Use of serum albumin coated allograft in bone replacement

January 2018

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What is BoneAlbumin?
It is less known: albumin is a key for bone formation

Albumin is a bone protein!
- 30% of circulating serum albumin is of bone origin
- Albumin is the first protein secreted by regenerating osteoblasts
- Albumin is required for stem cells to proliferate in culture
- Normal allografts do not contain albumin as cleaning and preserving of bone eliminates the highly water soluble albumin content
- Simple replenishment of albumin improves allograft function

BoneAlbumin
- OrthoSera’s patent covered impregnation technology is applied on human allografts
- BoneAlbumin has scientific, clinical and market traction

In vitro studies: a summary

Albumin itself, in high concentrations (>10% weight) provides a proliferative milieu for BMSCs on bone grafts.

Mode of action: activates the patient’s own stem cells’ proliferation on implanted allografts

In vitro: the problem of normal allograft is solved with albumin coating

Bone marrow derived stem cells (BMSCs) proliferate

Human albumin effect on BMSCs

Bone marrow derived stem cells (BMSCs) \textit{proliferate}

<table>
<thead>
<tr>
<th>Condition</th>
<th>3rd day</th>
<th>18th day</th>
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</thead>
<tbody>
<tr>
<td>Uncoated control</td>
<td>183</td>
<td>1</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>237</td>
<td>23</td>
</tr>
<tr>
<td>Collagen I</td>
<td>890</td>
<td>203</td>
</tr>
<tr>
<td>Human Albumin</td>
<td>1,659</td>
<td>2,083</td>
</tr>
</tbody>
</table>


Animal models: a summary

Albumin coating resulted in much \textit{faster bone healing} and \textit{stronger bone} than without albumin.
Animal study 1. – 3D microCT of rat femur
Three representative cases: faster bone healing

Uncoated graft

Albunin coated graft


Animal st. 2. – ex vivo microCT of rat calvaria
Three representative images: stronger bone

A

<table>
<thead>
<tr>
<th></th>
<th>Worst</th>
<th>Median</th>
<th>Best</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empty</td>
<td>![Empty Image]</td>
<td>![Median Image]</td>
<td>![Best Image]</td>
</tr>
<tr>
<td>DBM</td>
<td>![DBM Image]</td>
<td>![DBM Image]</td>
<td>![DBM Image]</td>
</tr>
<tr>
<td>DBM + Albumin</td>
<td>![DBM Albumin Image]</td>
<td>![DBM Albumin Image]</td>
<td>![DBM Albumin Image]</td>
</tr>
</tbody>
</table>

B

![Bone Volume Graph]

**DBM = Demineralized Bone Matrix allograft**

BoneAlbumin science summary
January 2018

Orthopedic clinical studies: a summary

BoneAlbumin resulted in faster bone healing than with autograft.

BoneAlbumin turns into living bone tissue leading to complete tissue healing.

Donor site pain is significantly lower with BoneAlbumin.

1. First in human: Hip and knee prosthesis revision study

Representative SPECT-CT (labeling active osteoblasts) of a structural tibia at 1 year follow-up: osteoblast activity is apparent in the albumin coated allograft.

- Aseptic revision of hip and knee prosthesis
- Single group (no control group), variable shape and size of bone loss
- Individually ordered structural bone grafts
- Multiple surgeons and sites
- Started with 10 patients, now over 30

Intraoperative pictures of an albumin-coated structural tibia allograft at revision surgery at 19 months – triggered by minor trauma (household injury). Parts of the allograft are bleeding, a clear sign of living tissue. The overall structure is suitable to support a revised prosthesis without any further fixation.


2. Double-blind controlled bone-tendon-bone harvest site filling study: the setup

- Very common sports (football, ski) surgery indication: ACL anterior cruciate ligament
- Young, healthy patient population
- Uniform shape and size of bone void
- Not a life-threatening indication, elective operation
- Allows a double-blind, well-controlled study design

Control arm:
- Patella: hematome
- Tibia: available autograft (standard of care)

Experimental:
- Patella: BoneAlbumin
- Tibia: available autograft mixed with BoneAlbumin

<table>
<thead>
<tr>
<th>OP</th>
<th>Physical examination</th>
<th>Physical + CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>start</td>
<td>6 weeks</td>
<td>6 months</td>
</tr>
</tbody>
</table>

2. Bone-tendon-bone harvest site filling study

There is a significantly lower remaining defect size with a significantly denser remodeled bone in the BoneAlbumin group, indicating a nearly complete tissue healing.


