MEDICAL
CONSIDERATIONS IN
ATHLETES WITH STRESS
FRACTURES

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Osteoporosis Update: 2015, 6-19-15

The Clark Miller Center for the Evaluation and Treatment of Stress Fractures and the Center for Accelerated Fracture Healing
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Topics for Discussion

- Stress fractures
  - Spectrum of bone stress injuries and Definitions
- Epidemiology
- Pathogenesis
- Evaluation: clinical, imaging, lab
- Treatment: basic to complex
- Outcome/s
- Bone marrow edema (syndrome)
  - New concepts of pathogenesis
  - Newer treatment/s
- Summary and Conclusions

“Spectrum” of Bone Stress: Injuries and Definitions
Definitions

• Shin Splints
• Stress Reactions
• Stress Fractures

There is no “official” definition of any of these presumably stress-related lesions in bone: AAOS, ACSM, ASBMR, etc.

A presumed “spectrum” of “overuse” injury

Bone marrow edema syndrome

Updated: June 6, 2007, 5:21 PM ET
Bonds held out of lineup with shin splints, aching knees

PHOENIX -- Barry Bonds was held out of the San Francisco Giants' starting lineup Tuesday night for the series opener against Arizona because of shin splints that have been bothering the slugger.
Mauer’s injury scares Twins but is not considered serious
The catcher will rest a few days after being diagnosed with a stress reaction in his left fibula.

By La Velle E. Neal III,
Star Tribune
Last update: March 22, 2007 - 9:31 PM

Joe Mauer Sidelined With a Stress Reaction

Stress Fracture/s

• A partial or complete bone fracture that results from repeated application of a stress lower than the stress required in order to fracture the bone in a single loading¹

• The change in the bone is usually focal, unlike shin splints, which results in a more diffuse injury

¹ Joseph M. Lane, MD, Hospital for Special Surgery, NY
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 Herm 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.
Elite Athletes and Teams Seen in Last 8 Years

- San Diego Chargers 2
- Houston Texans 1
- Oakland Raiders 4
- NY Football Giants 2*
- University of Georgia 1*
- UC Davis 1
- Los Angeles Lakers 1
- Golden State Warriors 4
- Philadelphia 76ers 1
- Houston Rockets 1*
- Charlotte Bobcats 1*
- Brooklyn Nets 1
- New Orleans Pelicans 1
- UC Berkeley 2
- San Diego State 2*
- Oakland Athletics 10
- Colorado Rockies 2
- Los Angeles Dodgers 1
- Los Angeles Angels 1
- Detroit Tigers 1
- Arizona Diamondbacks 1
- Cleveland Indians 1*
- US Olympic Skating 1**
- NBA free agent 1

*Consulted but not seen; **On the schedule to be seen

The Comprehensive Description of Stress Fractures: A New Classification System

Basic Physiology of Bone
The Goal: Increased Bone Strength

NIH Consensus Statement 2000


Bone Strength = Bone Quality and Bone Mineral Density

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

\[ \text{aBMD} = \text{g/cm}^2 \]
\[ \text{vBMD} = \text{g/cm}^3 \]

Stress Fractures
Epidemiology of Stress Fractures

• The findings from military recruits (many of whom are under-trained) may NOT generalize to athletes (many of whom are well or over-trained) as they may represent different populations¹

¹ Shima et al, Knee SurgSports Traumatol Arthrosc, pub online, 12-2-08

Epidemiology of Stress Fractures: Runners

• In 1998, there were 10.8 million runners in the US; runner—a person who runs at least 100 times per year (Amer Sports Data survey)
• 35-50% of runners injured per year¹
• 6-15% of running injuries were lower extremity stress fractures (4.6%)²
• 462,000 stress fractures per year³

Epidemiology of Stress Fractures: Runners

- Stress fx – 10% of all sports overuse injuries
- Runners comprise 72% of stress fractures in typical sports medicine practice

Stress Fracture Data in NBA Players 1988 to 2009

No data available on age, ethnicity, time from 1st complaint to time of diagnosis, time missed, cost, recurrence, op v no op, etc
Pathophysiology of Stress Fractures: Proposed Mechanisms

