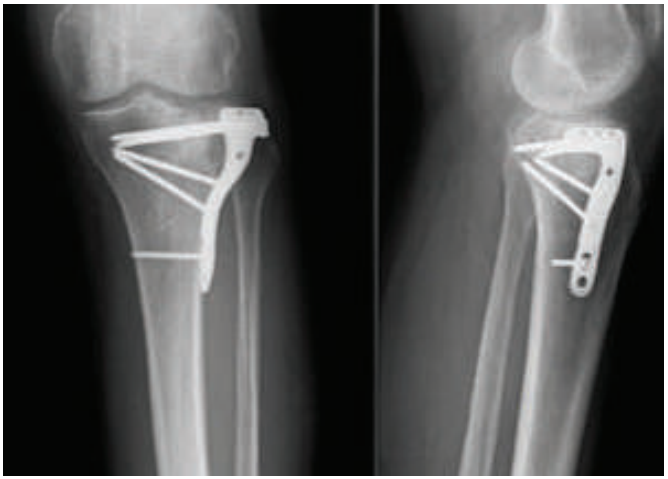

Figure 66. Follow-up 3 Months: Improvement of the clinical course.

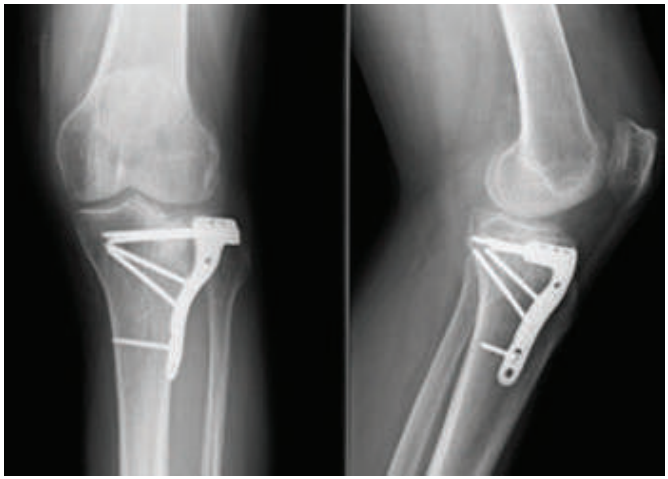

Figure 67. Follow-up 4 Months: Good osteintegration and acceptable clinical outcome.

CASE 19 - Left tibial plateau fracture

Patient: male, 32 years old.
Surgical procedure: synthesis reduction using lateral LCP with SmartBone® ORTHO.

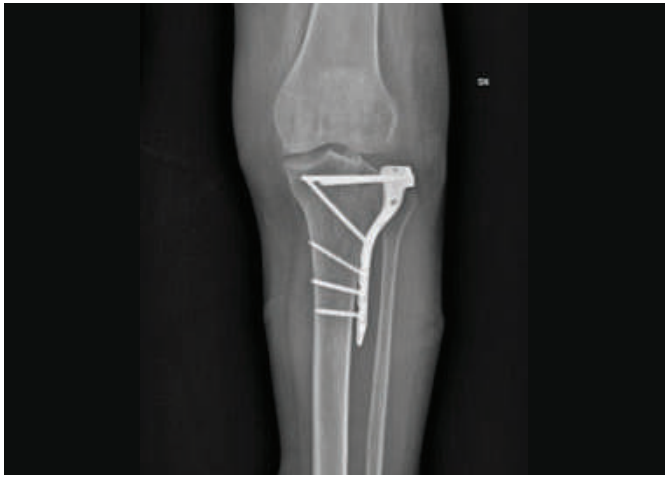

Figure 68. Follow-up 2 Months: Slight depression of the external margin of the tibial plateau is evident.

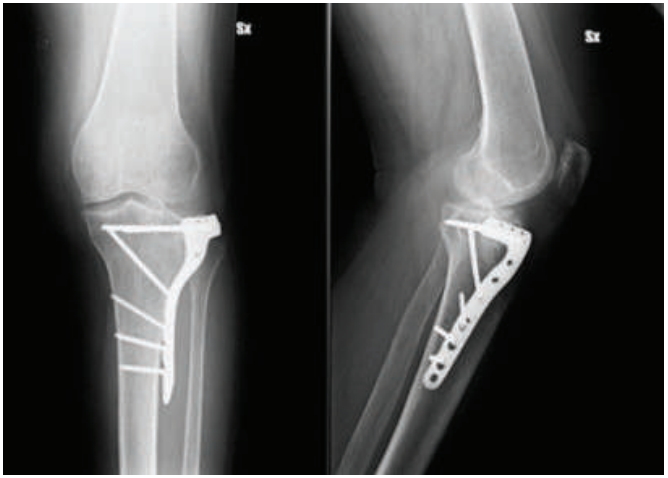

Figure 69. Follow-up 3 Months: Good clinical healing, walks without pain.

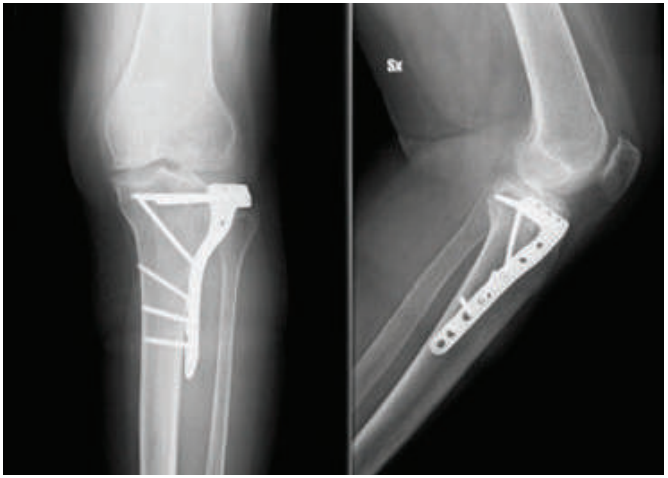

Figure 70. Follow-up 5 Months: Good bone density and good clinical outcome.

CASE 20 - Tibial plateau fracture

Patient: male, 32 years old.
Surgical procedure: synthesis reduction using SmartBone® ORTHO.

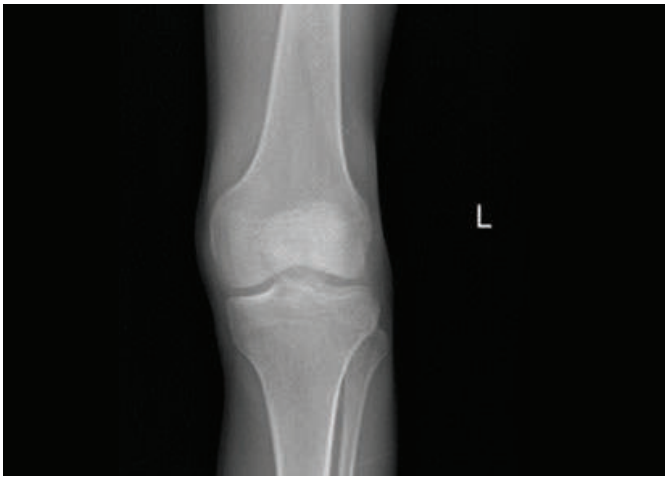

Figure 71. Pre operation: Fracture of the posterior margin of tibial plateau reduced with screws and SmartBone® ORTHO.

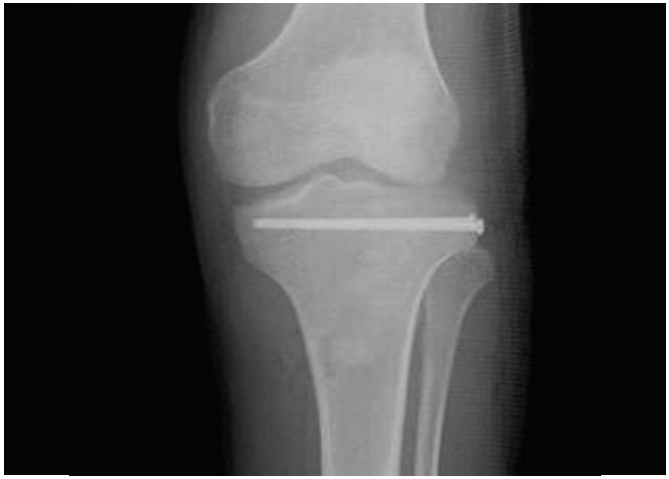

Figure 72. Follow-up 1 Month: Good clinical course.

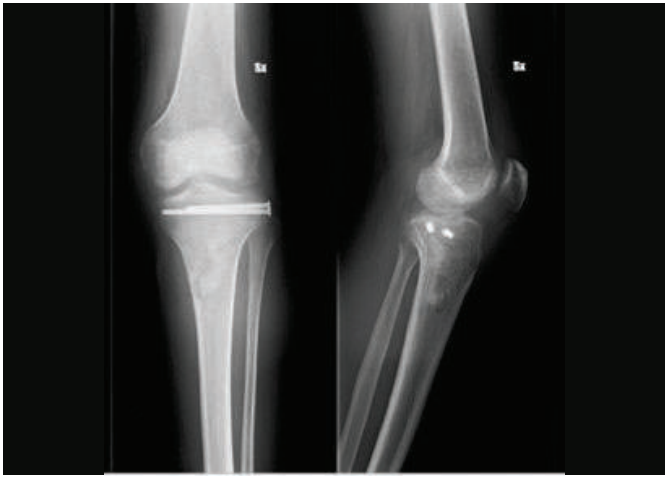

Figure 73. Follow-up 2 Months: Good consolidation of the ephyseal proximal tibia and good bone regeneration.

applied sciences

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Article

Composite Xenohybrid Bovine Bone-Derived Scaffold as Bone Substitute for the Treatment of Tibial Plateau Fractures

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Featured Application: 1. Fractures of the tibial plateau are common, representing 1% of all human fractures. Conservative and surgical treatments have been described for their management. 2. Comminuted or displaced fractures of the plateau can be challenging for orthopaedic surgeons, requiring often the use of bone grafts. 3. Autologous iliac bone graft (AIBG) is the clinical gold standard for bone transplantation. Still, this procedure exposes patients to some relevant risks. 4. Autologous iliac bone graft is the clinical gold standard for bone transplantation. Still, this procedure exposes patients to some relevant risks. 3. In order to overcome risks and limitation of AIBG, biomaterials are valuable bone substitutes when bone transplantation is required. 5. We treated our patients with a composite xenohybrid bovine bone-derived matrix, enriched in poly(L-lactide-co-caprolactone) (PLCL) and RGD-containing collagen fragments (obtained from gelatin).

Abstract: Introduction: Tibial plateau fractures represent a common challenge for orthopaedic surgeons, sometimes representing complex cases to manage, where augmentation using bone grafts is required for stabilisation. Autologous iliac bone graft (AIBG) is the current gold standard for bone grafting. In order to overcome limitations related to the procedure, alternative strategies, like allogenic and xenogeneic bone substitutes have been investigated. Here, within the framework of an observational clinical study, we report clinical and radiological outcomes of patients treated for tibial plateau fractures with a composite xenohybrid bone graft, aiming at assessing clinical and radiological outcomes. Materials and Methods: We performed a cohort retrospective study of patients treated for tibial plateau fractures from May 2017 to January 2018. Thirty-four patients, i.e. 100% of those having received the bone graft under investigation for tibial plateaux fracture treatment, met the inclusion criteria and were enrolled in the study. Patients were assessed at 2 weeks, and then at a 1-, 3-, and 6-months, and 1-year follow-up. At each evaluation patients filled a visual analogue scale (VAS) for the level of pain during the day life activities and underwent physical exam and anteroposterior and lateral projection radiographs of the knee. At 1 year the Tegner Lysholm Scoring Scale, International Knee Document Committee 2000 (IKDC 2000), and Short Form (36) Health Survey (SF-36) were administered. Results: At 1-year, mean VAS decreased from 6.33 ± 1.40 to 1 ± 0.79 ($P < 0.0001$); Tegner Lysholm Scoring Scale was 89 ± 4.10 and mean IKDC 2000 was 78.67 ± 3.31. No infections, neurovascular complications or adverse e ffects related to implants were

5.5. DISTAL RADIAL FRACTURES

Distal radial fractures represent a common orthopaedic problem accounting for 17% of all skeletal fractures. They are particularly frequent in male patients under 30 years old, most commonly due to high-energy traumas, and in over 60 years old female subjects, mostly due to falls. A stable, congruent, well-aligned, and painless wrist joint along with a wide range of motion are the goals of treatment of such fractures, in order to avoid potentially severe complications like e.g. post-traumatic osteoarthritis and stiffness. The volar approach and fixation with locked plate and screws is now of widespread use because open reduction internal fixation (ORIF) guarantees both an anatomical reduction of the fracture and best results from a clinical and functional point of view [Ferracini et all., 2020].

