Demineralized Bone Matrix (DBM)  
A Prospective Randomized Controlled Clinical Study

Pr D’AGOSTINO*, MD; O BARBIER**, MD,PhD  
*Department of Hand Surgery, Hand Institute - Jouvenet Clinic, Paris  
**Department of Orthopaedic Surgery, St-Luc University Hospital, Brussels
Deminerlized Bone Matrix (DBM)

- **DBM Definition**
  - Human Cadaveric Bone Graft = Allograft

- **Processing**
  - Pre-irradiation
  - Antibiotics and Solvent R/
  - Fragmentation ➤ Powder
  - Lyophilisation
  - DEMINERALIZATION by Acid Solution ➤ Preserve Non-Collagenic Proteins (BMPs, GFs,...)

➤ **ORGANIC MATRIX - DBM**
DBM Definition

- Blum B et al., Orthopedics 2004
**INTRODUCTION**

- **DBM Definition**
  - *Blum B et al., Orthopedics 2004*
  - *Wildemann B, J Biomed.Mat.Res. 2007*

**Organic Matrix (DBM)**

- Coll. Proteins 90%
- Network

**Osteoconduction**

- OI Proteins 10%
- BMPs-GFs (IGF-1, FGFs, PDGFs)

**Osteoinduction**
• BMPs (Bone Morphogenetic Proteins) Structure
  ◦ Low Molecular Weight Glycoprotein
  ◦ TGFβ Superfamily
  ◦ > 20 Identified

Crystal Structure of Human BMPs
• BMPs Definition

- In Vitro: Pathways of bone formation
**BMPs Definition**

- **In Vitro**: Pathways of bone formation

**INTRODUCTION**

- **MATERIAL & METHODS**
- **RESULTS**
- **DISCUSSION**
- **CONCLUSIONS**

**Demineralized Bone Matrix (DBM)**

BMPs signal Precursor Cells and stimulate Bone Formation at the defect site = **OSTEOINDUCTION**

• DBM Osteoinductive Property Definition

- Ability to induce bone formation in an extraskeletal site, such as in muscle

*Urist M, Science 1965*

Proportional OI related to [BMPs] - Dose-dependent Effect
Demineralized Bone Matrix (DBM)

INTRODUCTION

• DBM Product
  - Worldwide used in Orthopaedic Field
  - Several Formulations in the marketplace (Osteoset®, Ignite®, Allomatrix®,...)
  - Forms
Demineralized Bone Matrix (DBM)

• DBM Product
  - Worldwide used in Orthopaedic Field
  - Several Formulations in the marketplace (Osteoset®, Ignite®, Allomatrix®,...)
  - Forms
    - Gel
    - Putty
    - Paste
      INJECTABLE or NOT
Demineralized Bone Matrix (DBM)

- DBM Product:
  - Mixed with binding medium
    - Calcium Sulfate, Collagen, Sodium Hyaluronate, Carboxymethyl cellulose, Glycerol
  - Delivered with a Certificate of Osteoinduction (In vitro bio-assay)
  - Indicated to fill bony voids or gaps
• DBM Product:

- Mixed with binding medium

(Calcium Sulfate, Collagen, Sodium Hyaluronate, Carboxymethyl cellulose, Glycerol)

Impact on Osteoinductive Potency


- Delivered with a Certificate of Osteoinduction (In vitro bio-assay)

- Indicated to fill bony voids or gaps
DBM Product

DBM Osteoinductive Effect documented in Animals Studies

BUT ... in Humans
DBM Product

DBM Osteoinductive Effect documented in Animals Studies

BUT ... in Humans

NO PROVEN IN LITERATURE
**INTRODUCTION**

**Primary and Secondary Objectives**

- Enhance bone-healing ?
- Enhance motion and functional recovery ?
• Study Design

Between 2005 and 2008

Prospective Randomized Controlled

Ethical Committee Approval (UCL) / Registered by USA NIH

One Center / One surgeon (OB +/- Fellows)

