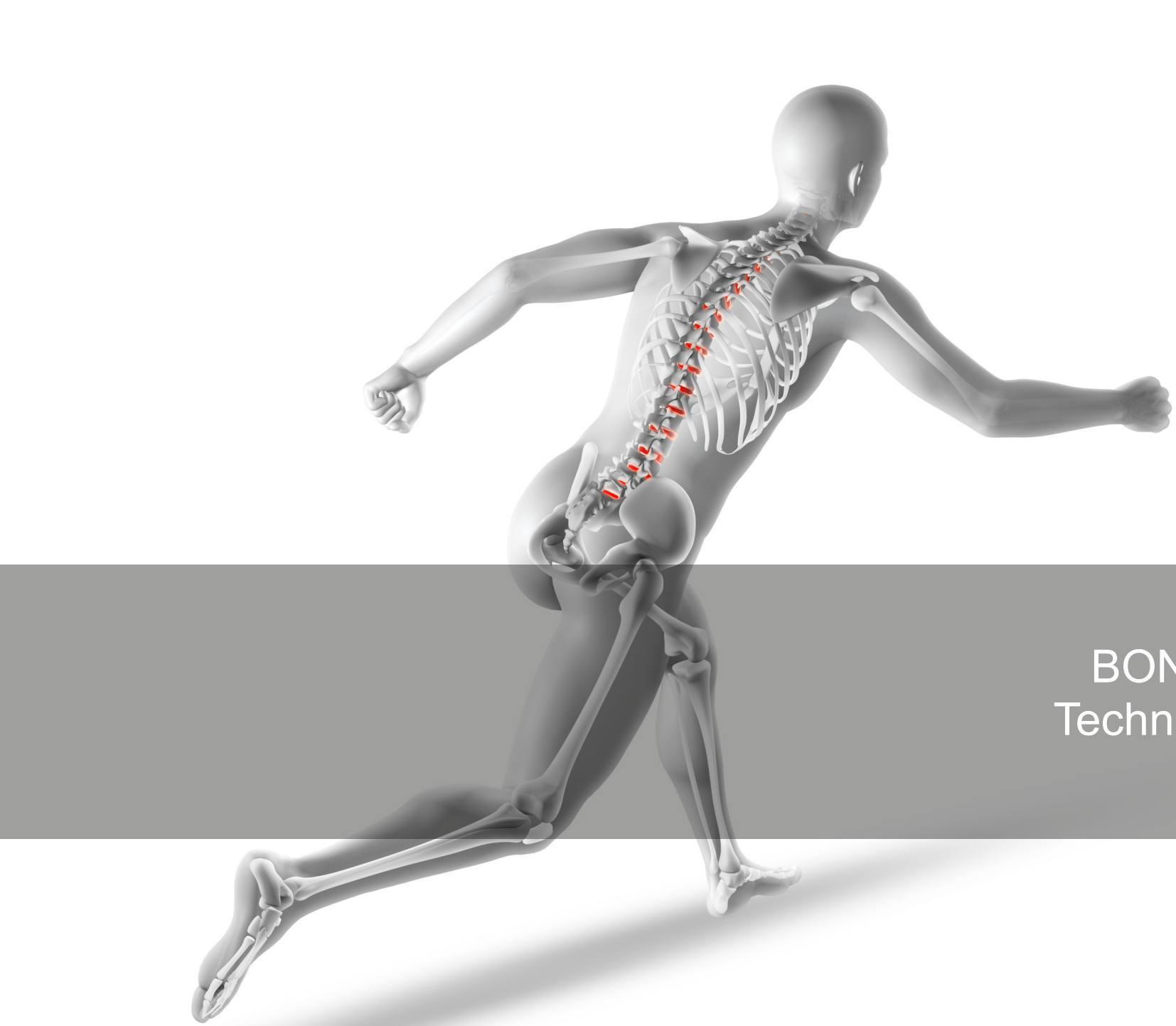
MAGGI Biotechnology



BONE TISSUES
Technical information

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DIFFERENCES BETWEEN BONE TISSUES AND BIOMATERIALS

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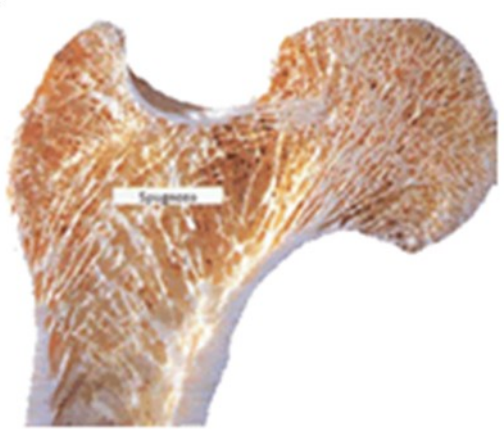

ELEMENT	BONE TISSUE	BIOMATERIAL
Mineral scaffold	yes	yes
Collagen	yes	no
Growth factors	yes	no
Load resistance	yes	no
Total physiological resorption	yes	no
Allotropic form of the apatite crystal	no	yes
Possibility to modify the mechanical characteristics	yes	no

SCAFFOLD

The scaffold is made up of the bone mineral component.

With experience it is possible to obtain a scaffold from breeds
animals such as horses, cattle and pigs that are completely similar to humans.

Inside the femur there are bone sections in certain anatomical points whose
trabeccular characteristics are superimposable to those of humans.

The quality of the bone does not depend on the genetic breed of the horse but
on the age

The horses used come from animals intended for human consumption. In Italy,
most of the equines come from eastern countries. These animals
they have serious health deficiencies and not infrequently end up in
butchering of riding or racing animals that may present
very high concentrations of prohibited drugs such as phenylbutazone etc.