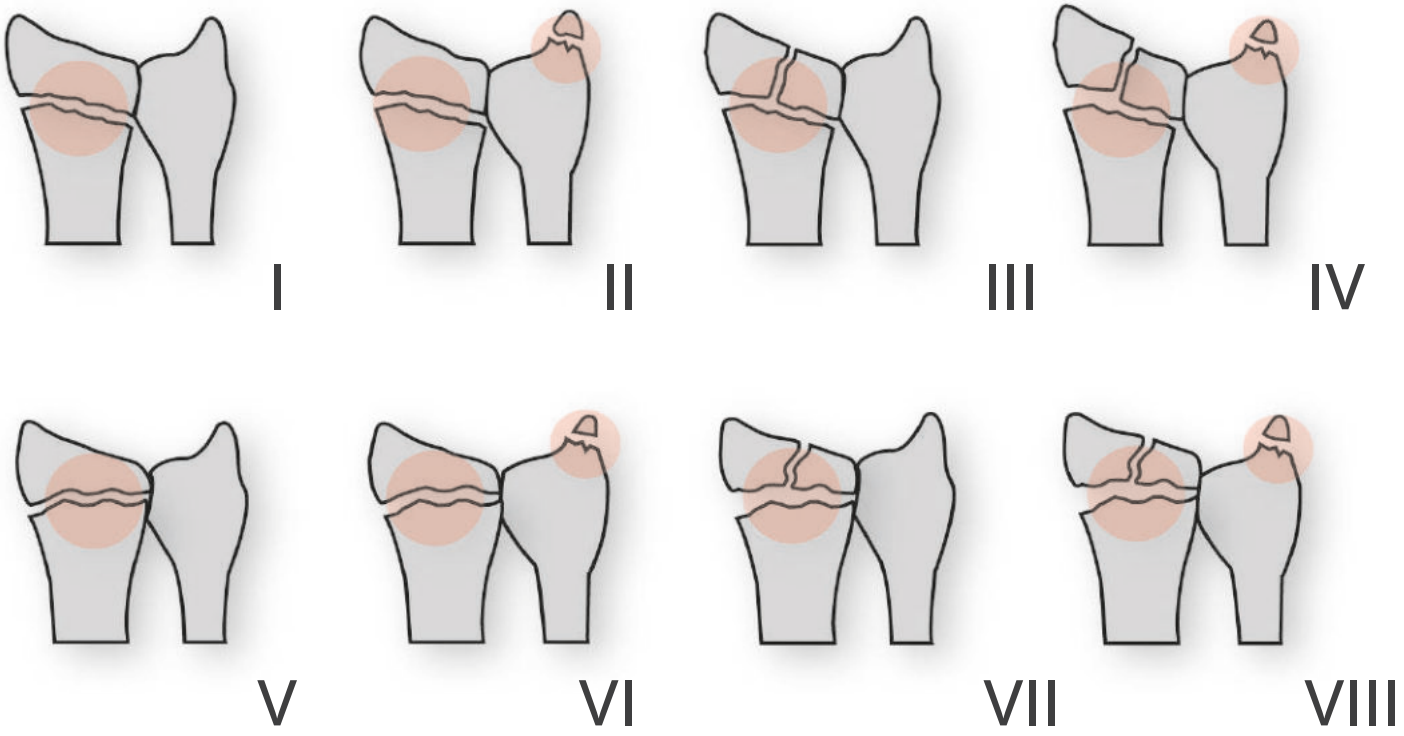
The use of bone graft in surgical treatment of distal radius fractures is still discussed and controversial. Nonetheless, in some cases, due to comminute fractures or excessive bone loss caused by traumatic trabecular collapse, bone graft can be useful to support bone fixation. This may occur in osteoporotic bone or impacted osteoarticular fragments that have lost metaphyseal support, and in dorsally plated comminute distal radius fractured.
The Frykman classification of distal radial fractures is based on the AP appearance and encompasses the eponymous entities of Colles fracture, Smith fracture, Barton fracture, chauffeur fracture. It assesses the pattern of fractures, involvement of the radioulnar joint and presence of a distal ulnar fracture.

FRYKMAN CLASSIFICATION

Although it appears complicated, it is actually only a four-type classification (odd-numbered types) with each type having a subtype which includes ulnar styloid fracture (these are the even-numbered types):

- **type I**: transverse metaphyseal fracture includes both Colles and Smith fractures as angulation is not a feature;
- **type II**: type I + ulnar styloid fracture;
- **type III**: fracture involves the radiocarpal joint includes both Barton and reverse Barton fractures includes Chauffeur fractures;
- **type IV**: type III + ulnar styloid fracture;
- **type V**: transverse fracture involves distal radioulnar joint;
- **type VI**: type V + ulnar styloid fracture;
- **type VII**: comminuted fracture with the involvement of both the radiocarpal and radioulnar joints;
- **type VIII**: type VII + ulnar styloid fractur

Frykman classification system:



5.5.1 CLINICAL CASES

CASE 21 - Plurifragmentary fracture of the radial epiphysis and detachment of the ulnar styloid

Patient: female 73 years old.
Surgical procedure: Multi-fragmentary fracture of radius epiphysis and detachment of ulnar styloid. Reduction and synthesis with plate and screws supported by SmartBone® ORTHO block, grafted to fill radius bone gap.

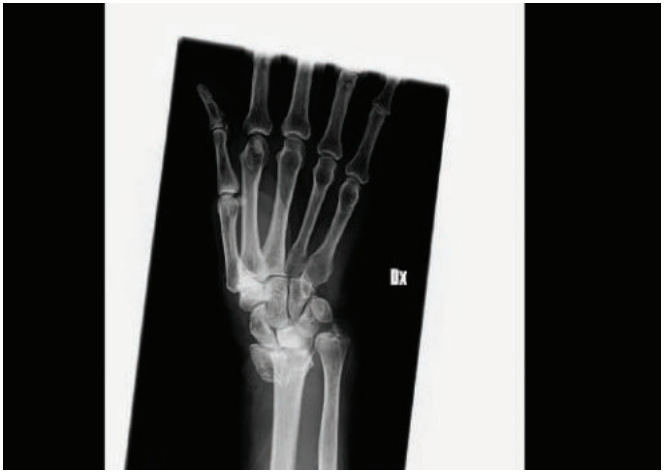


Figure 74. CT Scan of the multifragmentary radial distal epiphysis fracture.

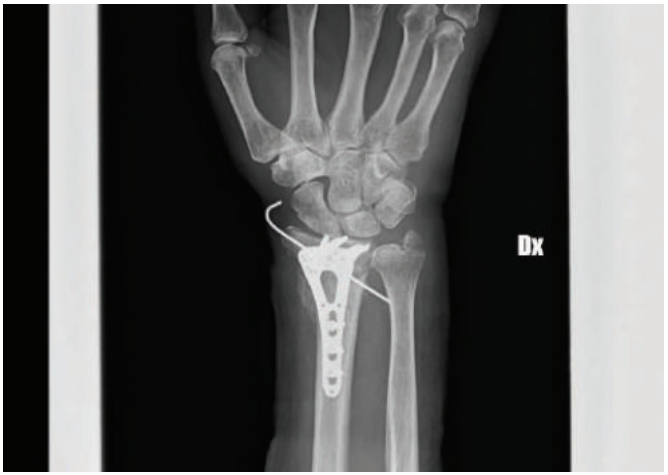


Figure 75. Follow-up 1 Month: after cast removal.

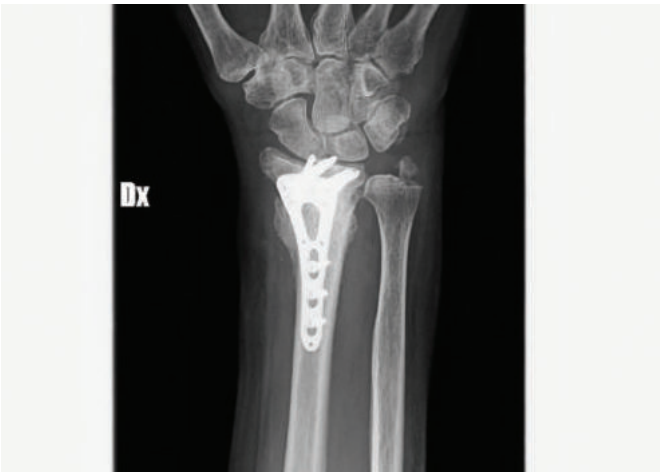


Figure 76. Follow-up 3 Months: Evidences of callus formation, good bone remodelling.

CASE 22 - Multifragmentary fracture of distal radial epiphysis

Patient: female, 70 years old.
Surgical procedure: Multifragmentary fracture of distal radial epiphysis treated with fixation devices and SmartBone® ORTHO, after 2 months a good consolidation of the bone tissue is documented.

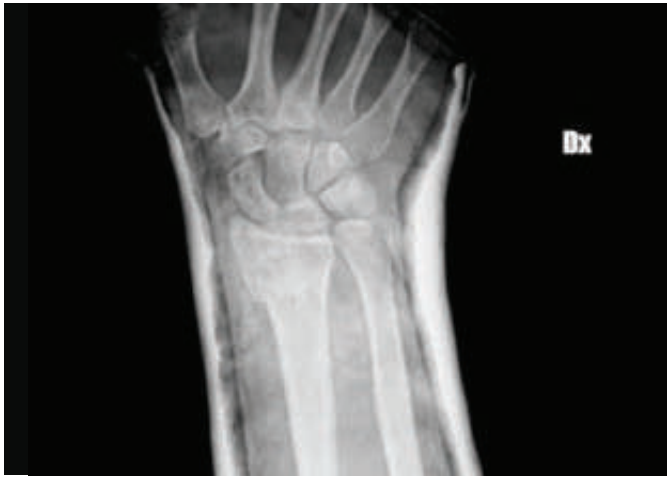


Figure 77. Pre operation.

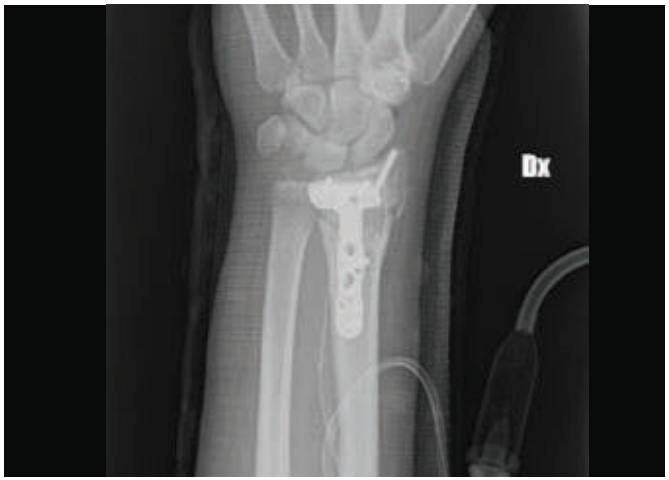


Figure 78. Immeditely post op.

