BIOLOGY OF NONUNION
FRACTURES IN FOOT
AND ANKLE
ORTHOPAEDICS

Elliott N. Schwartz, MD, CCD, CPD
Assistant Clinical Professor, UCSF
ISCD Clinician of the Year 2008
NAMS Menopause Practitioner (2008-2010)
Northern California Institute for Bone Health Inc
Orinda, CA,
Osteoporosis Update: 2015
Annual Meeting 6-19-15

Acknowledgement
Slides, References and Mentorship

• John Bilezikian, M.D., Columbia Univ Med Ctr, NY
• Davis Brimer, CEO, ActiveLife Scientific, Santa Barbara, CA
• Thomas A. Einhorn, M.D. Boston Univ Med Ctr, MA
• Erik F. Eriksen, M.D., Oslo Univ Hosp, Norway
• Louis C. Gerstenfeld, Ph. D., Boston Univ Med Ctr, MA
• Jerrald Goldman, M.D., for referral of Frank Thomas
• Sundeep Khosla, M.D., Mayo Clinic, Rochester, MN
• George Tischenko, M.D, Muir Orthopaedic Grp, Walnut Creek, CA, for referral of the patient detailed

Clinten Edmondson, Orinda, CA, for technical support
My first ankle nonunion
1-27-06
White Sox's Thomas out for season
37-year-old slugger has fracture in surgically repaired foot

Baltimore - Frank Thomas played in pain as long as he could, trying to be a big contributor for the Chicago White Sox as they forged the best record in the major leagues through the first four months.

"It appears Frank has re-injured his foot over the last two weeks while playing baseball, and recent evaluation shows a new fracture through the navicular in his foot," Ferkel said after examining Thomas recently. The 37-year-old Thomas is batting .219, and 12 of his 20 hits are home runs. He has 26 RBIs in only 105 at-bats after starting the year on the disabled list. The two-time AL MVP has been slowed by ankle problems all season and limited to 34 games.

Thomas broke a bone in his left ankle July 6, 2004, and played only 74 games a year ago. He had surgery last October and was activated from the disabled list on May 30.

Trainer Herr Schneider said the fracture is not the same one that was repaired last October.

"The initial fracture that Frank had casted is healed and the screws are in place. That's not the problem. It's a stress related problem to a non-healthy bone," he said.

"If this guy wasn't hurt, there wouldn't be a question we'd be talking about 600-plus home runs, not 450," Williams said.

Synopsis of case

- First navicular stress fracture-July, 2003
- ORIF 2004
- Second navicular stress fracture-2005
- ORIF 2005
- Nonunion both fractures; 1 cm gap
- Initiate Forteo and EXOGEN device 1-27-06
- Healed 6-27-06
Induction Ceremony-National Baseball Hall of Fame, July 27, 2014

Thomas moved on to the A's in 2006 and, then, the Blue Jays, where he totaled 65 HR and 209 RBI from 2006 to 2007. Injuries slowed him in 2008 at the age of 40 and he retired in 2010.

Followed by another 45 nonunions from 1-1-07 to 6-11-15
Economic Burden of Illness among US Patients Experiencing Fracture Nonunion

- 7.9 million fractures annually¹
- 2012 US²: Fracture of the Ankle: principal diag: 346,620; all diag: 405,669
- 2012 US²: Fracture of the Foot: principal diag: 409,756; all diag: 503,742
- 10% impaired bone healing (delayed union or nonunion¹ but this differs by site: displaced scaphoid fracture 55%; 5th metatarsal fracture 7-28%³
- AOFAS “does not collect this type of data”


Basics of Fracture Repair
Fracture healing is a complex physical process; regulated by cells, mediators, and growth factors with different phases of activity occurring over time to restore normal function.

Cellular recruitment, proliferation and differentiation under the guidance of signaling molecules with the involvement of extracellular matrix creates the foundation for a successful bone healing response.

If any stage of these events is disturbed, an impaired healing response, expressed as delayed union or nonunion, can occur in bone.

Signals associated with the injury stimulate progenitor cell proliferation and lead to a critical mass of cells necessary for tissue regeneration.