In collaboration with the National Institute of Health which issues ours
CE certified we have decided to use only horses from Spain and slaughtered in
slaughterhouses that serve the large distribution
constantly carries out analyzes on meat

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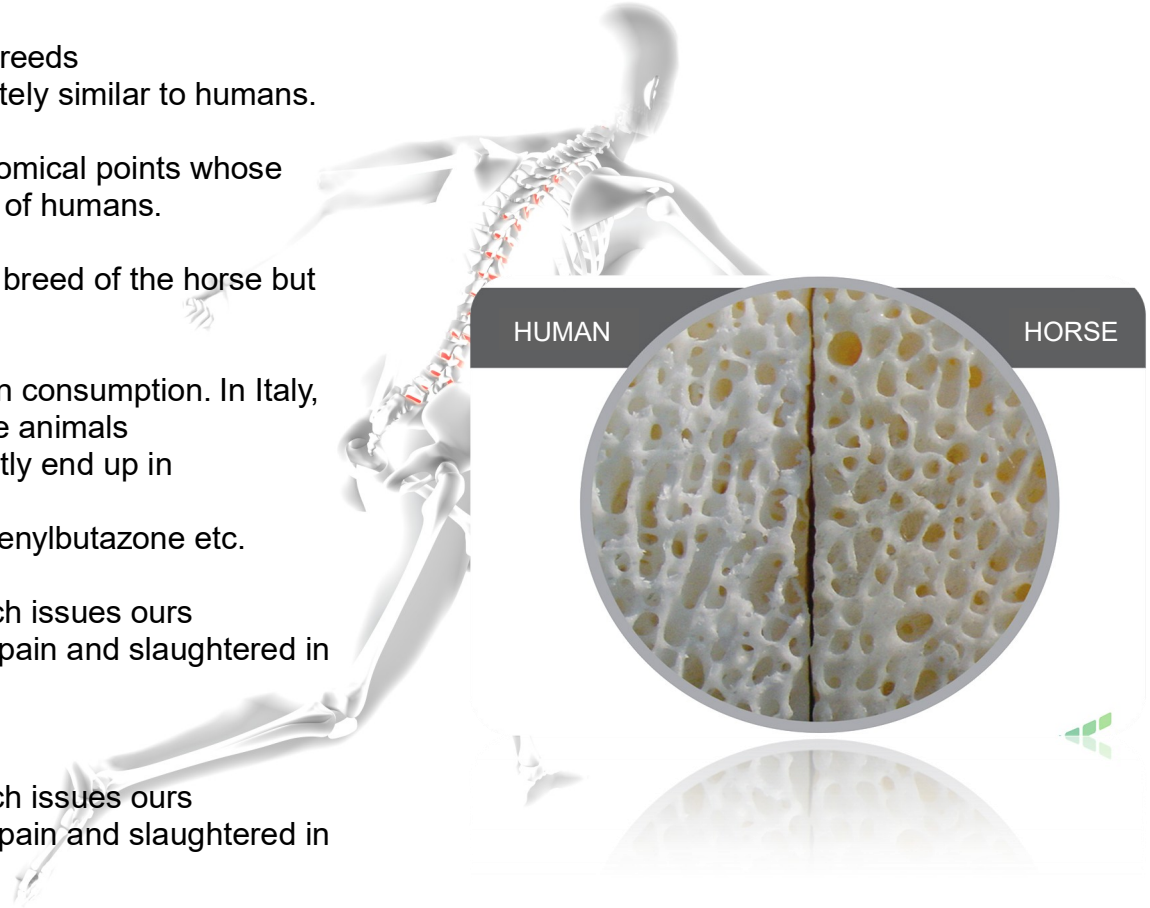


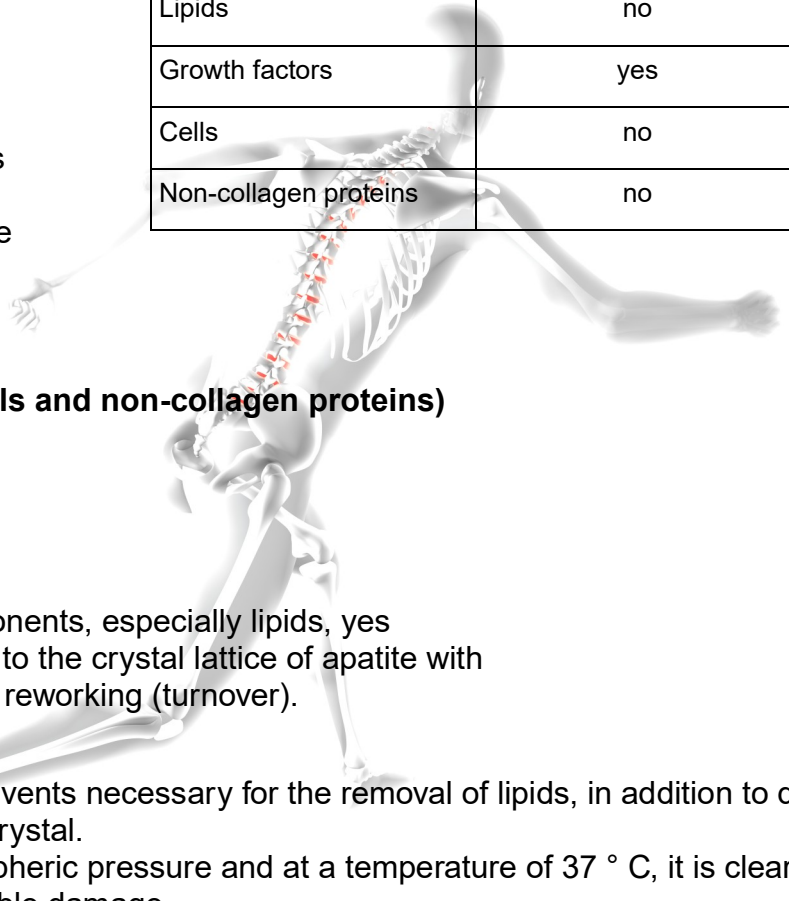
THE DEANTIGENIZATION SYSTEM

Man and horse belong to 2 different genetic species. It is not possible to fully transfer the tissue from one species to another without an intervention of the immune system to defend the entry into the body of antigens with a rejection response.