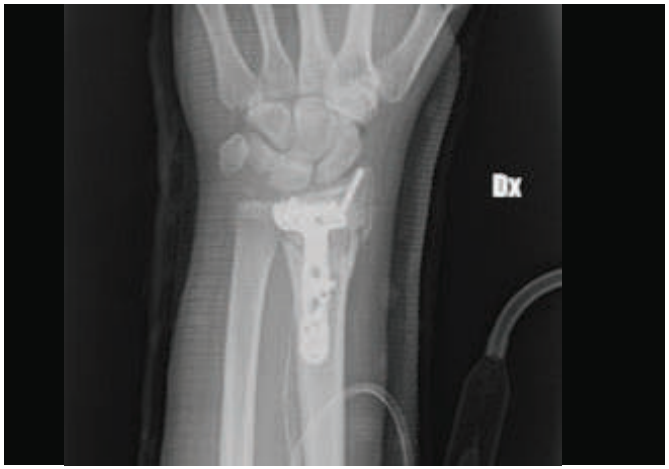


Figure 79. Follow-up 1 Month.

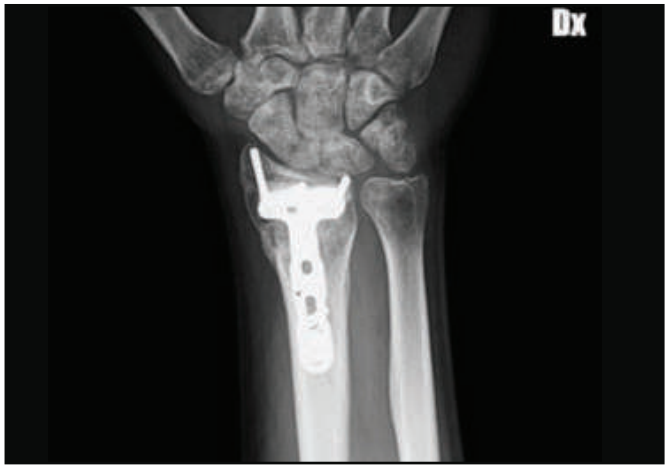


Figure 80. Follow-up 2 Months.

CASE 23 - Multifragmentary fracture of distal radial epiphysis

Patient: female, 72 years old.
Surgical procedure: Multifragmentary fracture of distal radial epiphysis treated with fixation devices and SmartBone® ORTHO, after 2 months a good consolidation of the bone tissue is documented.

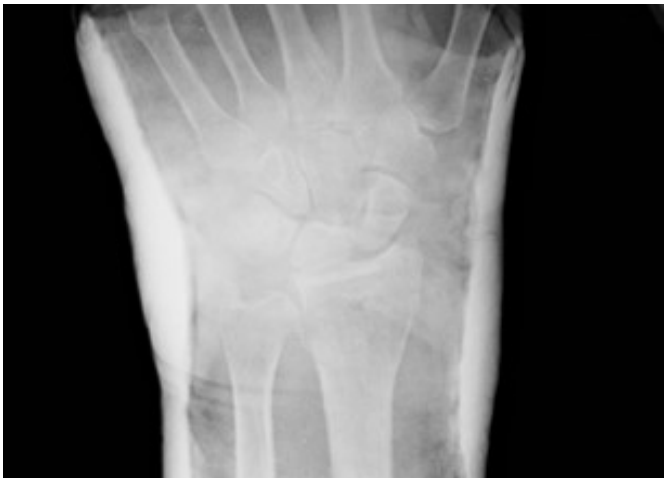


Figure 81. Pre Operation.

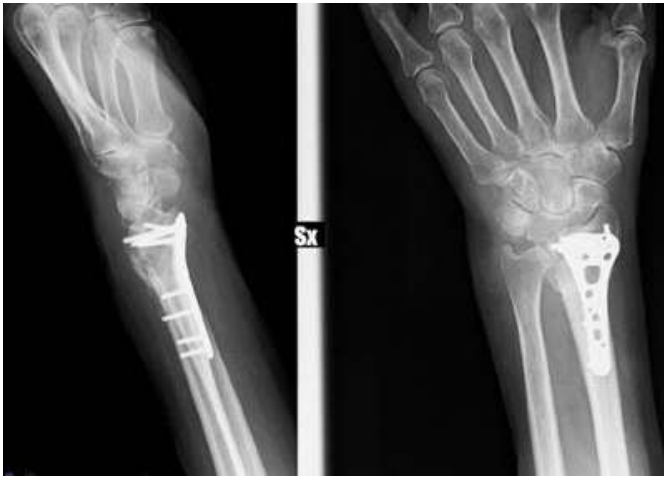


Figure 82. Follow-up 3 Days.

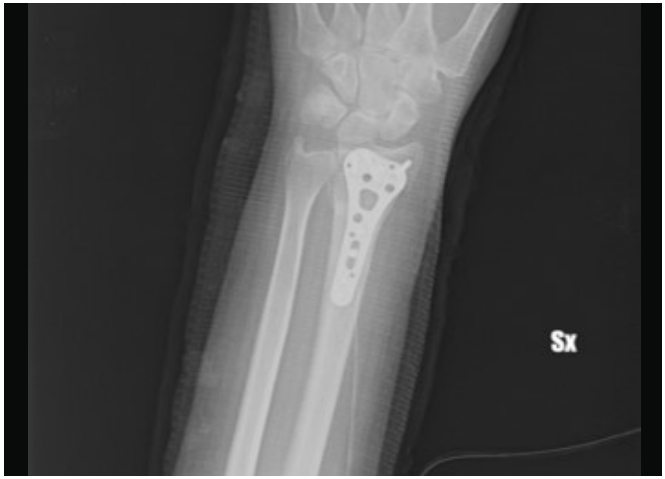


Figure 83. Follow 1 Month.

materials

MDPI

Article

Bone Loss in Distal Radial Fractures Treated with A Composite Xenohybrid Bone Substitute: A Two Years Follow-Up Retrospective Study

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3 Medical School, University of Turin, 10100 Turin, Italy; claudio.guidotti@edu.unito.it (C.G.); agnesebattista92@gmail.com (A.B.)
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Abstract: (1) Background: Recently, surgical treatment of distal radius fractures has increased exponentially. Many locking plates' fixation systems have been developed allowing a more stable reduction and early mobilization. Sometimes, open reduction and fixation of distal radius fractures may leave a residual bone loss requiring grafting. This retrospective study reports clinical and radiologic outcomes of distal radius fractures treated with xenohybrid bone grafting in order to assess (i) the safety of the investigated bone graft; (ii) its radiological integration and biomechanical performances, and (iii) clinical outcomes of the patients; (2) Methods: We performed a retrospective study on a cohort of 19 patients. Preoperative X-ray and CT scan were performed. The mean clinical and radiographical follow-up was two years. Safety of the xenohybrid bone graft was constantly evaluated. Clinical results were assessed through the DASH score and Mayo wrist score; (3) Results: No adverse reactions, infections, and local or general complication were related to the use of xenohybrid bone graft. The radiolucency of the xenografts suggested progressive osteointegration. No evidence of bone graft resorption was detected. All the patients reached consolidation with good to excellent clinical results; and (4) Conclusions: Clinical and radiological data demonstrated that xenohybrid bone grafting promotes new bone formation and healing in osteopenic areas caused by fracture reduction.

Keywords: xenograft; bone graft; radial fracture; xenohybrid biomaterial

1. Introduction

Distal radial fractures account for 17% of all skeletal fractures [1–3], which makes them quite common. The vast majority of them occurs in male patients under 30 years old, mostly due to high-energy traumas, and, in over 60 year-old female subjects, mostly due to falls. A stable, congruent, well-aligned, and painless wrist joint along with a wide range of motion are of paramount importance during the healing process, in order to avoid potentially severe complications like e.g., post-traumatic osteoarthritis and stiffness. The volar approach and fixation with locked plate and screws is now

5.6. SPINAL COLUMN INTRODUCTION

The spinal column (vertebral column or backbone) provides both structural and nervous system support for your entire body. Made up of 34 bones, the spinal column holds the body upright, allows it to bend and twist with ease and provides a conduit for major nerves running from the brain to the tips of the toes—and everywhere in between.

The entire spinal column consists of 24 individual bones called vertebrae (singular vertebra), plus 2 sections of naturally fused vertebrae—the sacrum and the coccyx—located at the very bottom of the spine. When most people talk about the spinal column, they're actually referring to the vertebral column: the 24 circular vertebrae that march down the middle of the back.

The vertebral column can be divided into 5 regions:

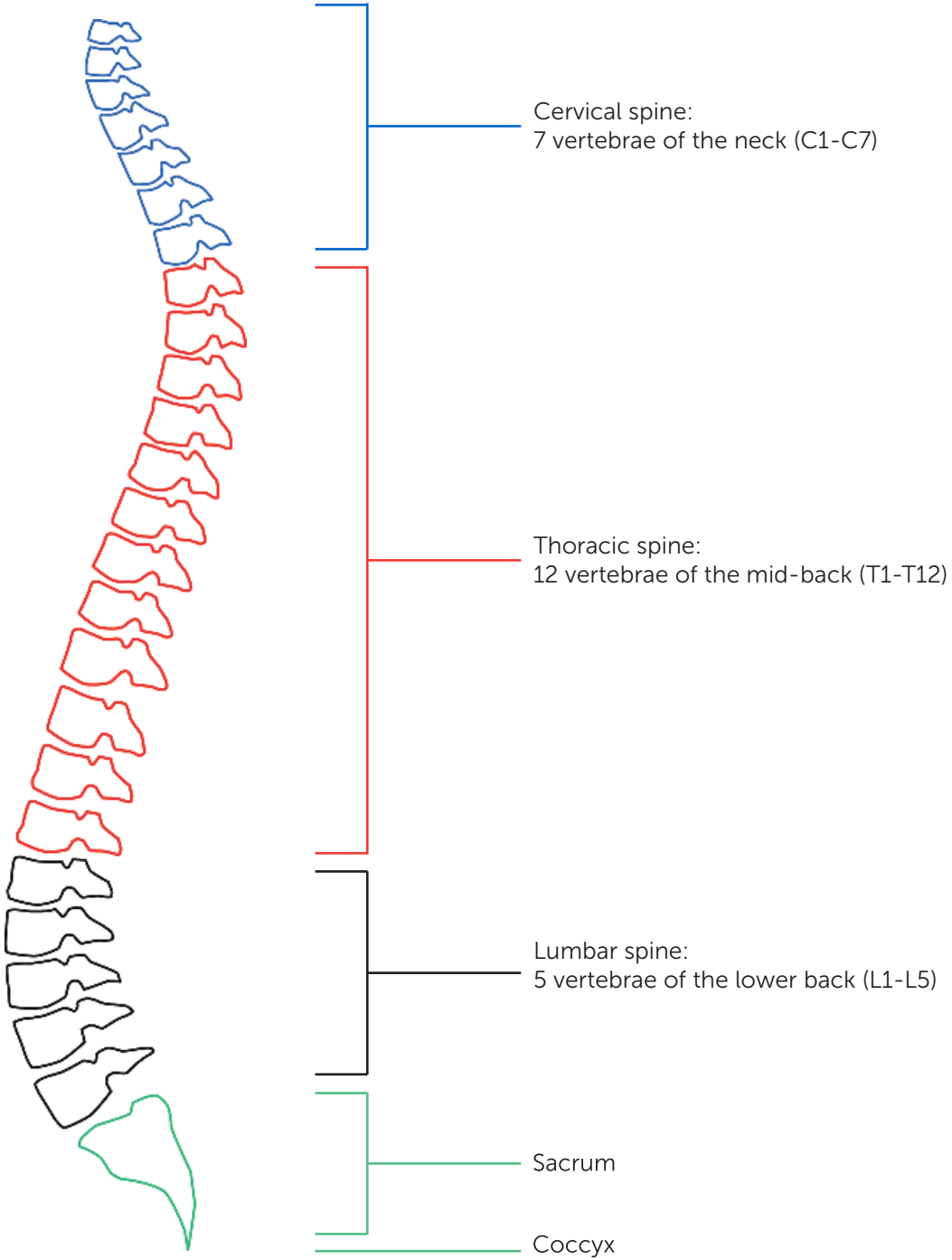
- Cervical spine: 7 vertebrae of the neck (**C1-C7**)
  - C1 is also known as the Atlas
  - C2 is also known as the Axis
- Thoracic spine: 12 vertebrae of the mid-back (**T1-T12**)
- Lumbar spine: 5 vertebrae of the lower back (**L1-L5**)
- Sacrum
- Coccyx

A normal vertebral column creates double-S curve when viewed from the side of the body. The cervical vertebrae gently curve inward, while the thoracic spine curves gently outward, followed by the lumbar spine, which curves inward again. This structure gives the spinal column great strength and shock-absorbing qualities.
The spinal column doesn't consist only of bones. To maintain its double-S shape, provide skeletal support and route the nerves where they need to go, the spine also relies on a number of supporting structures.
First among these structures are the spinal discs, called intervertebral discs starting at C3 through L5-sacrum. These discs act as interbody spacers and shock absorbers.