- Excessive repetitive loads
- Bone resorption ≠ formation
- ↑↑ duration, intensity, frequency of activity
- Lack of adequate rest may ↑ osteoclast activity
- Hyperphysiologic loading makes bone susceptible to micro-fractures → macro-cracks → stress frx
- FINAL COMMON PATHWAY MAY BE TISSUE ISCHEMIA INDUCED BY TISSUE INJURY AND SUBSEQUENT SWELLING IN THE TISSUES OCCLUDING CAPILLARIES

Boden, 2002; Romani, 2002
How Stress Fracture Incidence Was Lowered in the Israeli Army: A 25-yr Struggle

• PHARMACOLOGIC AGENTS: Their basic and human research (including implantation of strain gauges in the legs of elite military police) led them to conclude that tibial and femoral stress fractures are mediated by bone remodeling; when bone is subjected to strains or strain rates that are higher than usual or have a different distribution, it remodels to repair micro-damage and strengthen itself; during the initial resorption phase of remodeling, the bone is transitorily weakened and micro-damage can accumulate, leading to stress fracture


Conversations Among Bone Cells

1. Osteoclasts
2. Osteoblasts
3. Osteocytes

Courtesy of David Dempster, Ph.D.
The Osteocyte

Marotti G, 1996.

Key Points

• Bone remodeling occurs in specialized vascular compartments

• Osteoclasts are derived from circulating mononuclear cells…and this may also be true of a subset of osteoblasts

• The osteocyte protein, sclerostin, is a key regulator of bone formation

• The RANK ligand/OPG system is the key regulator of bone resorption


Normal Sclerosteosis / van Buchem’s
Key Points

- **Bone remodeling** is the biologic mediator of bone structure and strength.
- The mechanisms underlying the all-important coupling of formation to resorption are becoming clearer and there is growing evidence of bidirectional communication between **osteoclasts** and **osteoblasts**.
- We are beginning to appreciate the function of the **osteocyte** and the mechanisms by which they are able to sense and communicate changes in their mechanical environment.

The Osteocyte Mechanosensor

You et al, PNAS 2004
Microdamage Disrupts Canalicular Flow and Kills Osteocytes

Osteocyte Death Triggers Renewal

Aguirre, JBMR 2006
Thoughts for 2013

• Damaged bone requires replacement
• Micro-cracks can damage the osteocyte and its processes inducing signals for osteoclast recruitment to initiate bone removal and repair
• Microdamage and bone fatigue are associated with loss of osteocyte integrity
• Osteocytes are a key target cell for the anabolic actions of PTH due to down-regulation of osteocyte SOST expression¹
• “May play a role in stress fr pathogenesis: some people may have osteocytes that are less sensitive to mechanical loading and fatigue damage and so are more prone to develop stress fr”²


A Hypothesis for 2014 and Beyond¹

• Stress fractures may be due to disordered, dysfunctional or diseased osteocytes where fluid mechanics, shear/strain forces, mechanosensory forces, mechanotransducer forces and production and release of bone growth inhibitors (Dkk1, SOST) and stimulators (wnt signaling via β-catenin) at the cellular level result in abnormal bone remodeling, including bone resorption and bone formation

¹ Personal thoughts
Evaluation of the Stress Fracture Patient

INRINSIC AND EXTRINSIC FACTORS IN THE CAUSATION OF STRESS FRACTURES

Intrinsic Risk Factors
• Gender
• Age
• Ethnicity
• Body Mass Index
• Bone characteristics
• Muscle strength
• Pre-training fitness level
• Lower extrem morphol
• Nutrition factors
• Genetics
• Menstrual dysfunctions
• Muscle fatigue
• Flexibility
• Prev injury and adeq/inadeq rehab

Extrinsic Risk Factors
• Training errors
• Training surfaces
• Worn-out/inappropriate footwear
• Excessive training intensity
• Environment

Adapted from Rosenthal and McMillan, Recruit Medicine, Chapter 11, 2006
Pes Planus
Rearfoot Varus
Genu Valgum
Pes Cavus

Excessive Pronation
Femoral Neck Anteversion
Lower Extremity Malalignment

Plain Radiographs
Bone Scan & SPECT
CT Scan
MRI

History & Physical Exam

Imaging

Courtesy of G. Matheson, M.D.
DXA: Not for diagnosis of stress fracture but for diagnosis of low bone density to help differentiate fragility fractures from insufficiency fractures
Secondary Causes of Low Bone Mass

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

Adapted from ISCD BDC

There is NO study that looks at secondary causes of metabolic bone disease/osteoporosis in any population of stress fracture patients
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)

MULTIPLE FRACTURES:
Stress Fractures or Underlying Metabolic Bone Disease?