The deantigenization systems have the function of eliminating unnecessary components present in the bone tissue and harmful.

The system developed by Maggi srl was born in 1995 and has shown great reliability over time. In its non-original form it is used by several companies. The system takes into account the following criteria:

ELEMENT	COMPATIBILITY	PERCENTAGE
Bone mineral	yes	100%
Collagen	yes	98%
Lipids	no	0%
Growth factors	yes	100%
Cells	no	0%
Non-collagen proteins	no	0%



Complete elimination of antigen components (lipids - cells and non-collagen proteins)

Maintenance of collagen and growth factors

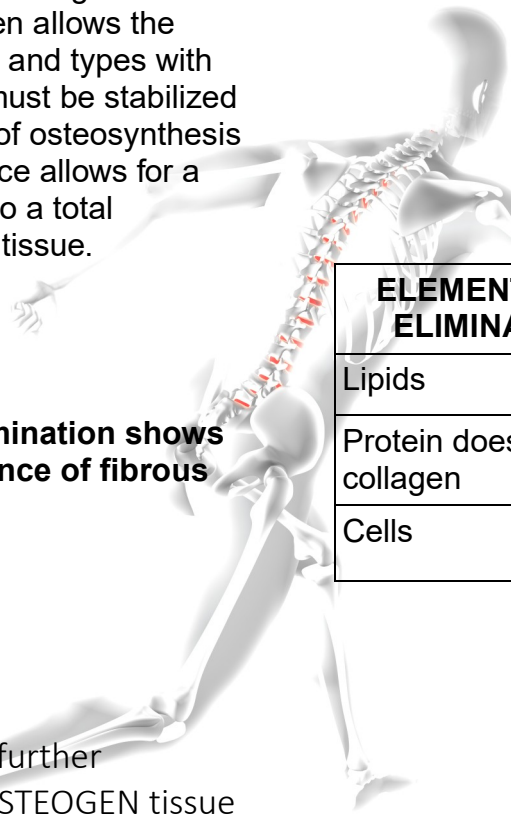
Intact mineral structure in non-allotropic form

It often happens that in order to eliminate unnecessary components, especially lipids, yes damage the bone structure by creating irreparable alterations to the crystal lattice of apatite with consequent modification of the physiological systems of bone reworking (turnover).

The high temperatures that are often used to eliminate the solvents necessary for the removal of lipids, in addition to damaging collagen and growth factors, promote an allotropic form of the apatite crystal.
Taking into account that mammalian bone is formed at atmospheric pressure and at a temperature of 37 ° C, it is clear how even not too high temperatures above 100 ° C create irreparable damage.

THE DEANTIGENIZATION SYSTEM

The system, operating at a maximum of 37 ° C, does not induce any substantial modification of the crystal lattice, preserving both the growth factors and the collagen natural. The maintenance of collagen allows the dissection of the tissue in the form of blocks of various sizes and types with high resistance to load and fracture. This material can and must be stabilized to structures skeletal residues to be regenerated by means of osteosynthesis without suffer any structural damage. The high load resistance allows for a immediate functional rehabilitation that over time will turn into a total regeneration of bone tissue without the presence of osteoid tissue.



ELEMENT TO ELIMINATE	SUBSTANCE DEANTIGENANT	TEMPERATURE
Lipids	Enzyme	37°C
Protein does not collagen	Enzyme	37°C
Cells	Hydrogen peroxide	18°C

Osteoid tissue is a regenerate that on histological examination shows residues of integrated "biomaterial" without the presence of fibrous but not viable tissue.

The bone material obtained with these systems allows further manipulations such as transformation into ELASTA or OSTEOGEN tissue adapt the product to different types of reconstructive surgery with characteristics superior to common bone that occurs in nature, changing both its mechanics and resorption times.