Facet joints are paired at the back of each vertebral body (C3-L5). These joints help stabilize the spine while allowing flexion (bending forward), extension (bending backward) and twisting movement (called articulation). Similar to other joints in the body, each facet joint is encased in a capsule of connective tissue that produces a nourishing fluid that lubricates the joint. Cartilage coats the joint surfaces ensuring smooth movement.

Different types of spinal ligaments—strong, tough, bands of tissue—connect the vertebrae, discs and facet joints to help stabilize and support the spinal column at rest and during movement. The ligaments act like stretchy-like tension cords that allow the spine's bones, discs and joints (facet joints) to move within a limited range.
And, of course, small and large spinal muscles and tendons help stabilize and strengthen the vertebral column while supporting and limiting extreme bending, flexing and twisting movements.

The vertebral column serves to protect the spinal cord and nerve roots, which are part of the central nervous system that starts at the base of the brain. The vertebral structures form a continuous round hollow space that houses the spinal cord from the cervical through lumbar spine.


Cervical spine:
7 vertebrae of the neck (C1-C7)
Thoracic spine:
12 vertebrae of the mid-back (T1-T12)
Lumbar spine:
5 vertebrae of the lower back (L1-L5)
Sacrum
Coccyx

5.7. SPINAL TUMORS

A spinal tumor is an abnormal mass of tissue within or surrounding the spine and/or the spinal cord. Spinal tumors can be benign or malignant and primary or metastatic: primary tumors originate in the spine or spinal cord, the metastatic or secondary ones result from cancer spreading from another site. They can be:

- **Intradural-extramedullary** – The tumor is located inside the thin covering of the spinal cord (the dura), but outside the actual spinal cord. Frequency of occurrence in this location is 40%. The most common of these types of tumors develop in the spinal cord's arachnoid membrane (meningiomas), in the nerve roots that extend out from the spinal cord (schwannomas and neurofibromas), or at the spinal cord base (filum terminale ependymomas). These tumors are usually benign but sometimes difficult to remove.

- **Intramedullary** – These tumors grow inside the spinal cord. They typically derive from glial or ependymal cells (a type of glial cell). Frequency of occurrence in this location is approximately 5%. Astrocytomas and ependymomas are the two most common types. Astrocytomas are more common in the thoracic region followed by the cervical. They are often benign, but can be difficult to remove. Intramedullary lipomas are rare congenital tumors most commonly located in the cervicothoracic spinal cord.

- **Extradural** – The tumor is located outside the dura, which is the thin covering surrounding the spinal cord. Frequency of occurrence in this location vs the ones above is approximately 55%. These lesions are typically attributed to metastatic cancer or less commonly schwannomas derived from the cells covering the nerve roots.

The bony spinal column is the most common site for bone metastasis. Estimates indicate that at least 30% and as high as 70% of patients with cancer will experience spread of cancer to their spine. The most common primary spine tumor (originated in the bony spine) is vertebral hemangiomas, benign lesions that rarely cause symptoms such as pain. Other common primary spine tumors are: Osteoid Osteoma, Osteoblastoma, Osteosarcoma, Ewing Sarcoma, Aneurysmal Bone Cyst, Chordoma, Chondrosarcoma, Giant-Cell Tumor Of Bone, Angiosarcoma.
Unlike adults, children have not achieved complete skeletal growth, which doctors must take into account when considering treatment.
Other cancers that spread to the spine include hematological disease like multiple myeloma and lymphoma.
Numerous factors can affect outcome, including the nature of the primary cancer, the number of lesions, the presence of distant non-skeletal metastases and the presence and/or severity of spinal-cord compression.

INCIDENCE AND PREVALENCE

When speaking of tumors of the spine, there are different incidences of tumor types related to the neural/dural elements vs the surrounding vertebral bony support. Intramedullary tumors are rare compared to metastatic tumors of the spine that are the most common type of spinal tumor. They occur in up to 10% of cancer patients.

CAUSES

The cause of most primary spinal tumors is unknown. Myeloma ad lymphoma are more common in people with compromised immune systems. In some cases there is also a genetic component.

TESTING & DIAGNOSIS

A thorough medical examination with emphasis on back pain and neurological deficits is the first step to diagnosing a spinal tumor. Radiological tests are required for an accurate and positive diagnosis such as X-razs, CT scans, MRI, Bone Scans etc. But the final diagnosis is determined by the biopsy of the lesion.

TREATMENT

Treatment decision-making is often multidisciplinary, incorporating the expertise of spinal surgeons, medical oncologists, radiation oncologists and other medical specialists. The selection of treatments including both surgical and non-surgical is therefore made keeping in mind the various aspects of the patient's overall health and goals of care. Nonsurgical treatment options include observation, chemotherapy and radiation therapy.

SURGERY

Indications for surgery depend on the type of tumor. Primary (non-metastatic) spinal tumors may be removed through complete en bloc resection for a possible cure. In patients with metastatic tumors, treatment is primarily palliative, with the goal of restoring or preserving neurological function. The approach to the tumor is determined by the tumor's location within the spinal canal. The posterior (back) approach is commonly used for tumors in the posterior aspect of the spinal column or to expose tumors inside the dura. The anterior (front) approach is excellent for tumors in the front of the spine. This approach allows placement of short-segment fixation devices. Not infrequently, a posterior (back) approach followed by a separately staged anterior (front) approach has been utilized to treat lesions involving both posterior and anterior part of the spine.

OUTLOOK

Outcome depends greatly on the age and overall health of the patient and on whether the spinal tumor is benign or malignant, primary or metastatic. A prompt diagnosis is very important for the final outcome. Surgery has been associated with a risk for major complications (reports of up to 14%). The most common complications are surgical site infection, systemic infections, and deep venous thrombosis.

5.7.1 SPINAL TUMORS CLINICAL CASES

CASE 24 - Vertebrectomy for osteoblastoma T2

Patient: female, 14 years old.
Surgical procedure: vertebrectomy en bloc, anterior access.

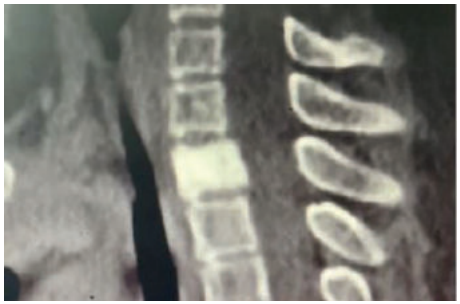


Figure 84. CT Scan of the initial situation: osteoblastoma T2.

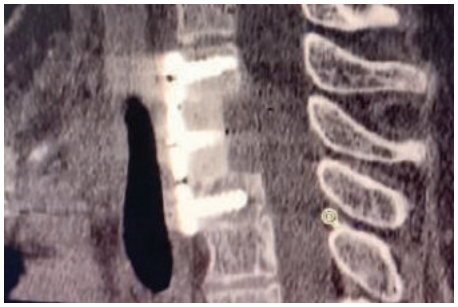


Figure 85. Follow-up 0 Months: Post operative X-Ray after bone replacement with fixation devices.

FOLLOW-UP FROM 6 MONTHS TO 1 YEAR

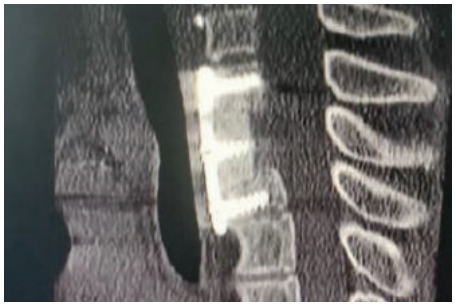


Figure 86. Follow-up 6 Months: Good osteointegration

Figure 87. Follow-up 1 Year: Good integration of SmartBone® ORTHO Block in the vertebrectomy

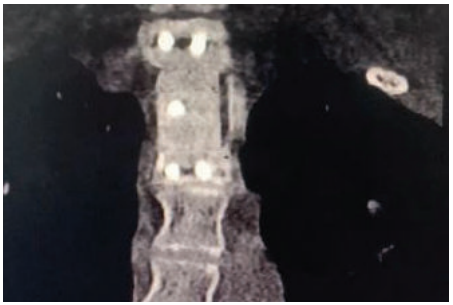


Figure 88. Follow-up 1 Year: Evidence of good integration and ongoing remodelling.

CASE 25 - Hemivertebrectomy for osteoblastoma L4

Patient: male, 20 years old.
Surgical procedure: hemi lumbar spine double access vertebrectomy.

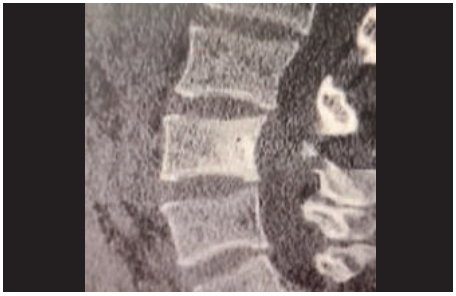


Figure 89. CT Scan of the initial situation: osteoblastoma L4.

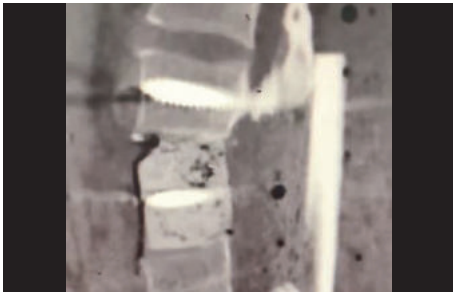


Figure 90. Follow-up 0 Months: Post operative X-Ray with fixation devices.

FOLLOW UP FROM 1 MONTH TO 8 MONTHS

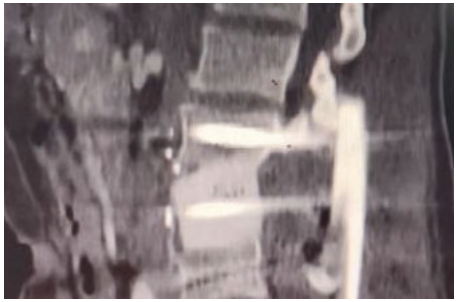


Figure 91. Follow-up 1 Month: Good osteointegration.

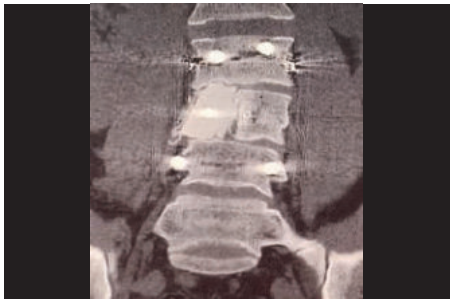


Figure 92. Follow-up 8 Months: Good integration of SmartBone® Block in the partial vertebrectomy.

