



### Fracture Healing Stimulation Where's the Evidence?



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Atlanta Trauma Symposium  
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### Disclosure

Member: AAOS Committee on Biologics  
Reviewer: Clinical Orthopaedics Related Research  
Faculty: AO  
Previous research funds Osteotech, LIPUS

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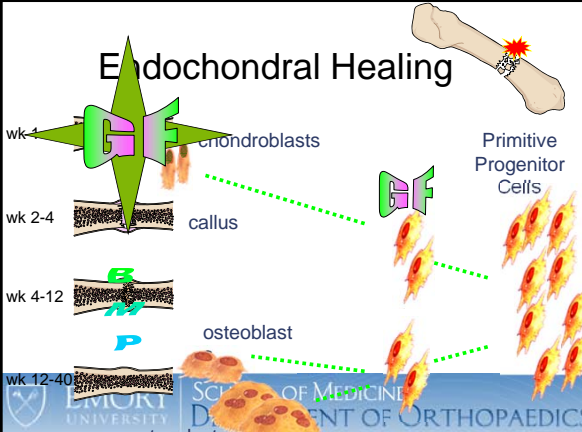
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### Endochondral Healing



wk 1 chondroblasts  
wk 2-4 callus  
wk 4-12 osteoblast  
wk 12-40 osteoclasts

Primitive Progenitor Cells

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### Nonunions

- Estimated 7.9 million fractures yearly in US:5-10% develop delayed/nonunion (**AAOS**)
- Vitamin-D deficiency in 68% of refractory nonunions ( Brinker **JOT** 2007)
- ↑ incidence of nonunion of tibia fx's with smoking (Moghaddam **Injury** 2011)
- ↑ incidence of nonunion in ORIF in HIV+ pts (CD-4 count < 200, serum albumen <2.5) (Moore **Clin Ortho Rel Res** 2013)
- ↑ incidence of nonunion with delayed wt bearing in LE fx's, impaired biological environment ( decreased circulation, indolent infection), inadequate mobilization (Moore **Essentials of Musculoskeletal Care**, 2015)



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### Variability in the Assessment of Fracture Healing in Orthopaedic Trauma Studies

- 123 studies in **JBJS** and **JOT**
- Union: 62% combination of radiographic and clinical criteria, 37% radiographic criteria only
- ↑ interobserver variability (Corrales **JBJS** 2016)
- 176 tibial fx's
- Any cortical bridging by 4mos: 100% union rate (Lack **JBJS** 2014)



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### Evidence Based Medicine: the Efficacy of Enhanced Fracture Healing Modalities

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### Electrical Stimulation for Fracture Healing: Current Evidence

- A meta-analysis of studies of electromagnetic stimulation to accelerate acute fracture healing, osteotomy, delayed union or nonunion healing is contradictory
- “Although the evidence supporting electrical stimulation does trend in favor of its use to achieve bony union, RCT are required to resolve the current uncertainty”



Boden rabbit fusion model  
ABG and electrical stimulation  
Bozic *Spine* 1999



Residents with Carl Brighton

Golstein *JOT* 2010

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### Low Intensity Pulsed Ultrasonography for Fx's: Systematic Review of Randomized Controlled Trials

- Low quality evidence in 3 trials: non-op managed fresh fx's-accelerated healing
- Low quality evidence in 3 trials: accelerated healing in distraction osteogenesis
- Low quality evidence in 1 trial: accelerated healing in established nonunions
- Low quality evidence in 4 trials: accelerated healing in operatively treated fresh fx's
- “Overall results are promising, but establishing the role of ultrasound in the management of fx's requires higher evidence”



Busse, Bhandari, Tornetta *BMJ* 2009

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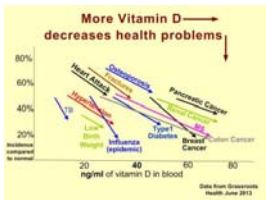
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### What is the Role of Vit D Supplementation if Acute Fracture Care? A Meta-Analysis of the Prevalence of Hypovitaminosis and Supplementation Efficacy

- Pooled analysis: prevalence of hypovitaminosis D in fracture patients was 70% (63.7%-76.0%)
- Vit D supplementation in accepted safe doses increases serum 25(OH) D levels (ave post fracture serum 25(OH)D levels 19.5 ng/ml) in fracture patients
- 1 pilot study: Vit D supplementation reduced risk of nonunion after single loading dose of Vit D