OSTEOINTEGRATION AND REGENERATION

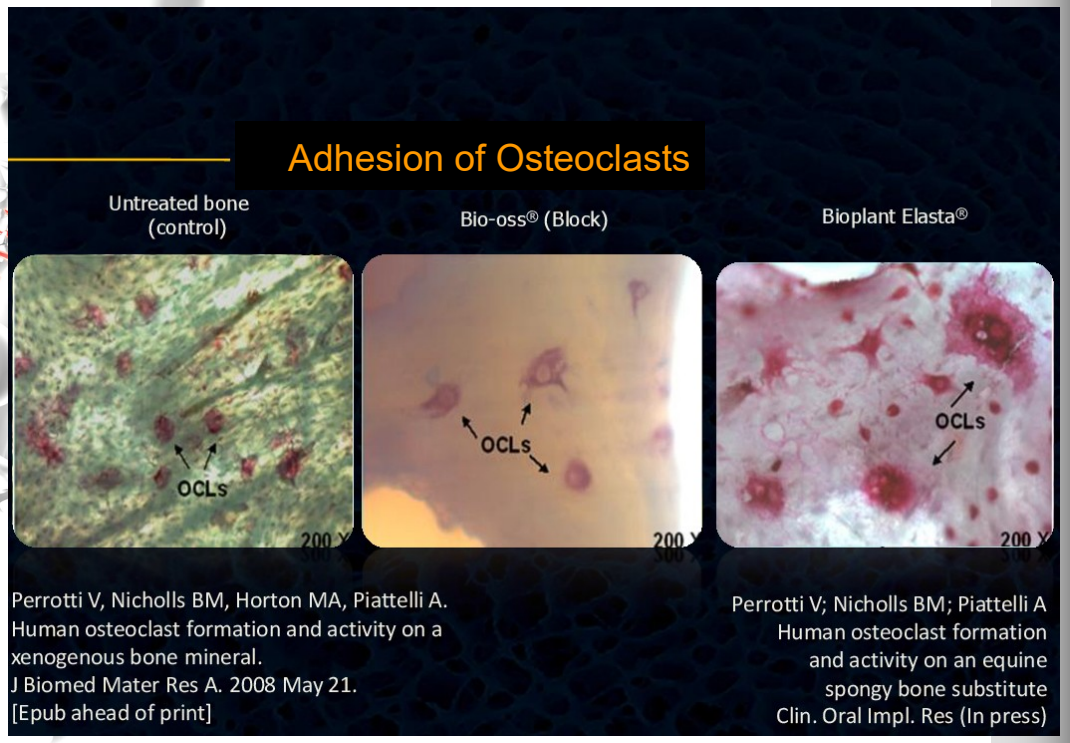
The process of repairing a bone lesion using material external to the body goes through 2 phases.

PHASE 1: inclusion of the material in the newly formed bone matrix

PHASE 2: total replacement of the included material with neo bone.

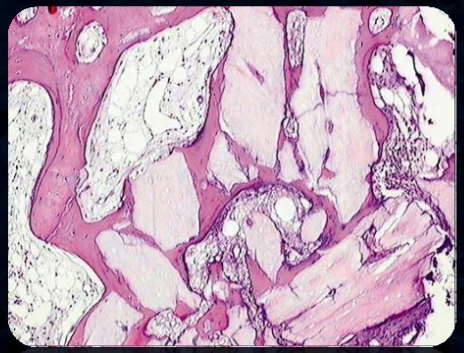
In PHASE 1 the material is required only the biocompatibility, so it will behave like a dental implant in titanium, the newly formed endogenous bone will encompass it without the formation of reactive fibrous tissue.

PHASE 2 in the case of using a material of bone origin can take place in whole or in part depending on the deantigenization method used and any allotropic modifications made to the grid crystalline of bone apatite.