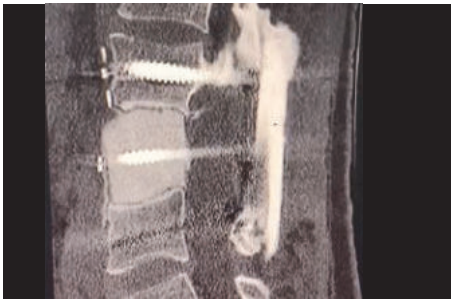


Figure 93. Follow-up 8 Months: Evidence of good integration and ongoing bone remodelling.

CASE 26 - Kidney solitary metastasis T3

Patient: male, 39 years old.
Surgical procedure: vertebrectomy double access thoracic rachis.

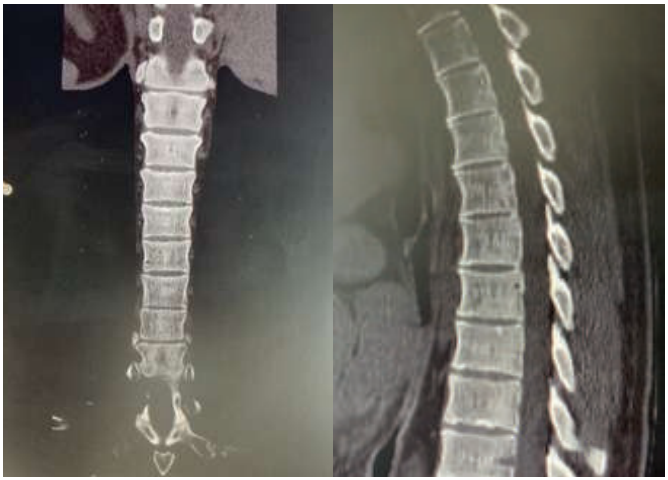


Figure 94. Initial condition of the metastatic area T3.

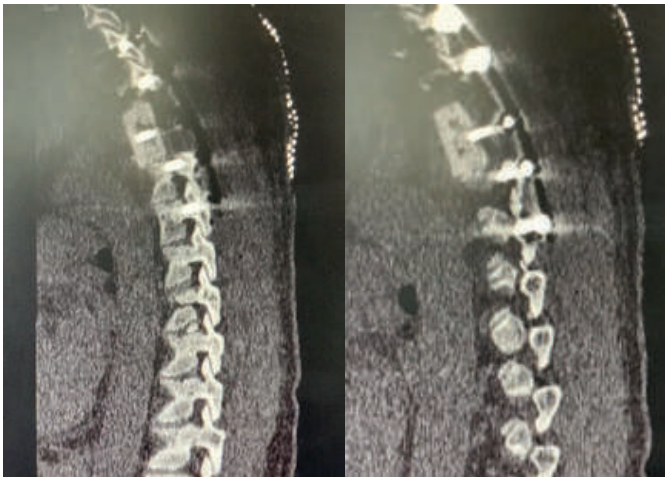


Figure 95. Follow-up 5 days.

CASE 27 - Liposarcoma metastasis T8

Patient: male, 51 years old.
Surgical procedure: thoracic spine metastasis removal with thoracoscopic surgical access.

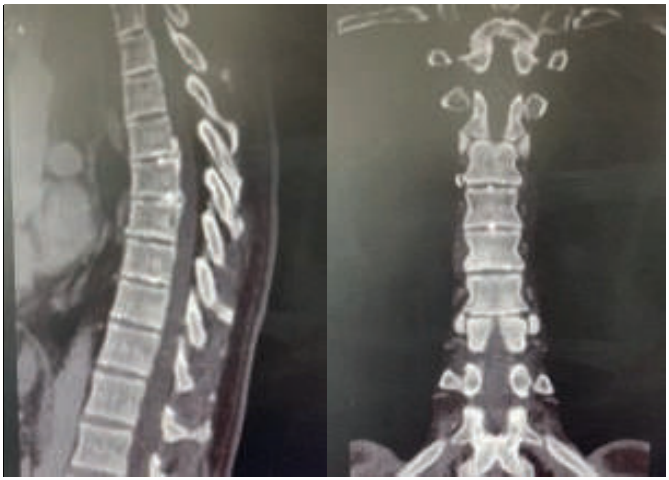


Figure 96. Pre operation: Initial condition of the liposarcoma metastasis T8.

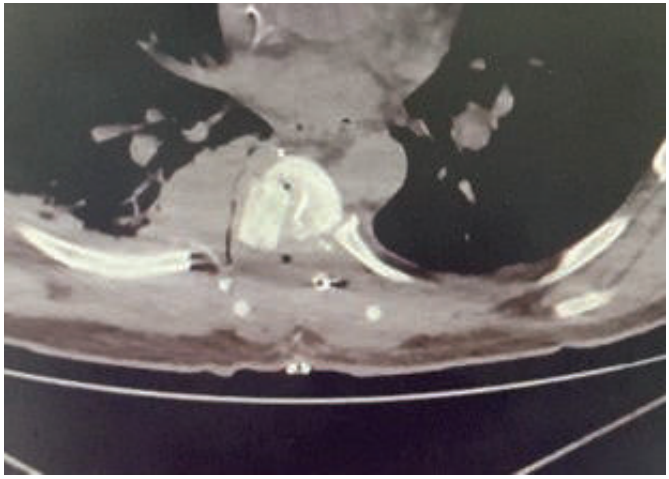


Figure 97. Follow-up 5 Days: The SmartBone® ORTHO Block is in full contact with the remaining vertebral bone.

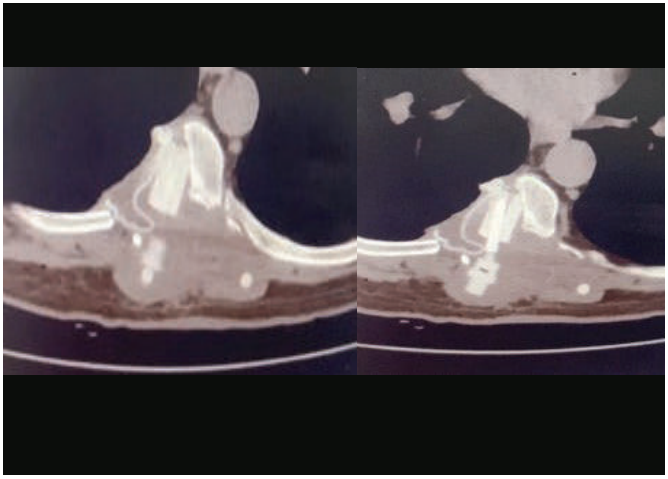


Figure 98. Follow-up 4 Months: Initial signs of integrations evidence and interface between the host bone and SmartBone® ORTHO Block.

CASE 28 - Tumor T6 Giant cell tumor (GCT)

Patient: male, 31 years old.
Surgical procedure: Hemivertebrectomy using thoracic approach and posterior arthrodesis on 5 levels.

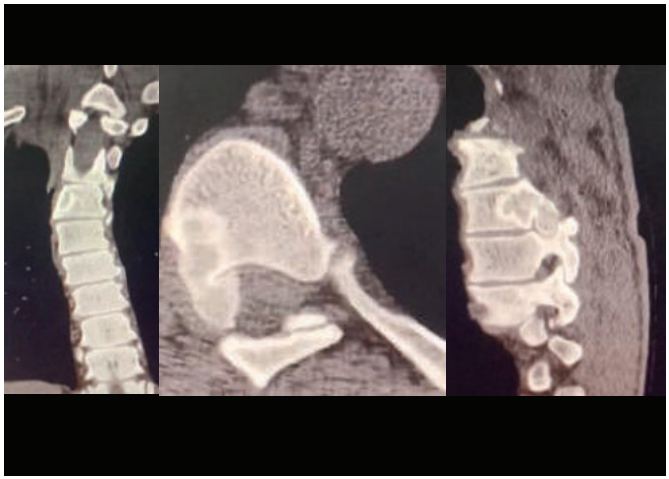


Figure 99. Pre operation.

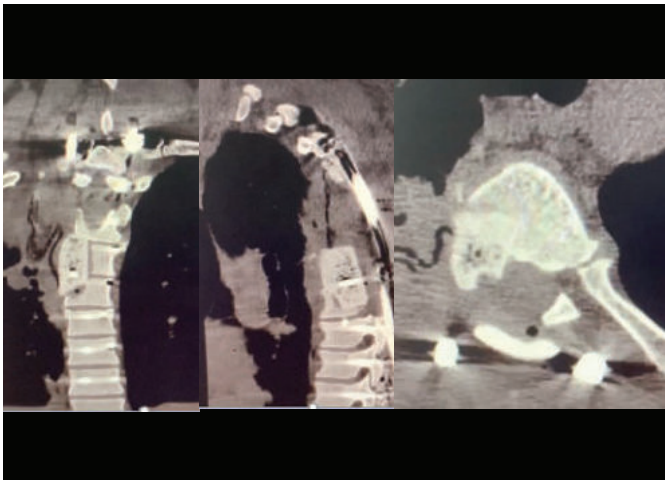


Figure 100. Follow-up 10 Days: The presence of the SmartBone® ORTHO Block is well documented. It appears stable and in close contact with the host bone.

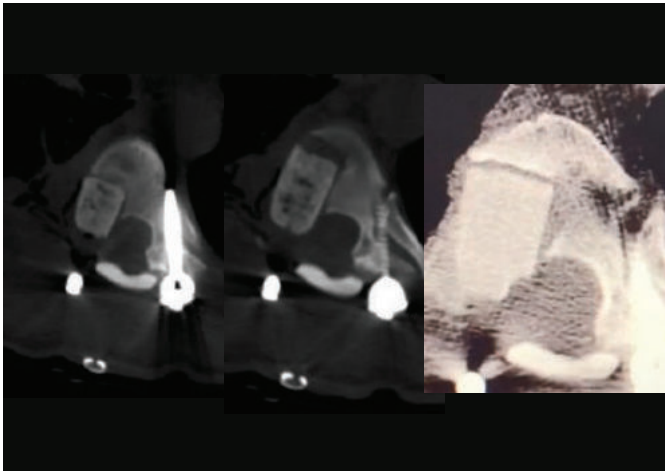


Figure 101. Follow-up 5 Months: The SmartBone® ORTHO Block remains in contact with the host vertebrae. No signs of the resorption of the graft are documented.

CASE 29 - Ewing sarcoma L3

Patient: female, 12 years old.
Surgical procedure: vertebrectomy rachis and lumbar double access, reconstruction with SmartBone® ORTHO.