More Vitamin D → decreases health problems

Heart Attack, Osteoporosis, Falls, Infections (problems), Type 2 Diabetes, Breast Cancer, Prostate Cancer, Lung Cancer, Colorectal Cancer, Pancreatic Cancer

20% 40% 60% 80% (relative compared to normal)

20 40 60 80 (ng/ml of vitamin D in blood)

Data from Osteoporosis Health June 2013

Sprague *JOT* 2016

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### Enhancement of Fracture Healing by Systemic Administration of Recombinant Human Parathyroid Hormone

- PTH is systemic mediator of calcium and bone metabolism
- RCT for fracture healing of osteoporotic pelvic fx's in elderly pts: accelerated fracture healing and better functional outcome

Della Rocca **JOT** 2010  
Peichl **JBS** 2011

**PTH Effects on Bone**

PTH → Stimulates → Bone resorption →  $Ca$  into ECF → ↑ Ca

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### The Economic Benefit of Prophylactic Use of Bone Healing Modalities in Acute Fx's

- 3.9% of all fx's develop nonunion annually
- A 5% ↓ in nonunions from 8 weeks of Vit D supplementation would result in 4.6 fewer nonunions annually
- The mean estimate for nonunion care is \$16,941
- Vit D and calcium supplementation in all fx's (Annual cost \$12,164) would result in \$65,866 annual savings (Childs **JOT** 2016)
- The economics of Rx of tibial Fx's : \$15,600 unreamed IM nail
- \$13,300 functional brace and ultrasound (Busse Bhandari **ACTA Orthop** 2005)
- Significant cost savings with ultrasound in tibia fx's in Workmans Comp (Heckman **Bull Hosp Joint Disease** 1997)

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### The Use of BMP's in Orthopaedic Surgery

- FDA 2002 approval of rhBMP-2 for 1 level anterior lumbar interbody fusion with LT-cage
- Majority of BMP usage off-label. AAOS: "any physician may administer any legally marketed product for an off-label use, according to the physician's well-informed medical judgment for the best interest of the patient"
- 165K pts received Infuse 2011

1 nanogram BMP per cc of normal bone

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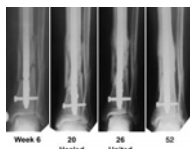
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### BMP-2 for Open Tibial Fractures

- Prospective, randomized study
- 450 patients
- All received IM nail and appropriate soft tissue management
- Randomized to 3 treatments at time of definitive wound closure
  - Placebo
  - 0.75 mg/ml BMP-2/ACS
  - 1.50 mg/ml BMP-2/ACS



BESTT Study Group, *J Bone Joint Surg* 2002.




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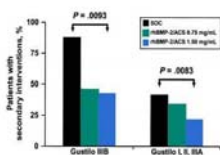
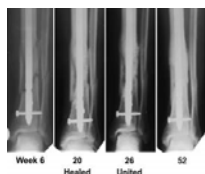
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### Results

- 44% reduction in risk of nonunion/delayed union with high dose BMP-2
- Significantly accelerated fracture healing
- Significantly fewer
  - invasive interventions
  - hardware failures
  - infections



BESTT Study Group, et al. *J Bone Joint Surg* 2006




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### The Use of BMP in Orthopaedic Surgery

- FDA 2008: warning of "life-threatening" complications of cervical fusion use of BMP's
- **JBJS-B** 2009: retraction of article on rhBMP-2 Rx of tibial fx's from Walter Reed Army Hospital for falsification
- 2011 Eugene Carragee in **The Spine Journal**: 1. complications of rhBMP-2 use in spine including retrograde ejaculation, ectopic bone formation, infection and possible malignancy were under reported 2. significant author's conflicts 3. bias against the ICBG group in favor of the rhBMP-2 group
- Senate Finance Committee 2011: concern about significant financial ties of BMP researchers to industry ( Medtronic)




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### Cancer Risk after Use of rh-BMP-2 for Spinal Arthrodesis

- Level II study of spinal arthrodesis: Group 1-224 pts with iliac crest ABG, Group 2-239 pts with high dose rhBMP-2
- At 2 years, new cancer per 100 person-years : 3.37 in rhBMP-2 group, 0.50 in ABG group
- Conclusion: rhBMP-2 in **high doses** is potentially carcinogenic