50 patients DRF

AlloMatrix™ Injectable Putty (Wright Medical Technology, Arlington, TN, USA)

Randomization Envelopes

2 groups: Static K-wires stabilization (Control) / + DBM graft (Grafted)
• Fracture Model

Orthopaedic Surgery most common fracture

• Study Population

Young patients

➤ Quality of anatomic result / Wrist residual capacity
### Fracture Model

Orthopaedic Surgery most common fracture  

*Court-Brown and Caesar, Injury 2006*

### Study Population

Young patients  

- Quality of anatomic result / Wrist residual capacity  

*Villar and March, JBJS 1987*  
*McQueen and Caspers, JBJS 1988*  
*Young and Rayan, JBJS 2000*  
*Kopylov et al., J Hand Surg 2002*  
*Hollevoet and Verdonk, Acta Orthopaedica Belgica 2003*
### Inclusion Criteria

- Unstable DRF
  - *Lafontaine et al., Injury 1989*
- High demand patient
- 18-70 years of age
- Follow-up possible
- Informed consent

### Exclusion Criteria

- Complex DRF
- Bilateral DRF
- Other skeletal injury
- Pregnancy
- Preexisting conditions
Surgical Protocol

Previous closed reduction (manual or Japanese fingers traps)

Friberg and Lundström, Acta Radiol Diagn 1976

Operated within one week

Static 2 or 3 K-wires Stabilization

2 transtyloid K-wires +/- 1 dorso-ulnar K-wire

Fernandez and Jupiter 1996; Fernandez and Wolfe 2005

Randomization envelope +/- Grafting by limited dorsal approach
**Surgical Protocol**

Previous closed reduction (manual or Japanese fingers traps)

*Friberg and Lundström, Acta Radiol Diagn 1976*

Operated within one week

Static 2 or 3 K-wires Stabilization

- 2 transtyloid K-wires +/- 1 dorso-ulnar K-wire

*Fernandez and Jupiter 1996 ; Fernandez and Wolfe 2005*

Randomization envelope +/- Grafting by limited dorsal approach
Patient Evaluation Protocol 1 Year F-Up

- Clinical Evaluation 1-3-6-9 W and 6-12 M Post-op
  - Functional Objective - Range of Motion (Goniometer) Solgaard et al., Scand J Rehab Med 1986
  - Strength (Jamar, Preston) Mathiowetz, Muscle Strength Testing 1990


- Radiological Evaluation Pre-op / Per-op / 1-3-6-9 W and 6-12 M Post-op
  - Plain Radiographics - DR morphology (RI-UV-RH-TD\(_x\)-VT) Medoff, Hand Clin 2005
  - Bone Union (Criteria) Morshed et al., JBJS 2008; Corrales et al., JBJS 2008
  - DBM Extraskeletal deposits

- BMDs of both wrists 1-6 W and 12 M Post-op
Preoperative Data

- G / NG groups comparable

Surgery Data

- Interval Inj-Surg = 1.9d G / 2d NG
- 52% 2 KW / 44% 3 KW / 4% others
- 24 G / 26 NG
- Mean Volume AlloMatrix = 2.3cc (1-4cc)
- Mean Time Tourniquet Inflation = 31.2min (0-65min)
- Mean Surgery duration = 45min G / 30min NG Significantly Higher in G (p=0.004)
- Mean Time Removal KW = 8.3 W (4-17 W)
• Preoperative Data
  - G / NG groups comparable

• Surgery Data
  - Interval Inj-Surg = 1,9d G / 2d NG
  - 52% 2 KW / 44% 3 KW / 4% others
  - 24 G / 26 NG
  - Mean Volume AlloMatrix = 2,3cc (1-4cc)
  - Mean Time Tourniquet Inflation = 31,2min (0-65min)
  - Mean Surgery duration = 45min G / 30min NG  Significantly Higher in G (p=0,004)
  - Mean Time Removal KW = 8,3 W (4-17 W)
• Patient Flow