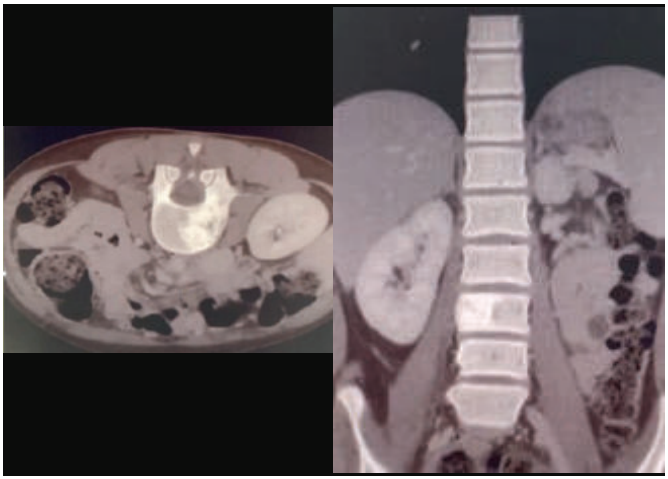


Figure 102. Pre operation: The tumor lesion clearly involves the body and pedicle of L1

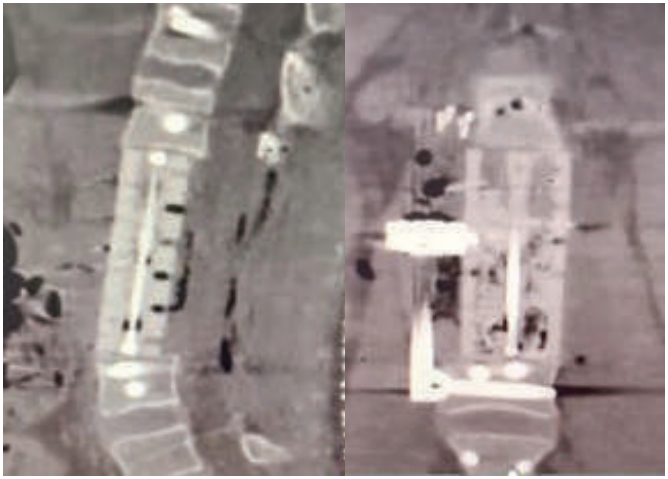
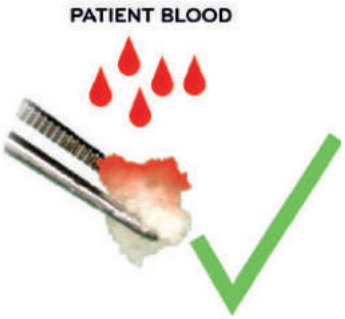


Figure 103. Follow-up 6 Days: SmartBone® ORTHO Block substitutes two vertebral bodies and is stabilized with hardware

DON'T

AVOID THE USE OF SALINE SOLUTION

DO



PREFER THE USE OF PATIENT BLOOD

DON'T

DON'T REUSE

DO

FOR SINGLE USE ONLY

6

Tip's, Tricks, Do's, Dont's

6. TIP'S, TRICKS. DO'S, DON'T'S

Whenever possible, the operation must be planned carefully in order to have the right material available (granules, blocks of various sizes, etc.). Do not forget that the smart bone can also be ordered in customized blocks. This feature can be convenient either in prosthetic reimplant surgery, in oncology or for osteotomy wedge addition surgery.

If the lesion has a volume to be filled with smart bone, ask the radiologist to evaluate in advance the shape and volume of graft necessary for the filling. Often times you end up with an insufficient amount of material.

Sometimes, the filling requires an intrinsic stability, especially when treating cavities with thin bone shells. As an example, when filling a bone cyst which was operated on for the risk of fracture, the use of a solid smart bone block is preferred. The areas around the solid block can be filled with graft granules after the solid block positioning.

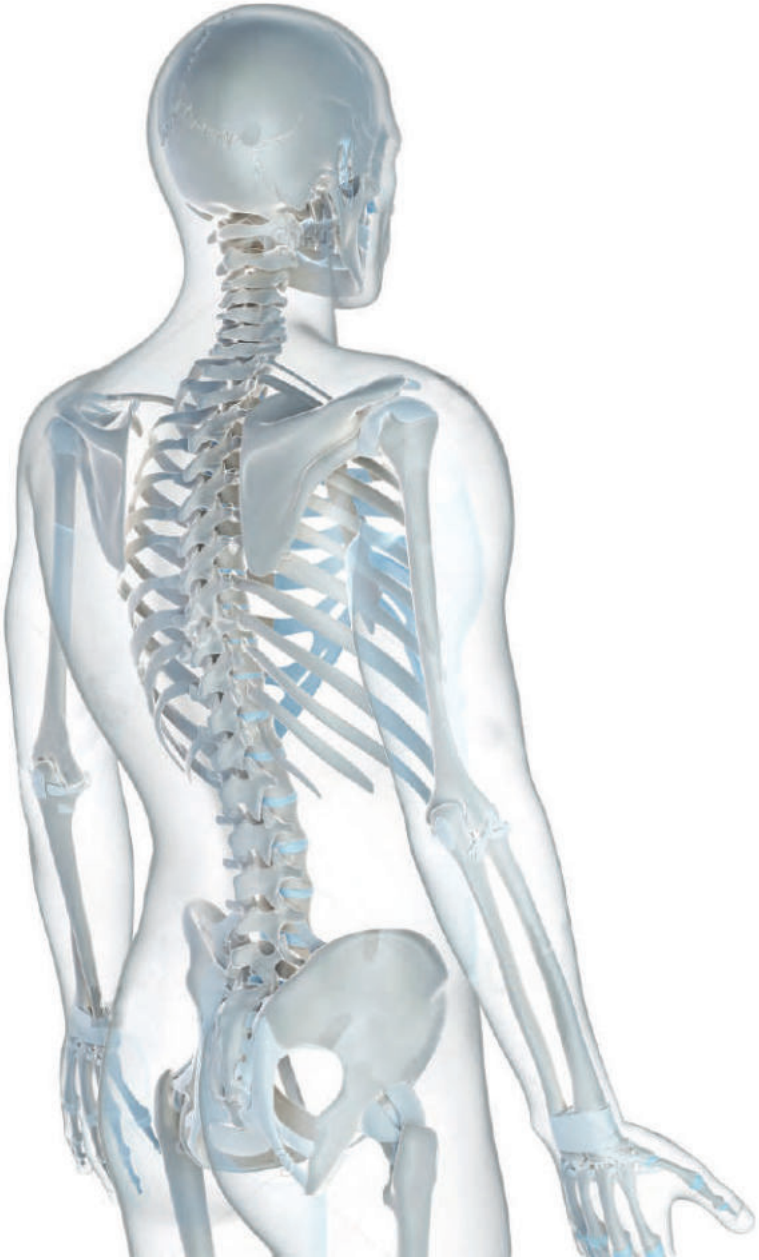
Some of the areas of treatment can be relatively poor in vascularization, especially in sclerotic bone region as in acetabulum, or in delayed union of long bones. These areas should be treated with diaphyseal canal opening if available, and/or with mini-drilling with 1.2/1.4 mm tips in order to obtain a medullary continuity with the lesion. The aim is to provide a source of stem cells, which might cooperate locally for the healing and for the graft integration.

The graft is designed biologically as a palatable docking site for local stem cells, to adhere and activate autocrine stimulation and differentiation. This is also the rationale for using stem cells extracted from medullary blood or from micro-manipulated adipose tissue, if available at your Institution. On the regulatory side, note that medullary blood and adipose tissue are present locally respectively in the medullary canal and in the connective surrounding bones. This observation overcomes possible legislative constraints that impose the use of such mesenchymal stem cells-rich extracts only omo-topically and omo-functionally. (EMA ...)

Do not forget that a measure of stem cells is available in the circulating blood. Therefore, the positioning of the graft in presence of fresh host blood is always preferred, especially in conditions of poor vascularization or limited access to medullary or healthy trabecular tissues.

On the mechanical side, keep in mind that the smart bone is derived from a very healthy young bovine trabecular bone, which is resistant to compression but also to traction and bending. Thus, it can be used in struts for cooperation with standard fixation devices in fracture or bone loss treatments.

Finally, when available, always preserve the periosteal membrane, especially in children, where it can be sutured directly in contact with the smart bone graft. The regenerative potential of the periosteum filled precursors can be exploited in the smart bone graft scaffold.

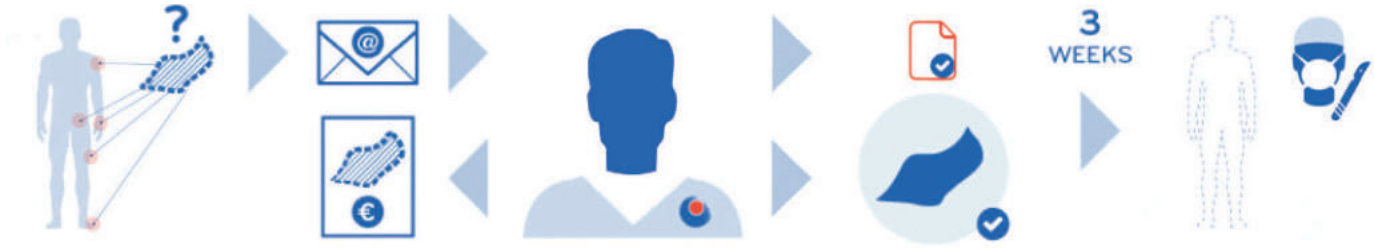



7
smartbone® on demand™

7.1. SMARTBONE® ON DEMAND™

Smartbone® On Demand™ is a service provided by Industrie Biomediche Insubri SA according to the 93/42/CEE Legislation regarding custom-made medical devices.

7.1.1. HOW TO GET YOUR GRAFT?



Diagnosis prescription

Take a CT Scan in DICOM format of the Patient concentrating on the defect. Please check on our website the guidelines.

Digital planning

Send the CT Scan to IBI-SA with a brief clinical description. IBI's trained Engineers will get in contact with you, discuss the plan and share with you the economical offer as well.

Custom made

You will receive a confirmation document that must be sent signed to IBI referring your unique case, in order to approve the project and let's start the production. IBI's trained Engineers, in conformity with your indications and suggestions, will design the graft until your approval.

Surgery

3 weeks later you will receive your graft ready for the surgical operation.
No sterilization or extra shaping required.

7.1.2. MODES OF SUPPLY

1 If you choose to send us the patient's DICOM file, together with his clinical prescription, IBI is able to plan the custom-made piece.

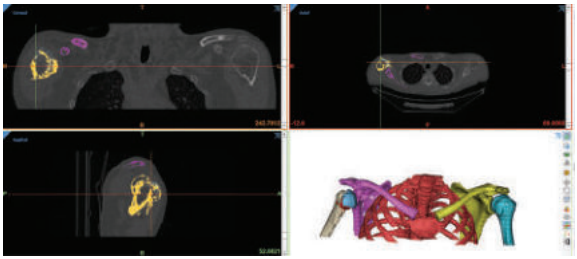


Figure 104. Design Software.

2 You can choose to send us the stereolithographic model directly, reproducing a plastic model of the missing piece of bone (usually the doctors rely on an external laboratory). IBI can use the stereolithographic model to reconstruct the custom-made piece, by previous HD scan.

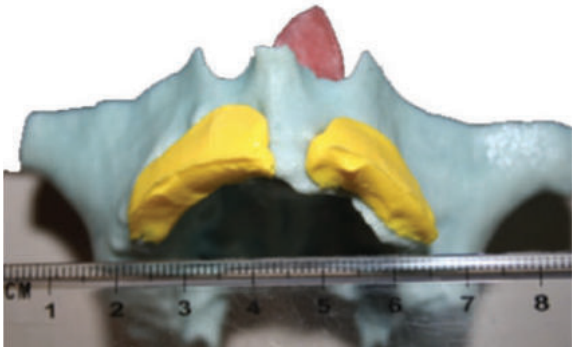


Figure 105. Stereolithographic model.

3 If you send the design file (.STL), IBI can produce directly the piece, without additional costs. After the IBI's feasibility check.

Figure 106. .STL model, output of the design software.

7.1.3. HOW TO ORDER A SMARTBONE® ON DEMAND™?

You need to send your request to ondemand@ibi-sa.com, adding patient's and doctor's name/surname and a brief description of the clinical case. If the .STL file is not available, please send the DICOM file for our feasibility evaluation. In case of a positive evaluation, IBI's staff promptly generates a univocal identification code. The formal request for custom made grafts MUST be signed, dated and on the doctor's letterhead; patient's name and clinical needs must be indicated. You can find the request form on our website.

Request form for on demand bone grafts

Industrie Biomediche Insubri SA – IBI SA
Via Cantonale 67 CH-6805 Mezzovico-Vira Switzerland

Place..... Date.....