Copuroglu, et al., Injury, Int J Care Injured 2013, 44:1379-1382;
Nonunion

• Defined as the cessation of all reparative processes of healing without bony union¹
• In humans, failure to show any progressive change in radiographic appearance for at least 3 months AFTER the period of time during which normal fracture union would be thought to have occurred¹
• “…, it is difficult to imagine at what point fracture healing may cease completely”
• FDA definition (1986): Fracture that is over 9 months and that has not shown any radiographic signs of progress toward healing for 3 consecutive months²
• FDA definition (1998): Fracture that shows no visibly progressive signs of healing; no timeframe³


A Lack of Consensus in the Assessment of Fracture Healing Among Orthopaedic Surgeons

• Despite improvements in treatment strategies and emphasis on standardization of outcome measures in trauma, definition of delayed fracture union and nonunion are subject to variable interpretation
• There is no universally accepted or validated approach to evaluating the progression of fracture healing in the lower extremities
• Usually, use clinical or radiographic assessment or clinical plus radiographic assessment
• Questionnaire survey of members of the Orthopaedic Trauma Association; 444 of 577 (77%) responded

Bhandari, J Ortho Trauma, 2002, 16(8):562-566
A Lack of Consensus in the Assessment of Fracture Healing Among Orthopaedic Surgeons

"The designation of a delayed union or nonunion is currently made when the surgeon believes the fracture has little or no potential to heal."

No official AAOS, ASBMR, or other organization definition

Wiss and Stetson, J Amer Orthop Surg, 1996
Classification

1. Hypertrophic
2. Oligotrophic
3. Atrophic = Avascular
4. Pseudarthrosis

Weber and Cech, Pseudoarthrosis, Grune & Stratton, 1976

Risk Factors for Impaired Bone Healing-Patient Dependent

- Age and Sex
- Nutritional State
- Comorbidities
  - Diabetes
  - Hypothyroidism
  - Anemia
  - Osteoporosis
  - Vascular disease
- Alcohol abuse
- Smoking
- Radiation therapy
- Drugs
  - Steroids
  - NSAIDs
  - Chemotherapy

Pountos, et al., Injury, 2013. 44:1725-1732
Risk Factors for Impaired Bone Healing-Fracture Dependent

- Bone involved
- Pattern of fracture
- Comminution
- Fracture gap
- Extent of trauma
- Soft tissue damage
- Interposed soft tissue
- Lack of cortical apposition
- Surgical treatment
- Mechanical stability
- Infection

Pountos, et al., Injury, 2013. 44:1725-1732

Genetics of Nonunions

- Extensive research suggests a genetic predisposition to nonunions
- Genetic variations within the genes expressed during fracture healing and “disturbed” signaling pathways at the molecular level could contribute to the impaired bone formation seen in atrophic nonunions
- Differences seen in callus formation and time to union could be attributed to biological variations among individuals

Dimitriou, Injury, Int J Care Injured, 2013. 44:S1: S550-553
Genetics of Nonunions

• Downregulated gene expression of various BMPs, including BMP-2, -4, -6, -7, GDF-5 and -7 and various BMP inhibitors, such as Noggin and sclerostin in nonunions compared to standard healing fractures at several time points¹

• Gene expression of IGFs (IGF-III) and their binding proteins (IGFBPs [IGFBP-6]) significantly higher in nonunions and IGFBP-5 lower²

• FGF (FGFR-3) signaling delayed healing by inhibit stem cell differentiation to chondrocytes³


Genetics of Nonunions

• Specific SNPs (single nucleotide polymorphisms) located on Noggin and Smad6 genes were assoc with a signif greater chance of nonunion¹

• Signif assoc of PDGF haplotype with nonunions of the lower extremity ²

• Polymorphisms in genes reg local antimicrobial response showed variants of TLR-4 and TGF-β in pts with impaired fracture healing allowing prolonged pathogen existence³

• Neurofibromatosis type 1 (NF-1), autosom dom, 1 in 3000; congenital pseudoarthrosis of tibia; nonunion and re-fracture are common⁴

Genetics of Nonunions

• In the near future, clinically, “simple genetic testing and analysis of genetic variants linked to aberrant bone healing can be used as a potentially powerful tool to … identify patients [early]…at risk of developing atrophic non-union and [applying] the on-time intervention…of bone healing biological response modifiers [leading] to clinical application [expansion] if the hypothetical potential role of genetic variations in the fracture healing response is established”

Dimitriou, Injury, Int J Care Injured, 2013, 44:S1; S550-553

The Convergence of Fracture Repair and Stem Cells:  Interplay of Genes, Aging, Environmental Factors and Disease

• Chondrocytes and osteoblasts secrete collagen matrices that calcify and bridge the fracture site and are responsible for the secondary signals that maintain the regenerative process and induce angiogenesis and remodeling
• Fracture repair involves intramembranous ossification whereby progenitor cells differentiate into osteoblasts and endochondral ossification forming cartilage that calcifies and remodels into bone
• Intramembranous ossification occurs at the periosteal surface and endochondral ossification occurs at the center of the fracture site