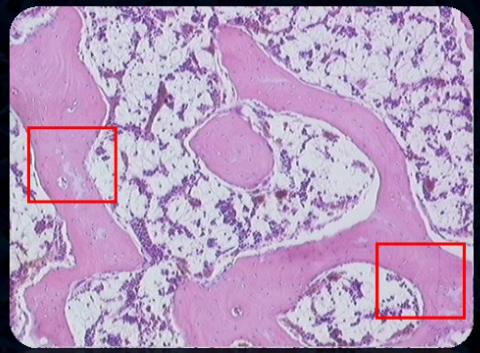


OSTEOINTEGRATION AND REGENERATION

Enzymatic Deantigenization

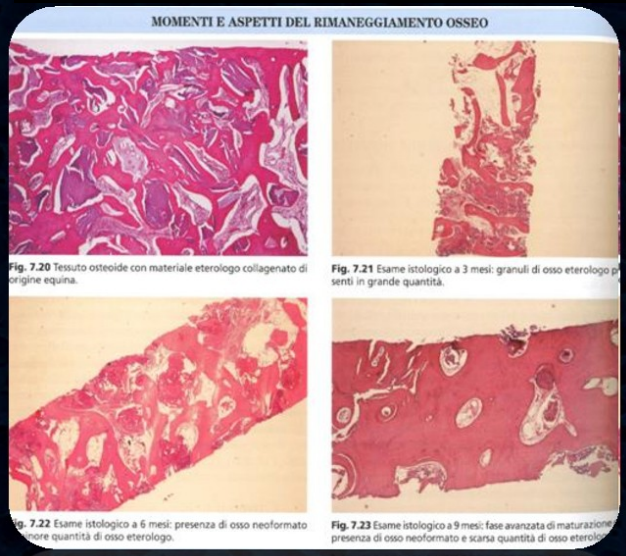


Cortical and spongy bone, t = 1 month



Cortical and spongy bone, t = 1 year

Remodeling of osteoid tissue



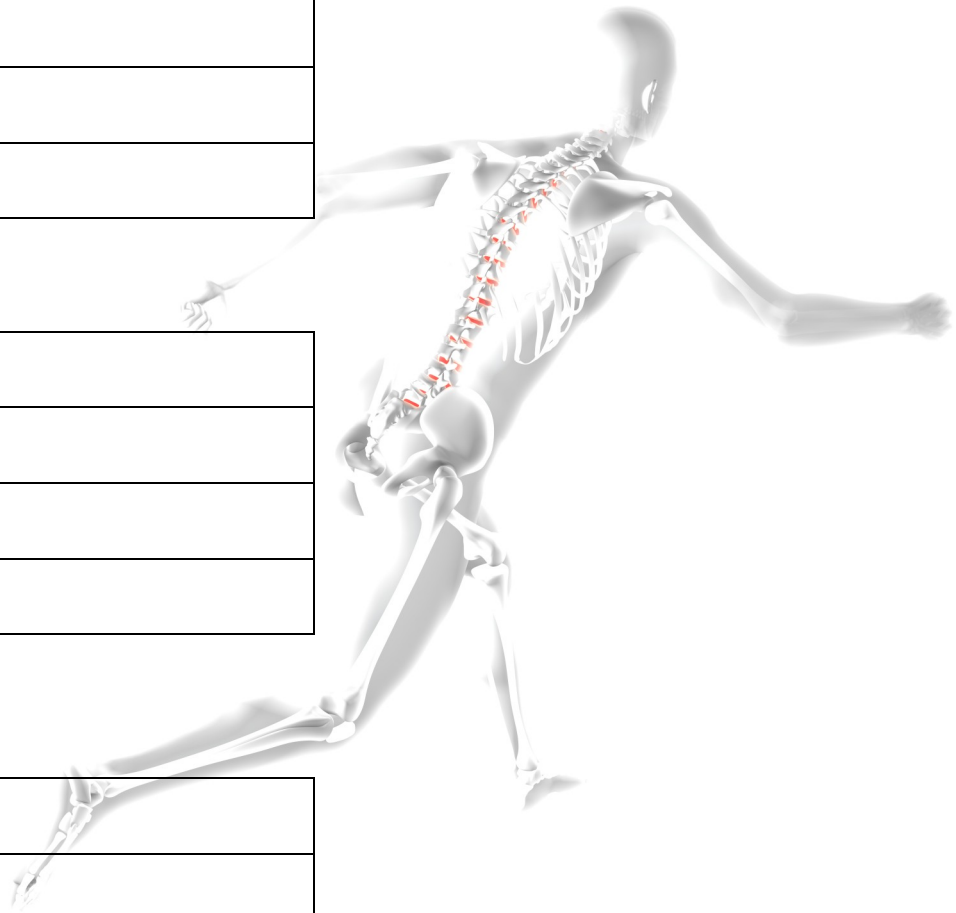
BONE PRODUCTS

MAGGI Biotechnology

BIOPLANT
High load-bearing bone mineral scaffold
Natural bone collagen
Angiogenic and osteogenic growth factors

BIOPLANT ELASTA
Demineralized bone mineral scaffold
Trabeccolare natural bone collagen
Angiogenic and osteogenic growth factors

OSTEOGEN
Weakened bone mineral scaffold



BIOPLANT

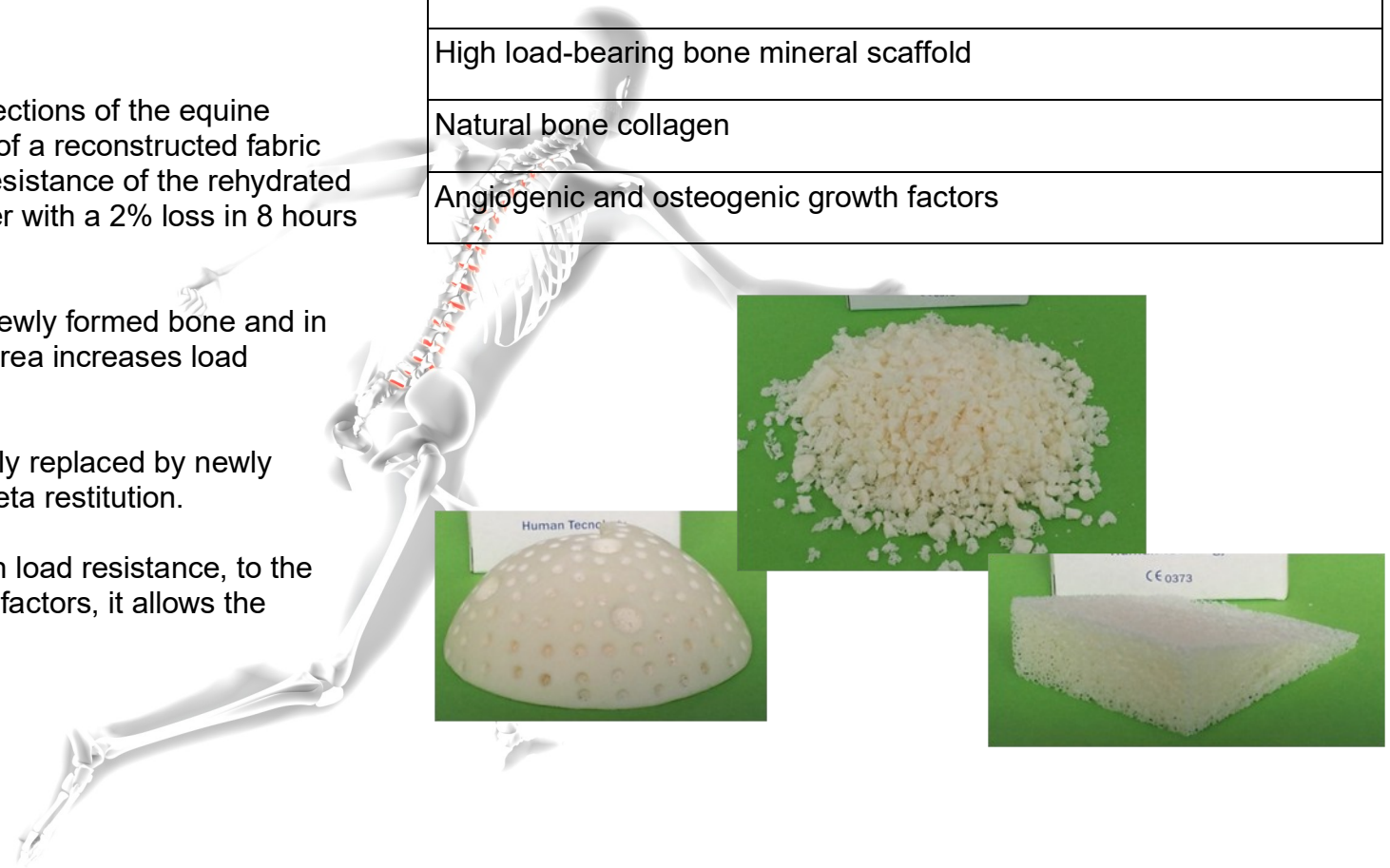
BIOPLANT
High load-bearing bone mineral scaffold
Natural bone collagen
Angiogenic and osteogenic growth factors

The tissue is obtained from intact sections of the equine femur. It is therefore not a question of a reconstructed fabric but of the whole natural. The load resistance of the rehydrated fabric is 350 kg. per cubic centimeter with a 2% loss in 8 hours following.