Clinical - Radiological - BMDs F-Up

➡ No statistical significant difference between both groups (p=0,9)

Mean post-op F-Up = 15M G / 14,2M NG
Demineralized Bone Matrix (DBM)

**INTRODUCTION**

**MATERIAL & METHODS**

**RESULTS**

**DISCUSSION**

**CONCLUSIONS**

---

**Patient Flow**

Clinical - Radiological - BMDs F-Up

- No statistical significant difference between both groups (p=0,9)

Mean post-op F-Up = 15M G / 14,2M NG

---

**Preoperative Radiological Results**

- No statistical significant difference in Fracture Morphology

<table>
<thead>
<tr>
<th>PA projection parameters</th>
<th>Graft group *</th>
<th>No Graft group *</th>
<th>P Value **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ri (°)</td>
<td>13 (SD: 5,94)</td>
<td>15,4 (SD: 6,32)</td>
<td>0,19</td>
</tr>
<tr>
<td>UV (mm)</td>
<td>0,6 (SD: 1,97)</td>
<td>1,1 (SD: 1,82)</td>
<td>0,63</td>
</tr>
<tr>
<td>RH (mm)</td>
<td>7,5 (SD: 3,60)</td>
<td>6,4 (SD: 3,30)</td>
<td>0,27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard lateral projection parameters</th>
<th>Graft group *</th>
<th>No Graft group *</th>
<th>P Value **</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT (°)</td>
<td>28,1 (SD: 6,67)</td>
<td>25 (SD: 10,24)</td>
<td>0,46</td>
</tr>
<tr>
<td>TD ± (°)</td>
<td>41,8 (SD: 11,7)</td>
<td>39,1 (SD: 12,56)</td>
<td>0,46</td>
</tr>
</tbody>
</table>

---
**Postoperative Results**

- **Clinical Results (Objective-Subjective)**
  - Did AlloMatrix improve and allow a faster functional recovery?

- **Radiological Results**
  - Did AlloMatrix increase postoperative fracture stability?
  - Did AlloMatrix enhance bridging of the skeletal gap, bone union?

- **BMDs Results**
  - Did AlloMatrix enhance bone density?
• Postoperative Results

๏ Clinical Results (Objective-Subjective)

➔ Did AlloMatrix improve and allow a faster functional recovery? 
No statistical significant differences

๏ Radiological Results

➔ Did AlloMatrix increase postoperative fracture stability? 
No statistical significant differences

➔ Did AlloMatrix enhance bridging of the skeletal gap, bone union? 
No statistical significant differences

๏ BMDs Results

➔ Did AlloMatrix enhance bone density? 
No statistical significant differences
Demineralized Bone Matrix (DBM)

Postoperative Results

- Union Rate: Complete bridging of the fracture gap at 9W
**Postoperative Results**

- **Union Rate**: Complete bridging of the fracture gap at 9W

![Graph showing Union Rate over Weeks]

- Bridging Cortices
- Weeks

**Demineralized Bone Matrix (DBM)**
**Postoperative Results**

- **Improvement between 1 W - 1Y**

<table>
<thead>
<tr>
<th>Range of Motion</th>
<th>Strength</th>
<th>Fracture-healing</th>
<th>Bone density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant improvement (p&lt;0.001 for all)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DASH scores**

**Weeks**
**Postoperative Results**

- **Improvement between 1 W - 1 Y**

  - Range of Motion
  - Strength
  - Fracture-healing
  - Bone density

  **Significant improvement**
  
  \( p < 0.001 \) for all

  - DASH scores

  - Weeks

  - NG

  - G
### Complications

Did AlloMatrix enhance *morbidity*?