Re: Request offer for supply of on demand bone substitutes
Dear I.B.I. S/A

We hereby request an offer for the supply of n..... on demand bone substitutes (Custom Made Medical Devices according to....., made with your technology, intended for grafting purposes as necessary in our clinical case no. (mandatory)....., patient (insert only the name and surname initials).....for the use in (indicate brief clinical regeneration purpose):

.....
.....

providing to Industrie Biomediche Insubri SA:

- ☐ CT/CBCT scan (DICOM format);
- ☐ geometric shapes as contained in the mathematical .STL files attached (n.....files attached),
- ☐ stereolithographic file of the graft attached;

under the personal responsibility of the undersigned requesting doctor who hereby confirms the accuracy and conformity of intended use of such medical devices.

We ask you to kindly confirm the technical feasibility and to provide a commercial offer with the supply conditions (technical information, payment methods and delivery time).

Best Regards,

The requesting doctor, (name and sign) Dr.....

After the technical approval, IBI will send a form that must be completed in its entirety and then signed in order to proceed with the production order.

Producibility confirmation under doctor responsibility

Dear Dr.
REQUESTING DOCTOR
Structure, address

Mezzovico-Vira, DATA

Re: offer for bone substitutes tailored for case IBI-OD-ID NUMBER

Dear Dr. REQUESTING DOCTOR,
Upon your request submitted on DATE, we hereby confirm that your order has been taken in charge by our company and was assigned the unique case code IBI-OD-ID NUMBER.
Please always refer to this code in any further communication with us regarding your clinical case PATIENT'S ID.
We have successfully verified the technical feasibility of your request which can be accomplished using SmartBone, a bone substitute of bovine origin, equipped with all the required certifications in accordance with the law for human use, shaped accordingly to the geometry of the shape designed according to your indication on DATE, which will be kept in our archives in accordance with the law.

The conditions for the service are the following:

- economic conditions, time of delivery and payment, as in the attached offer n. NUMBER;
- the responsibility of the Requesting Doctor for the use of on demand bone substitutes;

We remain at your disposal for any further information.
Please use this document to confirm your acceptance, completing and signing the field below and returning this form to IBI.
Sincerely

FOR ACCEPTANCE OF:
- THE ECONOMICAL OFFER;
- THE CONDITIONS REPORTED HEREIN AND FOR THE ASSUMPTION OF RESPONSIBILITY BY THE APPLICANT DOCTOR CONFIRMING:
- THE ACCURACY AND COMPLIANCE OF THE GEOMETRIC SHAPES AND THEIR MATHEMATICAL FILES TO THE REQUIREMENTS OF THE CASE,
- THE FINAL USE OF THE ON DEMAND MEDICAL DEVICES SHAPED AS REQUESTED BY ME ON DATE.

Place, Date

The requesting Doctor

7.1.4. HOW TO SEND US THE DICOM FILE?

You can send the DICOM files using an online file-transferring platform.

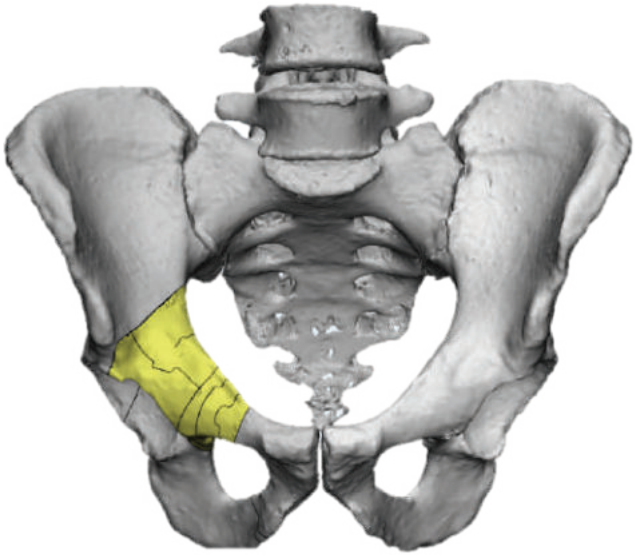
As soon as we get the file, we make an offer on the basis of the estimated graft volume. Once you accept the offer, we get in touch within 72h to start the design project of the custom made graft together, that will end only once you approve it.

After completing the design project, we send the responsibility documentation, stating that the project itself accomplishes your prescription. The documentation needs to be signed from you, then we confirm the order and the estimated shipment date.

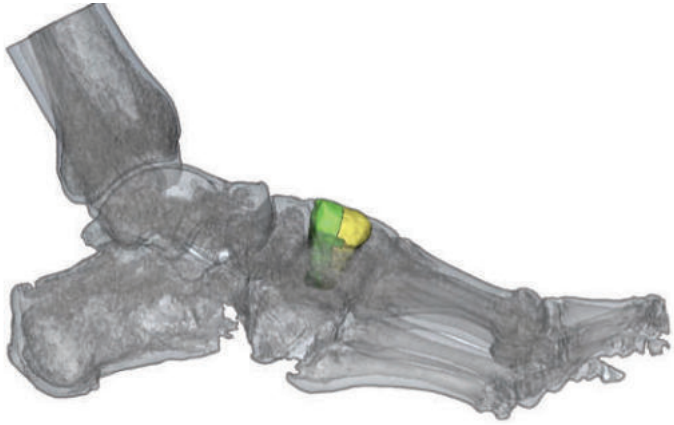
If it is easier for you, you can send the file on DVD together with your prescription to :

Industrie Biomediche Insubri SA – IBI SA
SmartBone® On Demand™ Customer Service
Via Cantonale 67
CH-6805 Mezzovico-Vira
Switzerland

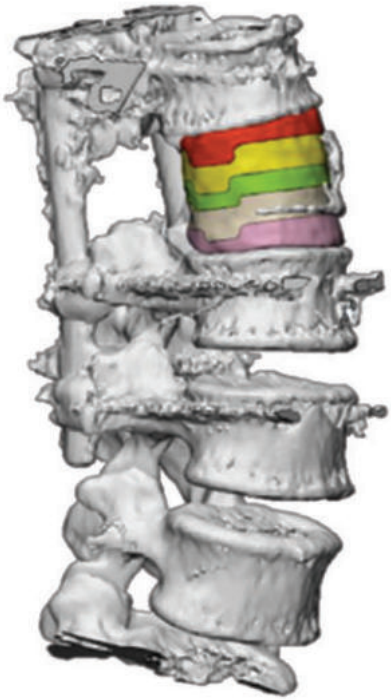
7.4. CLINICAL CASES DESIGN



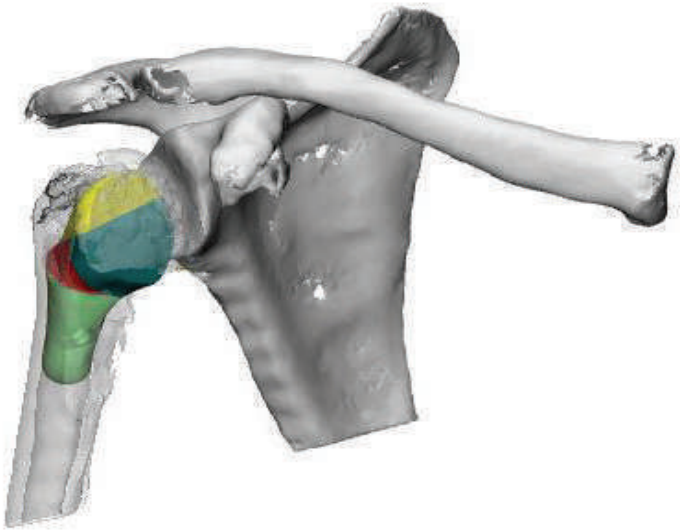
Oncological hip reconstruction with 14 grafts
Courtesy of Dr. C. Zoccali,
Istituto Regina Elena, Roma



Reconstruction of the 3rd cuneiform of the foot
Courtesy of Prof. Dr. D. A. Campanacci,
Azienda ospedaliera universitaria, Firenze

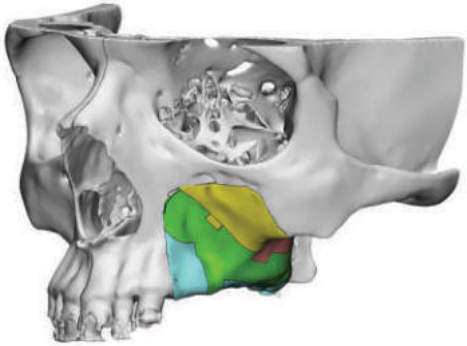


Replacement with vertebral fusion T12/L1
Courtesy of Prof. Dr. A. Gasbarrini, Istituto Ortopedico Rizzoli, Bologna

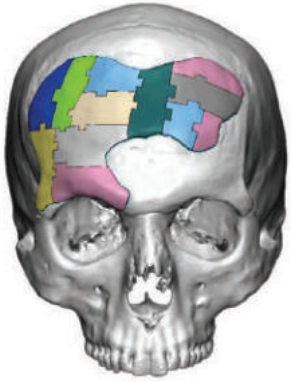


Bone intramedullary nail for head omerus reconstruction

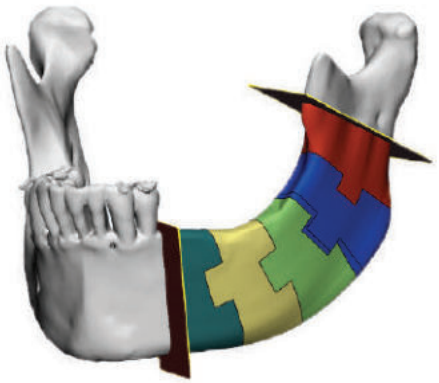
Oncological vertebrectomy
Courtesy of Prof. Dr. A. Gasbarrini, Istituto Ortopedico Rizzoli, Bologna



Zygomatic, crestal and hemipalatin reconstruction with 4 grafts
Courtesy of Prof. Dr. M. Innocenti / Dr. M. Squadrelli, Azienda Ospedaliera Universitaria, Firenze



Aesthetic cranial reconstruction with 12 grafts
Courtesy of Dr. E. Facciuto, Azienda Ospedaliera "A. CARDARELLI", Napoli