Hadjiargyrou, J Bone Min Res, 2014;29:2307-2322
The Convergence of Fracture Repair and Stem Cells: Interplay of Genes, Aging, Environmental Factors and Disease

• Chondrocytes differentiate and form a cartilaginous soft callus in the hypoxic environment lacking blood vessels
• The hypoxia induces angiogenesis-related genes, stimulates blood vessels and restores the circulation
• Osteoprogenitor (stem) cells are derived from pericytes in the invading blood vessels
• Stem cells have self renewal capacity, persist throughout life and are responsible for tissue homeostasis where they replace damaged cells
• Multipotent stem cells can differentiate into multiple cells and tissues and are recruited to fracture sites

Hadjiargyrou, J Bone Min Res, 2014;29:2307-2322
The Convergence of Fracture Repair and Stem Cells: Interplay of Genes, Aging, Environmental Factors and Disease

- Progenitor cells in the periosteal tissue serve as the source of progenitor cells for fracture repair
- The initial response of the progenitor cells leads to the formation of callus which drives the recruitment of cells from surrounding tissues for angiogenesis and remodeling
- Genetically modified mice have been studied with altered inflammatory mediators, altered growth factor signaling and altered integrins
- Aging exerts inhibitory effects on all the steps of the process through telomere shortening

Hadjiargyrou, J Bone Min Res, 2014;29:2307-2322

The Convergence of Fracture Repair and Stem Cells: Interplay of Genes, Aging, Environmental Factors and Disease

- Environmental factors compound the inhibitory effects: cigarette smoke, alcohol abuse, poor nutrition and heavy metal exposure
- Cigarette smoke contains more than 4000 different compounds; nicotine easiest to study; reduces differentiation of chondrocytes and osteoblasts; smoke delays formation of cartilage and bone and bone remodeling and results in accelerated aging
- Heavy metals: Cadmium, major component of cigarette smoke, major risk factor of cadmium exposure, leads to DNA damage and telomere shortening; Lead, osteopenia and reduced childhood growth, reduced osteoblast formation, delayed union

Hadjiargyrou, J Bone Min Res, 2014;29:2307-2322
The Convergence of Fracture Repair and Stem Cells: Interplay of Genes, Aging, Environmental Factors and Disease

- **Diabetes** impaired fracture repair with reduced callus formation, accelerated loss of cartilage and decreased healing; reduced mononuclear cells that express osteocalcin and elevated levels of sclerostin and reduced serum $\beta$-catenin; reduced biomechanical strength

- **Obesity** multiple adverse effects but sometimes hard to separate from diabetes effects; leptin receptor deficient mice have reduced fracture repair, delayed periosteal progenitor cell osteogenesis, premature apoptosis and impaired vascular invasion of the cartilage callus

- **Mitochondria**-limited activity

Hadjiiargyrou, J Bone Min Res, 2014:29:2307-2322

---

Basic Physiology of Bone
The Goal: Increased Bone Strength

NIH Consensus Statement 2000\(^1\)

Bone Strength \(=\) Bone Quality

and

Bone Mineral Density

- Architecture
- Bone Remodeling
- Damage Accumulation
- Mineralization
- Bone Size and Shape
- Matrix Quality

\[ a\text{BMD} = \text{g/cm}^2 \]
\[ v\text{BMD} = \text{g/cm}^3 \]


Trabecular Bone Score (TBS) as assessed from DXA Image:

Just a Buzz or real clinical utility?

Prof. Didier Hans

Intellectual collaboration with Pr WD. Leslie (Canada)

Center for Bone diseases, DAL
Lausanne University Hospital, Switzerland
"Medimaps TBS iNsight is a software provided for use as a complement to a DXA analysis. ... TBS is derived from the texture of the [PA spine] DXA image and has been shown to be related to bone microarchitecture and fracture risk. This data provides information independent of BMD..."

“TBS is derived from texture of the DXA image and has been shown to be related to microarchitecture and fracture risk”

(extracted from FDA’s proposition for indications of use)
TBS predicts OP fracture independently of BMD and CRF

Hazard Ratio depending on fracture type

- Manitoba study
- JPOS study
- Manitoba study
- Manitoba study
- SEMOF study
- OFELY study