The material is integrated into the newly formed bone and in the following 3 months the grafted area increases load resistance and bone density.

Within 12 months, the tissue is totally replaced by newly formed endogenous bone with copleta restitution.

Thanks to the characteristics of high load resistance, to the presence of angiogenic-osteogenic factors, it allows the immediate functional rehabilitation.



BIOPLANT ELASTA

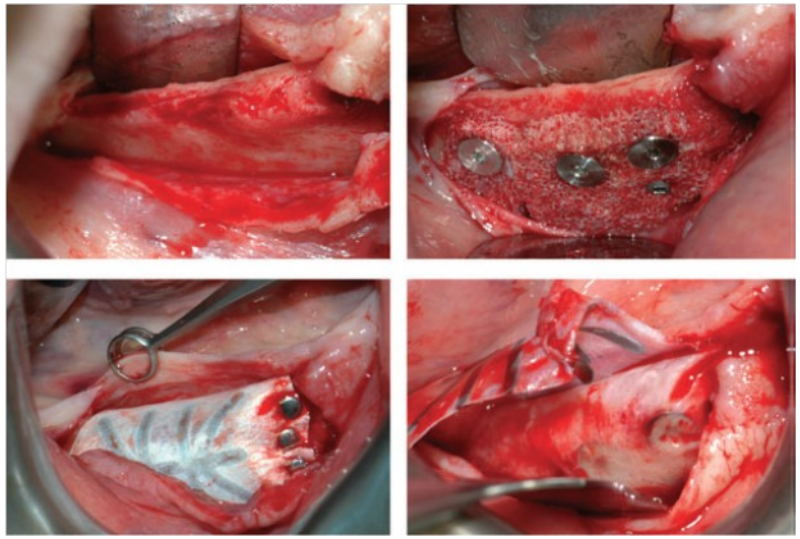
This type of fabric does not exist in nature and falls into the category of "engineered" fabrics.

The BIOPLANT bone tissue undergoes a partial demineralization process (30% residual mineral) with exposure of collagen fiber and growth factors.

BIOPLANT ELASTA bone tissue after rehydration becomes flexible and adapts to any skeletal conformation.

Thanks to the presence of WGF angiogenic factors, the correct trabeccular architecture and the reduced amount of bone apatite present, the preform is rapidly replaced by endogenous bone in a single phase of bone turnover.

BIOPLANT ELASTA
Demineralized bone mineral scaffold
Trabeccolare natural bone collagen
Angiogenic and osteogenic growth factors



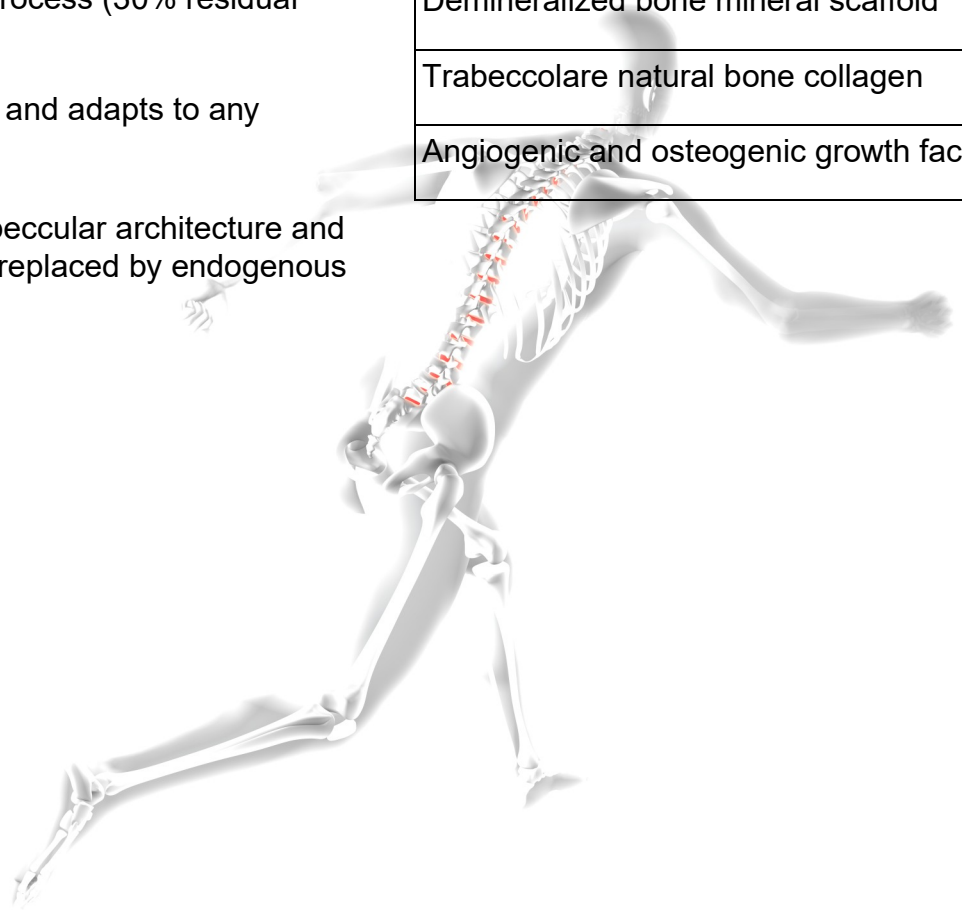


Figure 1 (*A*) A thin (3 mm) alveolar ridge is present. (*B*) The equine bone layer has been fixed, with osteosynthesis screws, as an onlayto the alveolar bone. (*C*) The onlay graft has been covered with a titanium-reinforced expanded polytetrafluoroethylene membrane.(*D*) The alveolar ridge 6 months after insertion of the implanted material, showing an increase of the ridge width (37 mm).