Unfortunately, never (or not yet) evaluated
Management of Stress Fractures

The Comprehensive Description of Stress Fractures: A New Classification System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Pain</th>
<th>Radiographic Findings (CT, MRI, Bone Scan, or Radiograph)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No</td>
<td>Imaging evidence of stress fracture, no fracture line</td>
<td>Asymptomatic stress reaction</td>
</tr>
<tr>
<td>II</td>
<td>Yes</td>
<td>Imaging evidence of stress fracture, no fracture line</td>
<td>Symptomatic stress reaction</td>
</tr>
<tr>
<td>III</td>
<td>Yes</td>
<td>Non-displaced fracture line</td>
<td>Non-displaced fracture</td>
</tr>
<tr>
<td>IV</td>
<td>Yes</td>
<td>Displaced fracture (≥2 mm)</td>
<td>Displaced fracture</td>
</tr>
<tr>
<td>V</td>
<td>Yes</td>
<td>Nonunion</td>
<td>Nonunion</td>
</tr>
</tbody>
</table>

Stress Fracture History of an NBA Center: Seen on 5-19-15

- Last time foot well was early in 2011/2012 season; foot became “sore;” imaging: stress fracture; placement of a screw; played 3-5 games; after All Star game, foot “didn’t feel right;” imaging: “not healed;” and “shut down” for rest of season
- Played 2012/2013 season with foot pain-free; at end of season, “routine” X-ray showed screw bent so bigger screw placed; there was still “a tiny line”
- Played 20 games (out of 82) of 2013/2014 season; foot pain recurred; new screw placed and 1st metatarsal osteotomy with bone graft performed 1-4-14; Forteo 2 months (1-14 to 3-14); didn’t play any more
- Played 2014/2015 season but, at end, routine X-ray on 5-7-19 saw “a line;”
Approaches to the Management of Stress Fractures

• “Classical” Non-medical Approach—physical therapy, non- and partial weight-bearing, bone stimulation devices, shock-wave lithotripsy, surgery

• “New” Medical Approach—calcium, vitamin D, teriparatide (Forteo™) and bisphosphonates, newer anabolic agents on the horizon; BMPs, PRP, HBO, MSC

Calcium and Vitamin D Supplementation Decreases Incidence of Stress Fractures in Female Navy Recruits

• 5201 female navy recruits randomized to 2000 mg of calcium and 800 iu of vitamin D or placebo (dbRCT)
• 8 week basic training program
• 309 fracturing individuals sustained 496 fractures (53 femur and pelvis, reminder tib/fib, foot)
• 20 % reduction in stress fx in treatment grp

**Vitamin D**

- Worldwide, 50% of individuals are vitamin D insufficient or deficient
- Studies of the GSW at preseason physicals in 2007, 2008 and 2009 showed between 9-12/16 individuals per year were deficient or insufficient; NY Football Giants (2010) 80%, <32 ng/mL, 28% < 20ng/mL; Oakland A’s (2011) 90% “low” (<30ng/mL)
- Vitamin D supplementation, in the elderly, well known to improve muscular, neurologic and bone status (prevent falls, improve coordination, prevent fractures)

**Association Between Serum 25(OH)D Concentrations and Bone Stress Fractures in Finnish Young Men**

- 800 randomly selected healthy Finnish military recruits starting training, mean age 19
- 90 day trial
- 30 stress fractures in 22 recruits: 13 tibia, 10 metatarsals, 3 calcaneus, 2 tarsal navicular, 1 inf pubic ramus, 1 femur
- Developed avg or 39 (4-70) days after start of training
- VD in str fr indivs avg 25.7ng/mL vs 30.5 in non-fr (p < 0.017); below median 81.8% (p <0.002)

Higher 25(OH)D Levels Are Associated With Better Lower Extremity Function in Ambulatory Women

- 4,100 ambulatory adults included in NHANES III
- 60 to ≥90 years
- Functional measurements used to assess lower extremity function:
  - 8-ft walking speed test
  - Timed sit-to-stand test

LOWESS = locally weighted regression plot.
Reference range of 22.5–94.0 nmol/L (9.0–37.7 ng/mL).
N = 4,100; P<0.001.