0,0 1,0 2,0 3,0

All fracture types
Hipfracture type
Vertebral fracture type

TBS: How is the Number Interpreted

<table>
<thead>
<tr>
<th>BMD</th>
<th>TBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>normal TBS ≥ 1.350</td>
</tr>
<tr>
<td>normal</td>
<td>normal TBS ≥ 1.350</td>
</tr>
<tr>
<td>low bone mass</td>
<td>-1 &lt; T-score &lt; -2.5</td>
</tr>
<tr>
<td>low bone mass</td>
<td>partially degraded 1.200 &lt; TBS &lt; 1.350</td>
</tr>
<tr>
<td>osteoporosis</td>
<td>T-score ≤ -2.5</td>
</tr>
<tr>
<td>osteoporosis</td>
<td>degraded TBS ≤ 1.200</td>
</tr>
</tbody>
</table>

http://www.medimaps.fr/tbs-insight
TBS is More Sensitive Than BMD to Diabetes-Related Fracture Risk

LS TBS predicted fractures in those with diabetes (adjusted HR 1.27, 95%CI 1.10-1.46) and without diabetes (HR 1.31, 95%CI 1.24-1.38).

Odds ratios (95% CI bars) for lowest vs highest tertile according to presence of diabetes (adjusted for age, BMI, osteoporosis therapy, glucocorticoids, prior fracture, rheumatoid arthritis, COPD, alcohol abuse).

Patients with same BMD may not have the same risk of fracture

Different TBS value

Different patient management?
OsteoProbe® 1

Courtesy of Davis Brimer, ActiveLife Scientific, 2014

OsteoProbe® 4

Fig. 3: Measurement procedure for testing bone through tissue with the Osteoprobe.

Randall, ASBMR, 2013
IN VIVO BONE MICROINDENTATION TESTING

- The OsteoProbe® (Active Life Scientific Inc., Santa Barbara, CA), is a hand-held microindentation instrument designed for in vivo measurements of bone material properties in humans at the midshaft of the non-dominant anterior tibia (Rev Sci Instrum 83(4):044301, 2012)

- After administering local anesthesia (1% lidocaine), the probe is inserted through the soft tissue and periosteum until residing on the bone surface

- While keeping the device perpendicular to the bone surface (within 10°), the measurement is actuated by slowly compressing the device’s outer housing unit, compressing the internal primary spring until the trigger mechanism initiates an impact

![Image of OsteoProbe®](Image)

OsteoProbe® 5

![Graph](Image)

**Fig. 1:** Measurement of displacement vs. time of a typical indentation measured with the Osteoprobe.

Randall, ASBMR, 2013
DEEP ATOMIC FORCE MICROSCOPY LINE SCANS


Evaluation of the Nonunion Fracture Patient
Patients with stress fx. exhibit impaired bone material properties

Sosa and Eriksen, ASBMR, Abstract MO 0028, Sept. 2014, S350
Secondary Causes of Underlying Bone Disease

• Endocrinopathies
• Drugs
• Gastrointestinal disorders
• Eating disorders
• Vitamin D insufficiency/deficiency
• Marrow-based and neoplastic disorders
• Inherited diseases

Adapted from ISCD BDC

How Often Is Osteoporosis Associated With Secondary Disorders?

In 664 peri/postmenopause women, T-score < −2.5
• 53% (355) had secondary osteoporosis by history
• 47% (309) had no history of secondary etiologies
  ▪ 173/309 had comprehensive lab testing
    ◇ 32% (55/173) previously unrecognized factors
    ◇ 44% (76/173) if low vitamin D is < 20 ng/ml*
• Conclusion: Previously undiagnosed disorders are common

Tannenbaum C. J Clin Endocrinol Metab. 2002;87(10):4431.
*Luckey, personal communication
There is only ONE study that looks at secondary causes of metabolic bone disease/osteoporosis in any population of nonunion fracture patients

Metabolic and Endocrine Abnormalities in Patients With Nonunions

• Screening criteria: 1) unexplained nonunion despite adequate reduction and stabilization (and debridement); 2) history of multiple low-energy fractures with at least 1 progressing to nonunion; or 3) a nonunion of nondisplaced pubic rami or sacral alii fracture

• From 683 consecutive nonunion patients over 7 year interval, 37 patients referred to consulting endocrinologists for evaluation

Metabolic and Endocrine Abnormalities in Patients With Nonunions

- 31 of 37 patients (83.8%) had one or more (21 of 31 [68%]) metabolic or endocrine abnormalities
- Most common: vitamin D deficiency (25 of 37); 21 of 37 (68%) had 25 vit D defic; 3 had 1,25 vit D defic; 19 of 25 (76%) had 25 vit D < 20ng/mL or 1,25 vit D < 15pg/mL
- Abnormal 24 hr urinary calcium was 2nd most common; 13 of 37; 10 also had vit D defic


Metabolic and Endocrine Abnormalities in Patients With Nonunions

- 9 of 37 had abnormal thyroid function; 3 of 9 had hyperthyroidism
- 8 of 37 had abnormalities of one or more hormones of reproductive system; 4 men and 1 woman had newly diagnosed central hypogonadism
- 6 of 37 had elevated alkaline phosphatase
- 4 of 37 had elevated PTH
- 2 of 37 had hyperprolactinemia; 1 elev GH

What is Optimal Bone Turnover?