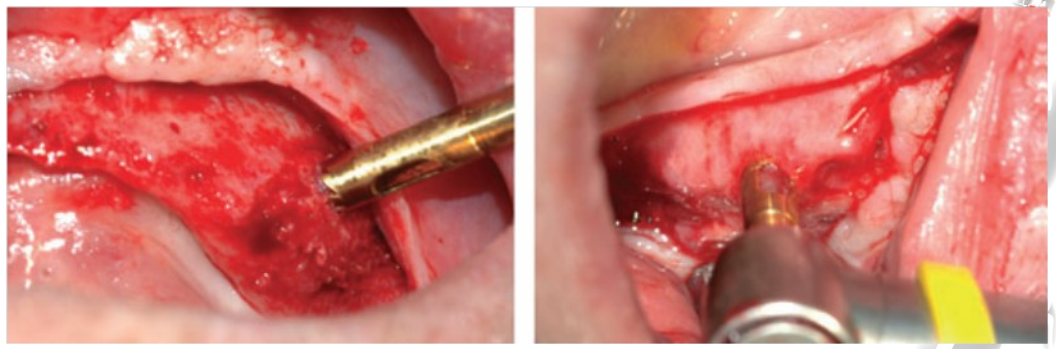


Figure 2 The bone cores were retrieved with a 3.5 ¥ 10-mm-diameter trephine in a vestibulolingual direction, (A) in the area immediately behind the graft (control) and (B) in the area where the grafting procedure had been performed (test).

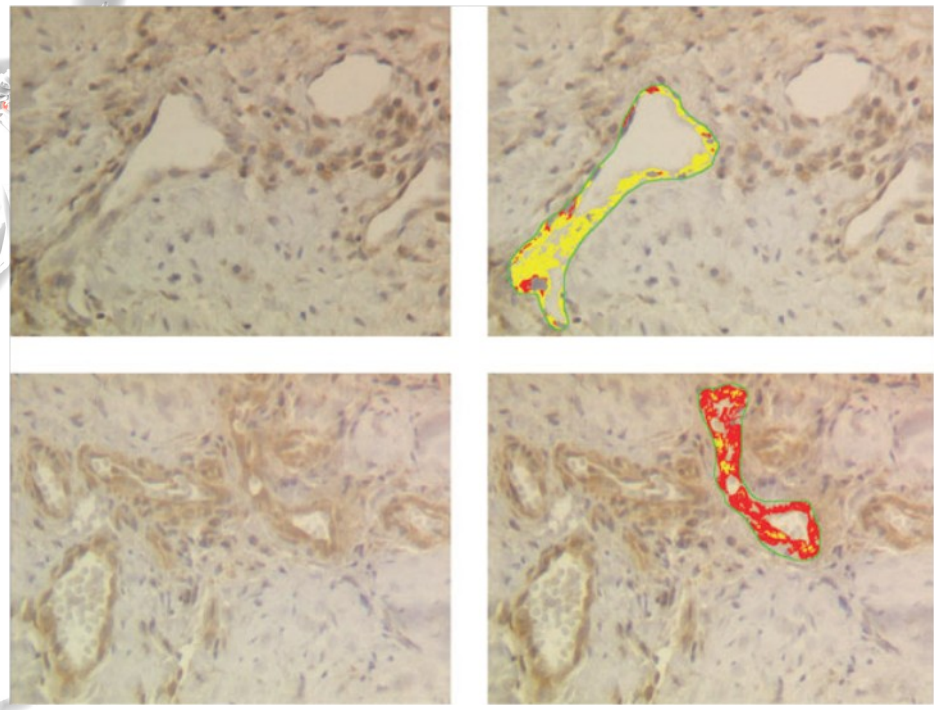


Figure 3 (*A*) Vascular endothelial growth factor (VEGF) showing a low positive staining of endothelial cells lining the blood vessels. (*B*) Low intensity (+) of VEGF expression. (*C*) VEGF high positive staining of endothelial cells lining the blood vessels. (*D*) High intensity (++) of VEGF expression. VEGF staining (alkaline phosphatase anti-alkaline phosphatase) 30¥.