Athletic Performance and Vitamin D

- Reviewed the world’s literature for evidence about vitamin D and athletic performance
- UV light (producing vitamin D, improves athletic performance
- Physical and athletic performance is SEASONAL: peaks when 25 (OH) vit D levels peak (Sept-Oct), declines as vitamin D levels decline, reaches lowest level when vitamin D at nadir (Apr-May)
- Increases number and size of Type II (fast twitch) muscle fibers
- Most RCTs in older individuals
- PEAK ATHLETIC PERFORMANCE MAY OCCUR WHEN 25 (OH) VITAMIN D LEVELS ARE “AT LEAST 50ng/mL.”

Sports teams start using vitamin D to “improve” performance

Athletic Performance and Vitamin D

“First Vitamin D Team in Modern Sports History”
Treatment Guidelines for Low-Risk Stress Fractures

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Suggested Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any pain level</td>
<td>Modify activity to a pain-free level for 4 to 8 weeks, depending on injury grade; modify risk factors</td>
</tr>
<tr>
<td>Pain with no functional limitations</td>
<td>Modify activity to a stable or improving pain level; close monitoring; modify risk factors</td>
</tr>
<tr>
<td>Pain with functional limitations</td>
<td>Decrease activity level until pain subsides and functional pain level has been reached; modify risk factors</td>
</tr>
<tr>
<td>Pain intensifies despite functional activity modification (patient unable to perform at any reasonable functional level despite modifications)</td>
<td>Complete rest, immobilization; surgery; modify risk factors</td>
</tr>
</tbody>
</table>


Ways to Accelerate Fracture Healing
Benefits of faster healing

Faster healing may result in
- Earlier return to work and normal daily activities
- Quicker time to weight bearing
- Faster time to cast removal
- Increased patient satisfaction
- Lower cost and less need for secondary procedures

What would faster healing mean for you and your patients?

Survey of 450 Canadian orthopedic trauma surgeons (Busse, Acta Orthop, 2008)¹
- 80% indicated that a reduction in healing time of 6 weeks or more that is attributed to fracture stimulation technology would be clinically important

Recent market research (Data on file)²
- 80% of surgeons said that accelerated healing by 4 to 6 weeks would justify their use of fracture stimulation technology

What percent decrease in healing time would prompt you to consider use of fracture stimulation technology?

BONE GROWTH STIMULATORS

DONJOY METATARSAL CASE STUDY

DONJOY SPINALOGIC (EMF)

EBI Bone Healing System

Exogen Bone Healing System (US)
Indications for Use of Non-Invasive Bone Growth Stimulators

- EXOGEN: Indicated for the non-invasive treatment of established non-unions* excluding skull and vertebra.

  Indicated for accelerating the time to a healed fracture for fresh, closed, posteriorly displaced distal radius fractures and fresh, closed or Grade I open tibial diaphyseal fractures in skeletally mature individuals when these fractures are orthopedically managed by closed reduction and cast immobilization.

NEW BONE. NEW STRENGTH
Effect of Teriparatide (Forteo™) on 2D and 3D Bone Histomorphometry

- Increased trabecular bone volume
- Increased trabecular bone connectivity
- Increased cortical bone thickness with no increase in cortical porosity
- Shifted trabeculae toward a more plate-like structure

Jiang et al. JBMR 2003; 18:1932-1941

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).