Bone Quality

Physiological

Bone Turnover

Too Little Turnover:
- Aging bone, un-repaired micro-damage, over-mineralized bone?

Too Much Turnover:
- Loss of bone mass and structure, stress risers, under-mineralized bone?

Biocemical Bone Turnover Markers

- **Bone Formation**
  - Total alkaline phosphatase (liver + bone)
  - Bone specific alkaline phosphatase
  - Serum osteocalcin
  - Serum P1NP (propeptide of the N-terminal end of type 1 procollagen)

- **Bone Resorption**
  - Urinary hydroxyproline (requires special diet-outmoded)
  - Urinary calcium (usually, a 24 hr collection including creatinine clearance)
  - Urinary collagen cross-links
    - pyridinoline
    - deoxypyridinoline
    - N-telopeptides (U-NTx)
    - C-telopeptides
  - Serum collagen cross-links
    - C-telopeptide (S-CTx)
Recent Advances in the Use of Serological Bone Formation Markers to Monitor Callus Development and Fracture Healing

• Fracture healing cannot proceed to completion without new bone formation (BF)
• In human studies of femoral¹, ankle² and distal forearm fractures³, BSAP, OC and P1NP have been followed from pre-injury to one year post fracture
• P1NP signif elev at 3 days, max incr of 55% at 6 wks; OC max incr at 26 wks; BSAP not as high; above pre-fracture level at 1 year¹


Recent Advances in the Use of Serological Bone Formation Markers to Monitor Callus Development and Fracture Healing*

• P1NP levels peaked 6 weeks after DFF and remained elev at 1 year¹
• P1NP linked to Achilles tendon healing²
• Reduced levels of OC have been reported in delayed fracture healing³
• P1NP has not yet been evaluated as an indicator of failing or failed fracture healing but, based on its kinetics in fractures, it is felt that it is "the best candidate for use as a serological marker of bone healing"*

Management of Fracture Nonunion

Figure 1. Overview of Treatment Decisions for Nonunion

AHRQ, Technology Assessment, September 21, 2005, p 19
### WHAT’S NEW – CALCIUM:

<table>
<thead>
<tr>
<th>Age</th>
<th>EAR</th>
<th>RDA</th>
<th>TUIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–8</td>
<td>800</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>9–18</td>
<td>1100</td>
<td>1300</td>
<td>3000</td>
</tr>
<tr>
<td>19–50</td>
<td>800</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>51–70</td>
<td>800/1000</td>
<td>1000/1200</td>
<td>2000</td>
</tr>
<tr>
<td>&gt;70</td>
<td>1000</td>
<td>1200</td>
<td>2000</td>
</tr>
<tr>
<td>Pregnant &gt;18</td>
<td>800</td>
<td>1000</td>
<td>2500</td>
</tr>
</tbody>
</table>

### WHAT’S NEW – VITAMIN D:

<table>
<thead>
<tr>
<th>Age</th>
<th>EAR</th>
<th>RDA</th>
<th>TUIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3</td>
<td>400</td>
<td>600</td>
<td>2500</td>
</tr>
<tr>
<td>4–8</td>
<td>400</td>
<td>600</td>
<td>3000</td>
</tr>
<tr>
<td>9–18</td>
<td>400</td>
<td>600</td>
<td>4000</td>
</tr>
<tr>
<td>19–50</td>
<td>400</td>
<td>600</td>
<td>4000</td>
</tr>
<tr>
<td>51–70</td>
<td>400</td>
<td>600</td>
<td>4000</td>
</tr>
<tr>
<td>&gt;70</td>
<td>400</td>
<td>800</td>
<td>4000</td>
</tr>
<tr>
<td>Pregnant &gt;18</td>
<td>400</td>
<td>600</td>
<td>4000</td>
</tr>
</tbody>
</table>
Ways to Accelerate Fracture Healing
# BONE GROWTH STIMULATORS

- **DONJOY METATARSAL CASE STUDY**
- **EBI Bone Healing System**
- **Exogen Bone Healing System (US)**