<table>
<thead>
<tr>
<th></th>
<th>Graft group</th>
<th>No Graft group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peroperative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial artery lesion</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection *</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Flow of graft</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CRPS I</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Neurosensitive complaints</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Tenderness on K-wires</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Tendons rupture *</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Trigger fingers</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dupuytren’s disease</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Wrist synovial cyst</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic metacarpal</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
### Complications

*Did AlloMatrix enhance *morbidity*?*

<table>
<thead>
<tr>
<th></th>
<th>Graft group</th>
<th>No Graft group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peroperative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial artery lesion</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Flow of graft</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CRPS I</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Neurosensitive complaints</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Tenderness on K-wires</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Tendons rupture</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Trigger fingers</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dupuytren's disease</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Wrist synovial cyst</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic malunion</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
### Complications

**Did AlloMatrix enhance morbidity?**  No increase in morbidity and surgical revisions in G

<table>
<thead>
<tr>
<th>Peroperative</th>
<th>Graft group</th>
<th>No Graft group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial artery lesion</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postoperative</th>
<th>Graft group</th>
<th>No Graft group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Flow of graft</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CRPS I</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Neurosensitive complaints</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Tenderness on K-wires</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Tendons rupture</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Trigger fingers</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dupuytren's disease</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Wrist synovial cyst</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic malunion</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
• Extraskeletal Allomatrix Deposits
• Extraskeletal Allomatrix Deposits

![Radiographs showing bone matrix deposition at different time intervals.](image)

- **Time interval**
  - 1 Week
  - 3 Weeks
  - 6 Weeks
  - 9 Weeks

- **Grafted Patients**
  - Extensor Tendons and/or Fracture Site: 15, 9, 2, 1
  - Flexor Tendons and/or Fracture Site: 2, 1, 1
  - Inter-Osseous Space and Extensor or Flexor Tendons: 1

---

**Deminerlized Bone Matrix (DBM)**

**INTRODUCTION**

**MATERIAL & METHODS**

**RESULTS**

**DISCUSSION**

**CONCLUSIONS**

dimanche 19 février 2012
• Safety and Morbidity

No adverse events observed

• Handling

Significant increase of surgical procedure time

Supplementary dorsal approach

Strength weakness / Dorsal wrist synovial cyst?

Difficulty for injection

Soft tissue deposits
• Graft Resorption

No significant difference in R1 zone bone density at 6W
No extraskeletal deposits on X-rays after 9W

RESORPTION

Inflammatory state → Strength weakness
No bone formation → Osteoinductive activity in humans?
(Not reported in animals or humans)
Variability in Osteoinductivity

Intervariability of BMPs in DBM grafts

Proportional osteoinduction related to [BMPs]

AlloMatrix DBM content is 40% by weight

Han et al., J Orthop Res 2003
Yoo et al., Spine J 2003
Edwards, IsoTis OrthoBiologics 2003
Attì et al., Spine J 2003
Peterson et al., J Bone Joint Surg 2004

DBM preparation and storage methods

Zhang et al., J Periodontol 1997
Han et al., J Orthop Res 2005
Ferreira et al., Clin Orthop Relat Res 2001
Alanay et al., Spine J 2008
Pinholt and Solheim, Ann Plast Surg 1994
**Variability in Osteoinductivity**

**Intravariability of BMPs in a DBM graft**

Highest variability in [BMPs] among lots of the same DBM formulation

*Bae et al., Spine 2006*

2 human cadaver donors lots (28 and 75 Y)

**Human cadaver donors age**

Young donors enhance osteoinductivity?

*Not supported in literature*

*Pinholt and Solheim, J Craniofac Surg 1998*

*Traianedes et al., J Biomed Mater Res B Appl Biomater 2004*

4/24 grafted with the oldest human donor
Variability in Osteoinductivity

PDGF in blood decrease DBM osteoinductivity


Patient blood never adjunct or mix to AlloMatrix

Sample Size

Power of the analysis limitation
Demineralized Bone Matrix (DBM)

• No significant clinical effect of AlloMatrix in this human model

• OI potency of AlloMatrix insufficient to induce bone formation

• Additional trials needed