OSTEOGEN

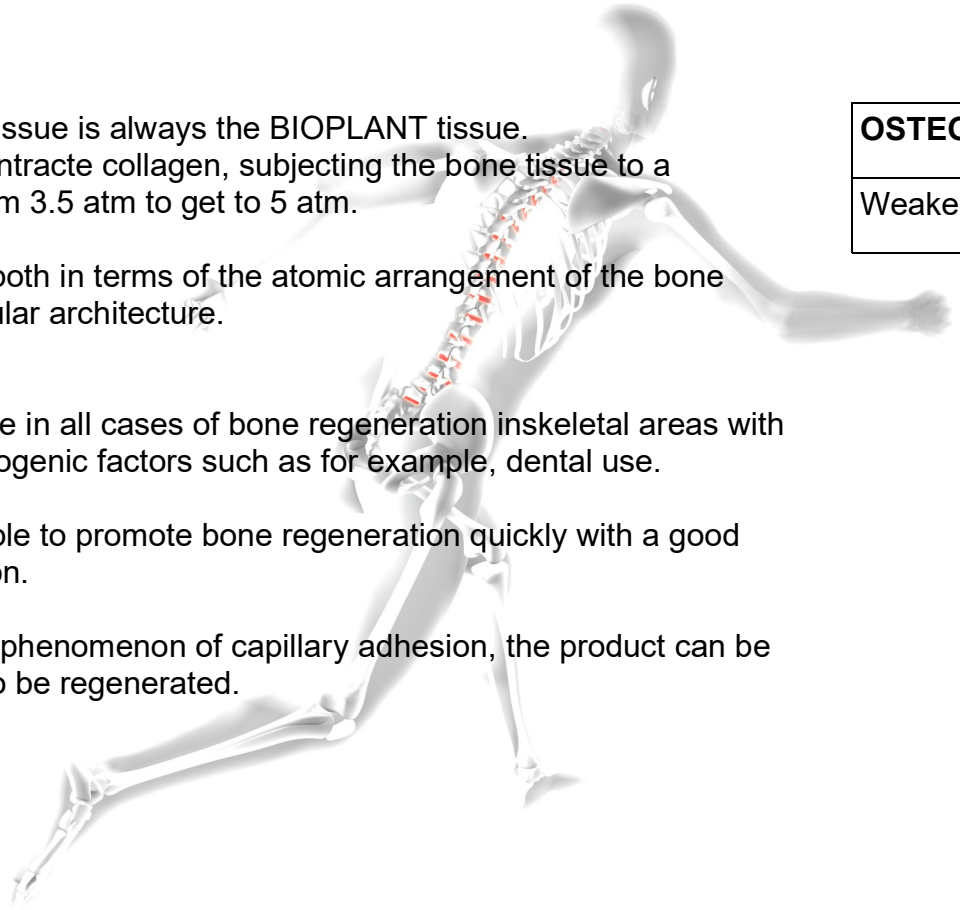
The starting point for this modified bone tissue is always the BIOPLANT tissue.
With a particular equipment, the fiber is entracte collagen, subjecting the bone tissue to a pressure to rise in 30 minutes starting from 3.5 atm to get to 5 atm.

The final result is an intact bone mineral both in terms of the atomic arrangement of the bone apatite crystal and in terms of its trabeccular architecture.

This type of material is particularly suitable in all cases of bone regeneration inskeletal areas with low cellular activity and low levels of osteogenic factors such as for example, dental use.

Thanks to the weakened structure, it is able to promote bone regeneration quickly with a good quality regenerate with early mineralization.

Thanks to its high hygroscopicity and the phenomenon of capillary adhesion, the product can be easily worked and positioned in the site to be regenerated.



OSTEOGEN
Weakened bone mineral scaffold

RAW MATERIAL SELECTION AND GROWTH FACTORS

The biggest problem in the use of preparations containing growth factors is represented by the uncertainty in the percentage of the same within the product.
As we can see from the table on the side of the lots different of the same product have very different levels in percentage of the components morphogenic.
In preparations of human origin this is due to the age of the multi-organ donor corpses that can range from the child to the elderly

For the production of bone tissues Maggi srl uses only horses of origin Spanish therefore safe, all slaughtered at the same age, therefore with constant and certain levels of growth factors and a single genetic breed selected according to the constant level of osteogenic and angiogenic components.

Table 4. Concentrations of BMP-2 and BMP-7 Assayed From Extracts From Various DBM Formulations

	Lot No. 1 ng/g DBM	Lot No. 2 ng/g DBM	Lot No. 3 ng/g DBM	CV
ELISA analysis of BMP-2 ng/g DBM				
Allomatrix® C bone graft putty[7]	97.5	30.1	28.2	76.01%
DBX® DBM putty[8]	51.4	40.9	36.6	17.72%
DynaGraft® II osteoinductive gel[9]	49.2	38.8	25.4	31.56%
DynaGraft® II osteoinductive putty[11]	39.5	30.8	29.5	16.34%
Grafton® gel[12]	85.6	33.6	20.2	74.35%
Grafton® putty[13]	61.3	51.9	29.0	35.05%
Grafton® crunch (written communication, February 2004)	40.8	30.5	29.0	19.21%
InterGro® DBM putty (written communication, November 2003)[14]	89.7	50.5	33.0	50.29%
Osteofil® allograft paste[15]	120.6	48.4	28.4	73.71%
BMP-2, lots: $F = 15.12$, $P < 0.0002$; products: $F = 1.29$, NS	70.6	39.5	28.8	
ELISA analysis of BMP-7 ng/g DBM				
Allomatrix® C bone graft putty[7]	118.8	67.8	66.3	35.45%
DBX® DBM putty[8]	179.7	94.1	90.9	41.43%
DynaGraft® II osteoinductive gel[9]	188.9	95.6	54.2	61.11%
DynaGraft® II osteoinductive putty[11]	226.8	67.9	55.0	82.08%
Grafton® gel[12]	70.5	69.9	60.3	8.56%
Grafton® putty[13]	84.7	80.0	78.6	3.95%
Grafton® crunch (written communication, February 2004)	73.5	68.1	66.9	5.06%
InterGro® DBM putty (written communication, November 2003)[14]	77.5	72.7	72.7	3.71%
Osteofil® allograft paste[15]	81.6	68.1	66.5	11.51%
BMP-7, lots: $F = 6.43$, $P < 0.01$; products: $F = 1.19$ NS	122.4	76.0	67.9	

NS indicates not significant, CV, coefficient of variation.

BIOPLANT

BIOPLANT ELASTA

OSTEOGEN

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