## Comparison of fracture stimulation technologies

<table>
<thead>
<tr>
<th>Technology and product</th>
<th>Daily treatment time</th>
<th>PMA heal rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-intensity pulsed ultrasound (EXOGEN® Bone Healing System)</td>
<td>20 minutes</td>
<td>38% acceleration†</td>
</tr>
<tr>
<td>Direct electrical current (implanted) OsteoGen®</td>
<td>24 hours</td>
<td>Not approved</td>
</tr>
<tr>
<td>Electrical capacitive coupling (OrthoPak®)</td>
<td>24 hours</td>
<td>Not approved</td>
</tr>
<tr>
<td>Pulsed electromagnetic field (PEMF) EBI Bone Healing System®</td>
<td>10 hours</td>
<td>Not approved</td>
</tr>
<tr>
<td>Pulsed electromagnetic field (PEMF) Physio-Stim®</td>
<td>3 hours minimum</td>
<td>Not approved</td>
</tr>
<tr>
<td>Combined electromagnetic field (CEMF) DonJoy® OL1000</td>
<td>30 minutes</td>
<td>Not approved</td>
</tr>
</tbody>
</table>

*EXOGEN is indicated for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibia diaphysis fractures in skeletally mature individuals when these fractures are orthopedically managed by closed reduction and cast immobilization.

**EXOGEN is a trademark of Smith & Nephew, Inc.

† EXOGEN PMA 900009: n=61, n=67 – 10/05/1994

‡† EXOGEN PMA 900009: n=74, Supplement – 02/23/2000

** EBI PMA P790005: Study 1: 66.7% healed, n=30; Study 2: 38.8% healed, n=58 – 01/25/1980

‡ Bioelectron PMA P850022: n=69 – 02/18/1986

‡‡ EBI PMA P790002: Based upon a four-year FDA follow-up, n=146 – 11/06/1979

μ Orthofix/AME PMA P850007: 02/21/1986

†† Includes inconsistent users, defined as the cohort whose average usage (1.1 hours/day) was significantly below recommended protocol (8.0 hours/day) n=14.

§ Includes consistent users, defined as the cohort whose average usage (7.1 hours/day) was not significantly different from recommended protocol (8.0 hours/day) n=135.

μ,a 80.0% healed μ,b 80.0% healed
Orthobiologics

• Bone grafts and bone graft substitutes:
  - Autologous bone: cancellous*, cortical
  - Allogenic bone: demineralized matrix
  - Calcium phosphate ceramics, hydroxyapatite, tricalcium phosphate, calcium phosphate cements*, calcium sulfate,

*Authors Preferred Method of Treatment

Wagner, et al. Chapter 5, Rockwood and Green’s Fractures in Adults, 8th ed

Orthobiologics

• Enhancement of Fracture Healing with Biologic Treatments
  - Mesenchymal stem cells and progenitor cells
  - Bone morphogenetic proteins*
  - Wnt proteins
  - Other peptide signaling molecules
  - Prostaglandin modulators
  - Nonsteroidal anti-inflammatory drugs

*Authors’ Preferred Method of Treatment

Wagner, et al. Chapter 5, Rockwood and Green’s Fractures in Adults, 8th ed
Orthobiologics

• Systemic enhancement of fracture healing
  - Parathyroid hormone
  - Growth hormone and insulin-like growth factor I
  - Statins
  - Bisphosphonates and osteoclast inhibitors
  No recommendation because no FDA approved indication*

*Authors’ Preferred Method of Treatment

Wagner, et al. Chapter 5, Rockwood and Green’s Fractures in Adults, 8th ed

Orthobiologics

• Physical enhancement of fracture repair
  - Mechanical and biophysical stimulation
    + Distraction osteogenesis
    + Electrical stimulation
    + Ultrasound stimulation
    + Extracorporeal shock wave lithotripsy
  No preferred method of treatment because of Methodological issues*

*Authors’ Preferred Method of Treatment

Wagner, et al. Chapter 5, Rockwood and Green’s Fractures in Adults, 8th ed
NEW BONE. NEW STRENGTH

FORTEO® [teriparatide (rDNA origin) injection] Stimulates New Bone Formation

These microCT images of iliac crest bone biopsies were obtained from a 65 year-old women who had a BMD response that is representative of the treatment group.

Jiang et al, J Bone Miner Res. 2002;17(Suppl 1):S135
Warning

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor), that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, teriparatide should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. Teriparatide should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget’s disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, or prior radiation therapy involving the skeleton) (see WARNINGS and PRECAUTIONS, Carcinogenesis).