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

The Addition of Forteo™ In The Treatment Of A Delayed Surgical Repair Of A Non-Union Scaphoid Fracture In An NCAA Division-1 Football Player: A Case Study

Seagraves BL, Muchnick PW, Courson RW, Bolgla LA: University of Georgia, Athens GA, and Medical College of Georgia, Augusta, GA

Scaphoid fracture in a 17-year-old African-American collegiate football player. Injury to the right wrist during his senior year of high school. X-rays and MRI to the right wrist confirmed an unstable, non-union scaphoid fracture. No evidence of avascular necrosis. Percutaneous pinning. Following surgery, the athlete began a 28-day course of the drug Forteo™ (750 mcg/3 mL SOL) via percutaneous injection. Cast immobilization. Customary scaphoid fracture management consisting of bone stimulation and progressive range of motion and strengthening exercises. Post-op month 2, the athlete exhibited improved right wrist function, with no side effects from the drug and signs of bone consolidation. At post-op month 4, the athlete was pain-free and demonstrated improved signs of bone consolidation. Returned to full contact practice. **Uniqueness:** The player in this case study initially presented with a non-union scaphoid fracture that had occurred a year earlier. Based on this presentation, the hand surgeon recommended a 28-day course of Forteo™ to promote bone strength. **Conclusion:** Findings from this case report inferred that the addition of Forteo™ resulted in the consolidation of a non-union scaphoid fracture that a collegiate football player sustained a year earlier.

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


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Why TPTD for Fracture Healing Applications?

- Anabolic therapy for osteoporosis
- Stimulates mesenchymal stem cell recruitment and osteoblastic differentiation
- Stimulates VEGF expression
- Works through signals similar to PGE2
- Effect on osteocytes?

Adapted from Marcus, Santa Fe Bone Symposium, 2010

Teriparatide & Fracture Healing
Animal Studies
More than 15 nonclinical studies of fractures demonstrate that treatment with TPTD:

- Enhances external callus volume and quality
- Improves callus calcification
- Improves biomechanical strength
- Reduces time to fracture healing

Adapted from Marcus, Santa Fe Bone Symposium, 2010
Studies of The Mechanism of Action of PTH in Murine Fracture Healing

PTH Treatment Leads to Increased Chondrogenesis
1-34 PTH at Physiologic Doses in Humans Shows Promise as a Helpful Adjuvant in Difficult to Heal Fractures: An Observational Cohort of 145 Patients

Susan Bukata, Lee Kaback, David Reynolds, Regis O'Keefe, and Randy Rosier
University of Rochester
Rochester, NY
Results

- 135/145 (93%)
  - radiographic and clinical union of fracture
- 6/145 (4%)
  - partial radiographic union
  - clinically functioned as healed fracture
- 4/145 (3%)
  - failed pain improvement and radiographic union
    - One humerus
    - One femoral neck nonunion
    - Two odontoid fracture nonunions

Adapted from Bukata, ISCD, 2010

Problems with observational cohort

- Obvious patient selection bias
- Not case matched controls
- May provide data to plan future clinical trials
  - Appropriate patients
  - Appropriate fractures/fusion sites

Adapted from Bukata, ISCD, 2010
ENS/NCIBH Series as of 16-19-15:
250+ cases: acute fractures, stress fractures and non-unions (non-FDA approved indications)

Over 1800 + cases of utilization of teriparatide for FDA approved indications

ENS/NCIBH Series as of 12-4-10
Major League and Minor League Baseball Players (n=11); Fractures 17 (+1)

• 1. Fractured 5th metacarpal (HBP); 25 VD 44; Forteo + EXOGEN; healed 3 weeks
• 2. Two courses of Forteo: 2 fractured ribs; stress fxs; swing; traumatic fractured ankle + EXOGEN (?bone spur); 25 VD 53; back pain ? stress fracture L5
• 3. Two courses of Forteo + EXOGEN; fractured thumb; fractured hand; healed 4 weeks; 25 VD 49
• 4. Stress fracture upper femoral shaft; landing leg; VD ?; Forteo + EXOGEN; healed 6 weeks
• 5. Two navicular stress fractures; 2 ORIF; non-union X 2 yrs; 25 VD 20; Forteo + EXOGEN; healed 4.5 months; 39 HRs; 114 RBI
• 6. Two ? long-standing tibial stress fractures with marked bony overgrowth; asymptomatic; 25 VD 32; Forteo + EXOGEN; no healing at 3 months. Apparent healing 1 yr later. No post tmt imaging.
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 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


Bisphosphonates
Use of bisphosphonates for the treatment of stress fractures in athletes

“…there is still no conclusive evidence to prove any effect of bisphosphonates on stress fractures in humans. Until the results of well-designed clinical trials are available, it is prudent to limit the use of bisphosphonates in the treatment of stress fractures.”