Carragee, Yoon JBJS 2013




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### Yale Open Data Access Project (YODA)

- Medtronic: released all study data, provided \$2.5million for independent study of Infuse for spinal fusion
- University of Oregon and University of York
- 1. rhBMP-2 “provided little or no benefit compared with autogenous bone graft and may be associated with more harms, possibly including cancer”
- 2. Found that published literature “does **not** seem to be substantially biased”
- 3. However, “adverse events were incompletely and inadequately described in the study publications”

Annals of Internal Medicine 2013




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### Organizing Stem Cell Engineering for Orthopaedic Applications

- *Embryonic stem cells*(ESC's): allographic and pluripotent
- *Induced pluripotential stem cells*(iPS): allographic, induced in vivo to become pluripotential cells
- *Adult stem cells* (mesenchymal stem cells-MSC's) can differentiate into only one or a few different cell lines
- Tissue engineering triad: Mesenchymal stem cells, biomaterial scaffolds, and signals



Broderick JAAOS 2014  
Rodeo AAOS Orthopaedics Now 2014




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### Stem Cells and the FDA

- **Human cells, tissues, tissue related products (HCT/P)**
  1. Minimally-manipulated
  2. Homologous use only (use for the repair, reconstruction, or supplementation of recipient's cells or tissues)
  3. No combination with any other substance except water or crystalloids
  4. No systemic effect

Since 2012, the FDA has closed clinics in violation of above



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### Stem Cells and the AAOS

- The use of stem cell therapy for musculoskeletal diseases should be in compliance of FDA regulatory oversight
- There should be high level studies to assess the safety and efficacy of stem cell therapy
- Informed Consent for stem cell therapy



Moore AAOS Orthopaedics Now 2014  
Moore ASTM National Meeting 2015



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### Conclusions



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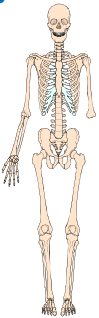
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### Bone Grafting

- Albee 1915: 1<sup>st</sup> autologous bone graft (tibia to spine)
- Levender 1930: 1<sup>st</sup> osteoinduction (extracts of bone to muscle)
- Marshall Urist 1965: isolated BMP
- World-wide: autografts or allografts 2.2 million/yr
- \$2.5 billion/yr





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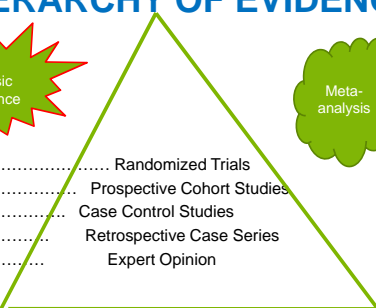
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### HIERARCHY OF EVIDENCE

Basic Science




Meta-analysis

Less Bias



Level 1.....	Randomized Trials
Level 2.....	Prospective Cohort Studies
Level 3.....	Case Control Studies
Level 4.....	Retrospective Case Series
Level 5.....	Expert Opinion



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### CLINICAL TRIAL DESIGN IN FRACTURE HEALING RESEARCH: MEETING THE CHALLENGE

- < 10% of surgical therapies are randomized, controlled trials, few studies on the efficacy of biologics

Fracture trials should include in the future

1. Fracture healing acceleration
2. Fracture healing in osteoporotic bone
3. Determination of fractures prone to nonunion
4. Cost analysis

Morshed, Bhandari **JBJS** 2008





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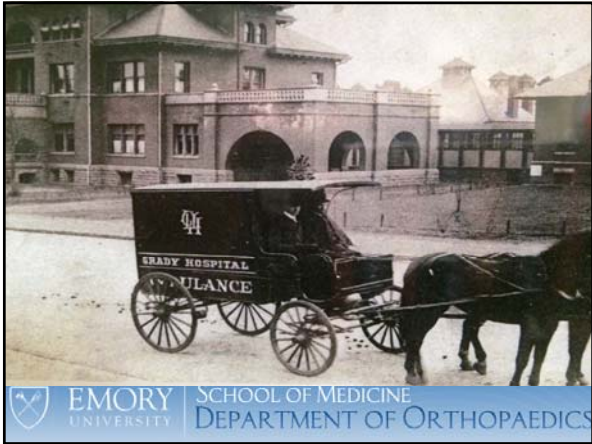
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