Safety of Osteoanabolic Therapy: A Decade of Experience

- Ten years of safety and use of teriparatide (PTH 1-34) by more than 1,000,000 pts avg about 12 mos of use; actual use of PTH 1-84 unknown
- 3 cases of osteosarcoma associated with use; all adjudicated by the FDA as unrelated to teriparatide: one case had osteosarcoma before started and two cases associated with XRT

The US Postmarketing Surveillance Study of Adult Osteosarcoma and Teriparatide: Study Design and Findings From the First 7 Years

• Established in 2003 to evaluate potential association between teriparatide and osteosarcoma in humans based on preclinical (animal) findings
• Between June, 2004, and September 30, 2011, 1448 cases were identified by participating cancer registries (est to be 62% of all adult cases in the US)
• Mean age 61 yrs, 46% female, 86% white
• After 7 years of study, there were NO osteosarcoma patients who had a prior history of teriparatide treatment


FORTEO® [teriparatide (rDNA origin) injection] Warnings

• The following categories of patients have increased baseline risk of osteosarcoma and therefore should not be treated with FORTEO:
  ▪ Paget’s disease of bone
  ▪ Pediatric populations (open epiphyses)
  ▪ Prior radiation therapy involving the skeleton
• Patients who have any of the following conditions also should not receive FORTEO:
  ▪ Bone metastases or a history of skeletal malignancies
  ▪ Metabolic bone diseases other than osteoporosis
  ▪ Pre-existing hypercalcemia
  ▪ Pregnancy and lactation
Studies of The Mechanism of Action of PTH in Murine Fracture Healing

PTH Treatment Leads to Increased Chondrogenesis

A. DAY 5 10

Con

PTH
Teriparatide (Forteo™): Human Studies in Fracture Healing

ENS/NCIBH Series as of 6-19-15:
250+ cases: acute fractures, stress fractures and non-unions (non-FDA approved indications)

Over 1800 + cases of utilization of teriparatide for FDA approved indications
Teriparatide (Forteo™) for Acceleration of Fracture Repair in Humans: A Prospective, Randomized, Double-blind Study of 102 Postmenopausal Women with Distal Radial Fractures

- 45-85 yo Pmp women who sustained a dorsally angulated distal radial fracture in need of closed reduction
- PBO n=34, 20mcg Forteo n=34, 40mcg Forteo n=34 for 8 weeks of tmt; start within 10 days of fracture
- Time to healing based on X-ray and CT scan
- Time to healing: PBO 9.1 weeks, 20mcg 7.4 weeks, 40mcg 8.8 weeks

Aspenberg, et al. J Bone Miner Res epub ahead of pub; accessed 12-7-09

Teriparatide (Forteo™) for Acceleration of Fracture Repair in Humans: A Prospective, Randomized, Double-blind Study of 102 Postmenopausal Women with Distal Radial Fractures

- Median time to healing 20mcg vs PBO $p=0.006$; 40mcg vs PBO $p=0.053$
- Median time to first CT scan evidence of cortical bridging at 3 of 4 cortiices was 9.1, 7.2 and 8.6 weeks for PBO, 20mcg and 40mcg
- No safety differences
- The clinically available dose performed better than a higher dose
- Other fracture sites may be more appropriate to try

Aspenberg, et al. J Bone Miner Res epub ahead of pub; accessed 12-7-09
Parathyroid Hormone 1-84 Accelerates Fracture-Healing in Pubic Bones of Elderly Osteoporotic Women

• 65 patients adm to hospital with acute pelvic fractures
• DXA, X-ray, CT of pelvis
• 21 pts tx w PTH 1-84, 100mcg once daily starting with 2 days of adm; 44 control grp; all received 1000mg of calcium and 800iu vit D
• CT q 4 weeks till cortical bridging at fx site
• Time to healing in PTH grp: 7.8 weeks comp w 12.6 weeks in control grp


• Newer evidence suggests that these fractures are stress or insufficiency fractures
• There is inconsistent evidence that teriparatide may advance healing of atypical femoral fractures
• At this time (2013), there is no randomized, placebo-controlled trial of teriparatide treatment
• There is anecdotal discussion in “chat rooms” of the use of bone stimulators in these cases

A recently treated patient
History

• The patient, a 66 y/o, RT handed married white male, a medically disabled butcher, was seen for the first time on 9-2-11 for evaluation of non-union of a right medial malleolar fracture. He stated that he didn’t know what happened to his ankle. He had been in a COPD exercise class for 7 weeks when his ankle “started to hurt.” He taped it up, but one week later, he saw his orthopedist. An X-ray in late April, 2011, showed a fracture. No trauma. When started program, “couldn’t hardly walk,” when done (7 weeks), “could walk for 1 hour without stopping.” Multiple previous fractures due to motorcycle accidents. Spinal fusion, 1983. Smoked 3 ppd for 30 years, stopping 12-14 years ago. Intermittent prednisone for COPD. NSAID for 2-3 years; none for 6 months. “Probable” alcoholic; none for 15 years. Taking a multivit for years and vitamin D3 1000iu “for a couple of months.”