Hemimandibular reconstruction

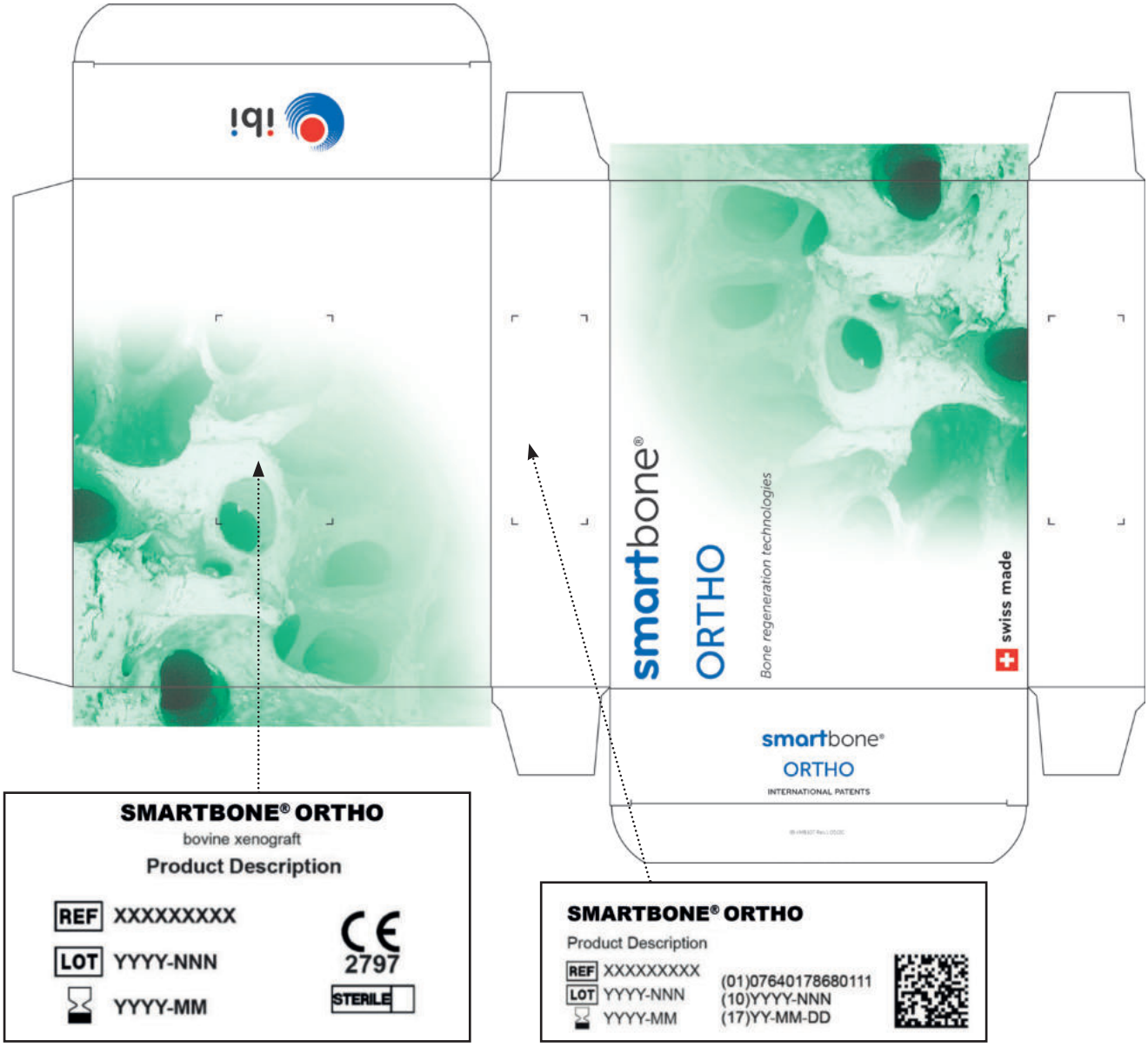

smartbone®
ORTHO
Bone regeneration technologies
swiss made
smartbone®
INTERNATIONAL PATENTS
ORTHO

8

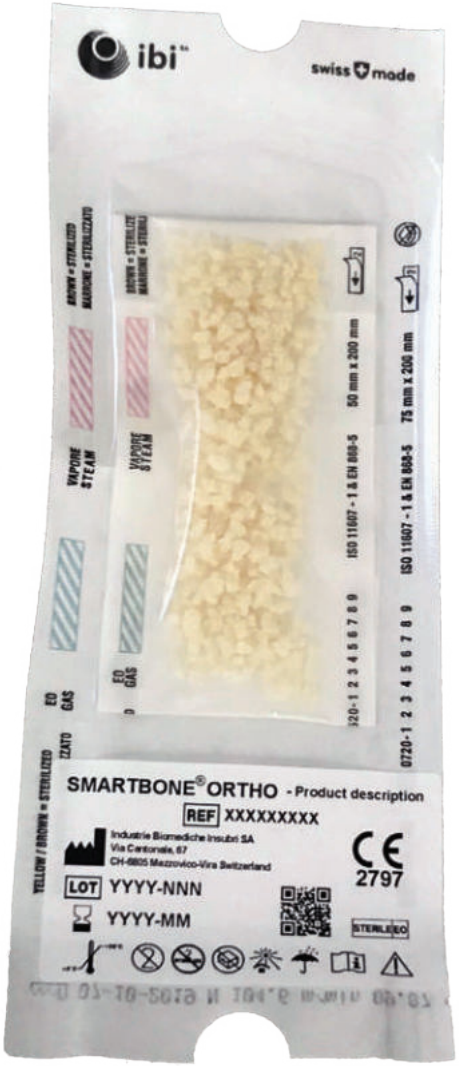
Technical information

EXTERNAL PACKAGING OF SMARTBONE® ORTHO

Hereunder you can find an example of a SmartBone® ORTHO 's labes, packagings and the description of the symbols used.



INTERNAL PACKAGING



SYMBOLS

Conformity Mark

Catalogue number

Legal Manufacturer

Sterilized using ethylene oxide

Use-by date

Batch code

Do not resterilize

Temperature range

Do not use if package is damaged

Do not re-use

Keep away from sunlight

Consult instructions for use

Keep dry

Caution

9

FAQs

IBI SA

- **What is IBI's "nationality"?**
  IBI is a Swiss company, headquartered in Canton Ticino, in the south-eastern corner of Switzerland.

- **Where are IBI products manufactured?**
  All IBI production is Swiss made, a guarantee of extreme excellence in terms of both quality and safety.

- **What are IBI's system certifications?**
  IBI is ISO13485:2016 certified.

TECHNICAL INFORMATION

- **What is SmartBone® ORTHO made of?**
  It's a composite material, made of a bovine derived mineral matrix, reinforced with biopolymers and collagen fragments of porcine origin.

- **What's the biological mechanism of osteointegration of a bone graft?**
  Bone generally has the ability to regenerate completely, but it requires a very small fracture space or some sort of scaffold to do so. Indeed, bone grafting is possible because bone tissue has the ability to regenerate completely if provided the space into which to grow, a bone graft.

  As native bone grows, it will generally replace the graft material completely, resulting in a fully integrated region of new bone. The biologic mechanisms that provide a rationale for bone grafting with composite grafts and xenografts are osteoconduction (guiding the reparative growth of the natural bone) and osteoinduction (encouraging undifferentiated cells to become active osteoblasts). Only few bone grafts ensure a complete remodeling, SmartBone® ORTHO is among these, together with autografts.

- **What are the top mechanical performances of SmartBone® ORTHO?**
  Breaking Stress of about 26MPa (av.)
  Elastic Modulus of about 1,2GPa (av.)
  Breaking torque under screw fixation (screw tenacity) >55Ncm (av.)

- **Is SmartBone® ORTHO an open-porous material?**
  Yes! SmartBone® ORTHO has an open interconnected porous structure.

- **How is SmartBone® ORTHO's microstructure?**
  SmartBone® ORTHO microstructure was specifically designed to mimic natural healthy human bone, in terms of composition and porosity.

- **Which is the expected (average) time of resorption of the biopolymers present within SmartBone® ORTHO?**
  They are degraded and resorbed in about 4-6 months, depending on grafted volumemeanwhile they degrade and get resorbed, new born bone is formed.

- **Is SmartBone® ORTHO hydrophilic?**
  Yes! Due to its composition SmartBone® ORTHO is extremely hydrophilic and can sustain a 38% w/w (av.) swelling in physiologic fluids. This feature allows the graft to quickly and massively absorb blood once *in situ*, hence sparkling a better and faster integration with the host tissue.

- **Which biopolymers are used?**
  We use biodegradable polymers, the same used in resorbable sutures.

- **Where does the bovine derived mineral matrix of SmartBone® ORTHO come from?**
  We supply our production with bovine derived tissues directly from fully certified companies in New Zealand, a "BSE negligible risk Country" (formerly known as "BSE free Country").

  We control all our supply chain, according to the most strict norms and highest quality standards, including those of ISO 22442.

- **How is SmartBone® ORTHO produced?**
  IBI applies a proprietary process to produce SmartBone® ORTHO.

- **Can the biomaterial be mixed with a saline solution?**
  ABSOLUTELY NOT, the saline solution extracts the proteins from the polymeric reinforcement surface, compromising performances of the graft and thus the final success!

- **Can the biomaterial be added with autologous bone?**
  Clinical experience shows that in particular cases, such as large breast augmentations, the use of patient bone improves the integration process, and it is hence recommended.

- **Can the biomaterial be added with cadaveric/donor bone?**
  The starting material has all the characteristics to achieve an excellent integration and a complete bone remodeling, the insertion of a cadaveric bone unnecessarily increases risk factors.

- **Can the biomaterial be added with synthetic bone (bioglasses, phosphate tricalcium, hydroxyapatite, polymers, collagen sponges, etc.)?**
  The starting material has all the characteristics to achieve by itself an excellent integration and a complete bone remodeling, the insertion of a synthetic bone unnecessarily increases risk factors.

- **Can the biomaterial be inserted into a syringe to increase perfusion and wettability?**
  The material has a very high wettability and hydrophilicity, does not require any kind of treatment. In case of use of larger blocks, or when looking for improved granulates handling, it is recommended to mix SmartBone® ORTHO with patient's blood.

- **Do I need to use a membrane?**
  The use of the membrane is recommended in oral surgery but not mandatory in orthopedics.

- **Once the vial or envelope has been opened, can I close it again, re-sterilise it and, if necessary, within what period of time should I use it?**
  Once the primary packaging has been opened (in sterile surgerical environment), the material must be used immediately on a single patient. The surplus material must be disposed of according to IFU. SmartBone® ORTHO IS SINGLE USE.

- **Why is SmartBone® ORTHO single use?**
  SmartBone® ORTHO is provided, in its intact packaging, as a sterile medical device; once opened, it must be used immediately. Storage after opening does NOT ensure safety! SmartBone® ORTHO is, hence, single use.

- **Can I keep the material in the fridge?**
  The material must be stored according to the instructions on the labels, therefore away from light or heat sources, in a dry place and between +2 and +25 °C.

- **The packaging arrived damaged. What should I do?**
  DO NOT USE THE PRODUCT! Contact your dealer immediately.

- **There were no IFU and/or adhesive label inside the box, what should I do?**
  DO NOT USE THE PRODUCT! Contact your dealer immediately.

SMARTBONE® ORTHO MECHANISM OF ACTION

- **When does osteoconduction occur in bone grafting?**
  Osteoconduction occurs when the bone graft material serves as a scaffold for new bone growth that is perpetuated by the native bone. Osteoblasts from the margin of the defect, that is being grafted, utilize the bone graft material as a framework upon which to spread and generate new bone. In the very least, a bone graft material should be osteoconductive.

- **Is SmartBone® ORTHO osteoconductive?**
  YES! Histological analyses performed during *in vivo* and clinical studies confirmed that SmartBone® ORTHO supports the ingrowth of stromal stem cells and osteoblasts, which then spread and colonize it, hence generating new bone.

- **How does osteoinduction occur?**
  Osteoinduction involves the stimulation of osteoprogenitor cells to differentiate into osteoblasts that then begin new bone formation.

- **Is SmartBone® ORTHO osteoinductive?**
  YES! SmartBone is a bone graft material that is both osteoconductive and osteoinductive: histological analyses performed during *in vitro* and *in vivo* and clinical studies confirmed that does not only serve as a scaffold for currently existing osteoblasts but will also triggers the formation of new osteoblasts, theoretically promoting faster integration of the graft.

- **What is SmartBone® ORTHO's osteointegration dynamic?**
  The cellular response to SmartBone® ORTHO graft can be described as a progressive neoformation of healthy bone, which occurs alongside the resorption of the graft: both osteoconductive and osteoinductive processes are involved.

- **Which is the timeframe for complete osteointegration of SmartBone® ORTHO?**
  SmartBone® ORTHO graft integration can be described as a progressive neoformation of healthy bone, which occurs alongside the reabsorbtion of the graft, involving both osteoconductive and osteoinductive processes on a 16-18 months time window (depending on grafted volume, anatomical position, patient age, sex, health conditions, *etc*).

- **Which type of bone is being formed after grafting with SmartBone® ORTHO?**
  The osteointegration of SmartBone leads to the formation of type II and type III bone.

- **What type of bone graft exists?**
  Bone grafts may be autologous (bone harvested from the patient's own body, often from the iliac crest), allograft (cadaveric bone usually obtained from a bone bank), or synthetic (often made of hydroxyapatite or other naturally occurring and biocompatible substances) with similar mechanical properties to bone

- **Which type of bone graft is SmartBone® ORTHO?**
  SmartBone® ORTHO is a composite bone graft made of a bovine derived mineral matrix, reinforced with biopolymers and collagen fragments: it can hence be categorized as a composite xeno-synthetic graft.

10

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