Pain at the donor site was significantly lower in the treatment group both at kneeling and crouching, while standing pain was negligible in both groups.

Dental clinical studies: a summary

BoneAlbumin has the same easy application as other grafts.

BoneAlbumin granulate filling resulted in faster bone regeneration than xenografts.

After BoneAlbumin what remains is not just some ‘hard tissue’ – like with xenografts – but true bone which remodels and ages naturally during the course of the patient’s lifetime.

Post-operative pain is significantly lower with BoneAlbumin than with xenografts or even than without treatment.

Application of BoneAlbumin in oral implantology
1. Double-blind controlled 8th molar extraction socket filling study

**Intraoperative pictures:** *Easy application*

- Extraction socket filling 3rd molar (wisdom tooth)
- Control I.: no treatment (standard of care)
- Control II.: BioOss (market leader bovine xenograft in Europe)
- Double-blind, randomised, self-controlled split-mouth design
- n=32

Post-operative pain at 7 days

1. Extraction socket filling study: **Lower pain**

*P < 0.05*

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*Pain was significantly lower in the treatment group* than in the other groups.
Cone beam CT at 6 weeks

1. Extraction socket filling study: *Faster bone regeneration and lower demarcation on graft-host border than BioOss*

<table>
<thead>
<tr>
<th>Control (no treatment)</th>
<th>BioOss filling</th>
<th>BoneAlbumin filling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete filling</td>
<td>Non-resorbed graft</td>
<td>Resembles ambient healthy bone structure</td>
</tr>
</tbody>
</table>

Under publication (2018)

2. Double-blind controlled sinus lift study

Histology data: *better transformation to new bone*

Quantitative micro-CT analysis showed that the newly formed bone in the BoneAlbumin group is closer to the native maxilla than that of the BioOss augmented group in several micro-morphometric parameters.

- Sinus lift plus implantation at 6 months
- Control: BioOss (market leader bovine xenograft in Europe)
- Treatment: BoneAlbumin
- Double-blind, randomised, controlled, n=32
- 6 months follow up with histology and microCT

BoneAlbumin turns into bone
Series of 100 dental cases

Panoramic radiography image after the implantation made 6 months after the bone grafting.

Gáspár L. "Experiences in the application of BoneAlbumin human allograft" Implantology, Dental Press (2018)

BoneAlbumin competitive comparison

*Osteoinduction* is key advantage over both xenografts and synthetic grafts

<table>
<thead>
<tr>
<th>Bone graft</th>
<th>Structural strength</th>
<th>Osteo-conduction</th>
<th>Osteo-induction</th>
<th>Osteo-genesis</th>
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</thead>
<tbody>
<tr>
<td>Autograft</td>
<td>low</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Allograft</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frozen</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>no</td>
</tr>
<tr>
<td>Freeze-dried</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>no</td>
</tr>
<tr>
<td>Demineralized</td>
<td>low</td>
<td>low</td>
<td>++</td>
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<tr>
<td><strong>BoneAlbumin</strong></td>
<td>++</td>
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<td>+++</td>
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<tr>
<td>Xenograft</td>
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<td>+++</td>
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<tr>
<td>Beta-TCP</td>
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<td>+</td>
<td>no</td>
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<tr>
<td>Growth Factors</td>
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<td>no</td>
<td>+++</td>
<td>no</td>
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<tr>
<td>Stem Cells</td>
<td>no</td>
<td>no</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Adapted from: American Academy of Orthopaedic Surgeons: Bone-graft substitutes: facts, fictions & applications
BoneAlbumin summary

• BoneAlbumin is the next generation human bone graft with superiority proven in:
  • Preclinical studies showing Stem Cell activation
  • Animal studies showed superiority of albumin coating in every bone regeneration metric
  • Human studies showed superiority in head-to-head comparisons with the market leader xenograft or even autograft
• Easy to use
• Works well both as a granulated bone filler as well as a large, structural graft
• Good remodelling signs on X-Ray and CT in each indication
• Less post-operative pain

References