Clinical Course

• Tallest remembered height: 6’1”; height measured on wall-mounted stadiometer 5’9 ¼”. Weight 298lbs. BMI 43.7. Swollen right ankle. Testes small, soft, DRE negative.
  ◊ 9-3-11 Start EXOGEN low dose pulsed US one treatment per day
  ◊ 9-23-14 Start Heart Healthy Diet
  ◊ 9-24-11 Start teriparatide (Forteo) 20 mcg subq daily
  ◊ Increase vitamin D3 from 1000iu to 2000iu per day
  ◊ 10-20-11 Start Androgel 1% 5gm pkt, apply one per day
  ◊ 5-12-12 Increase vitamin D3 to 5000iu per day
  ◊ 8-26-13 Weight 266 lbs, down 32 lbs
  ◊ 9-24-13 Stop teriparatide (Forteo), fracture healed
  ◊ 8-21-14 Weight 261 lbs, down 37 lbs
  Height measured on wall mounted stadiometer 5’9 ½”, BMI 38
  One year post-fracture healing follow-up
**DXA**

*These studies were performed on a Hologic Discovery A densitometer utilizing software version 13.3*

<table>
<thead>
<tr>
<th>Exam Date: 9-2-11</th>
<th>9/13/2012</th>
<th>9/24/2013</th>
<th>8/25/2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AP Spine (L1-L4)</strong></td>
<td>BMD g/sqcm</td>
<td>T-score</td>
<td>Z-Score</td>
</tr>
<tr>
<td>1.506</td>
<td>3.8</td>
<td>4.6</td>
<td>1.624</td>
</tr>
<tr>
<td>Femoral Neck (Right)</td>
<td>0.954</td>
<td>0.2</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Total Hip (Right)</strong></td>
<td>1.087</td>
<td>0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>1/3 Forearm (Right)</td>
<td>0.780</td>
<td>-0.7</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>VFA</strong>*</td>
<td>No VCF</td>
<td>No VCF</td>
<td>No VCF</td>
</tr>
<tr>
<td><strong>TBS</strong>**</td>
<td>1.127</td>
<td>1.019</td>
<td>1.166</td>
</tr>
</tbody>
</table>
Conclusions/ References

• Current osteoanabolic therapy can heal fracture non-unions but the length of time to do so may be prolonged.

3. Bukata, S. et al. #1-34 PTH at Physiologic Doses in Humans Shows Promise as a Helpful Adjunct in Difficult to Heal Fractures: An Observational Cohort of 145 Patients, ISCD Meeting, 2010
Summary and Conclusions

• To date, no clinical or scientific assessment can reliably predict successful fracture healing or nonunion¹

• The current problem of nonunion is delayed diagnosis leading to months of pain, suffering, physical therapy, inability to perform ADLs, additional surgeries and tremendous increase in costs

• Prevention (or early treatment) is not possible after waiting months to make the diagnosis of mature nonunion by clinical or radiographic tests

Summary and Conclusions

• Early intervention by changing conservative management or initiating surgical intervention or initiating anabolic therapy with bone growth stimulating devices, orthobiologics or newer anabolic agents could prevent further complications, prolonged patient distress, surgeon anxiety and disability

• An early review of risk factors, metabolic and endocrine abnormalities, bone turnover markers and other biomarkers (? bone quality) should be considered; in 5-10 years, this will include genetic analysis


FRANK and I thank you for this opportunity. We hope your understanding of nonunion fractures and NEW APPROACHES TO THEIR TREATMENT improves and your use of medical care to assist patient care increases.
For Your Reading Pleasure

- Technology Assessment Program. The Role of Bone Growth Stimulating Devices and Orthobiologics in Healing Nonunion Fractures, Agency for Healthcare Research and Quality, Rockville, MD, 9-21-05
- Zuscik, Skeletal Healing, Ch 11, Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 8th ed, ASBMR, 2013
- Morgan and Einhorn, Biomechanics of Fracture Healing, Ch 12, Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 8th ed, ASBMR, 2013
- Barnes, et al., Growth Factor Regulation of Fracture Repair, J Bone Miner Res, 14 (11):1805-1815
- Einhorn and Gerstenfeld, Fracture healing: mechanisms and interventions, Nat Rev Rheum, 2015, 11:45-54