Shima, Knee Surg Sports Traumatol Arthrosc, accessed on line, 1-2-09

Bone marrow edema syndrome
Bone marrow edema syndrome

• Bone pain, particularly in hip joints, with negative X-rays (sometimes, focal loss of radio-density), positive bone scans, first correlated with MRI findings, in 1988¹
• Also called “transient marrow oedema syndrome.” or “transient osteoporosis”
• Regresses in 6-12 months and requires no surgery
• Eventually, some felt it required core decompression

¹ Wilson et al. Radiology, 1988;167:757-760;

Effective and rapid treatment of painful localized transient osteoporosis (bone marrow edema) with intravenous ibandronate

• A rare disorder of unknown etiology characterized by acute onset of disabling bone pain
• Marrow edema on MRI; NMBS + indicating incr vascularization and bone turnover
• INCREASED BONE TURNOVER (on biopsy) = “high turnover osteoporosis”
• Core decompression now considered too invasive
• We see after traumatic sports injuries where bone marrow edema lasts for weeks to months with increased pain and decreased function

Ringe et al. Osteoporos Int, 2005; 16:2063-2068
Effective and rapid treatment of painful localized transient osteoporosis (bone marrow edema) with intravenous ibandronate

- 12 patients
- Initially treated with IV infusion of 4mg of ibandronate; a second IV infusion of 2mg optional after 3 months; (available in US in a 3mg vial)
- After 1 month, pain decreased by 43%; by 3 months, 78%; by 6 months, 94%
- No QOL study; not athletes, no data on rehab, return to play, etc.¹
- We have treated 4 professional basketball players (and assisted 2 college basketball players) with IV ibandronate 3mg once each with relief of pain within 2-4 weeks with return to play after missing 2 + months; 1 prof BB player got 2 doses 3 months apart²

¹Ringe et al. Osteoporos Int, 2005; 16:2063-2068; ²With TA Abdenour, Ph.D., ATC

Treatment of painful bone marrow edema syndrome with intravenous bisphosphonates

- Aim of study was to assess efficacy of IV ibandronate or zoledronate in treatment of BME around knee and ankle
- 30 pts with ankle-BME and 41 pts with knee-BME (ibandronate 3x6mg or zoledronate 1x5mg)
- Mean pain score decreased from 8.1 and 7.9 to 1.6 and 2.0, respectively, at 6 months; various function scores increased signif from bsl to 6 months; MRIs showed signif decrease in BME-size or complete normalization in 70% of cases in both groups
- Both IV BPs were very effective and shorten the course of the disease³

³Bartl et al. Podium Presentat, AAOS, No. 242, 3-10-10
Table 4. Comparison of stress fractures incidence by sites and grades before (1983) and after (2003) the modifications of the training program (minimum sleep requirement and decreased cumulative marching).

<table>
<thead>
<tr>
<th>Variable</th>
<th>1983</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence of stress fractures (%)</td>
<td>30.8</td>
<td>11.6</td>
</tr>
<tr>
<td>% of stress fractures-tibia</td>
<td>56.1</td>
<td>35.7</td>
</tr>
<tr>
<td>% of stress fractures-femur</td>
<td>33.6</td>
<td>50.0</td>
</tr>
<tr>
<td>% of stress fractures-metatarsus</td>
<td>7.6</td>
<td>8.9</td>
</tr>
<tr>
<td>% of stress fractures-other sites</td>
<td>2.7</td>
<td>5.4</td>
</tr>
<tr>
<td>% grades 1-2 stress fractures</td>
<td>52.8</td>
<td>91.1</td>
</tr>
<tr>
<td>% grades 3-4 stress fractures</td>
<td>47.2</td>
<td>8.9</td>
</tr>
</tbody>
</table>

How Stress Fracture Incidence Was Lowered in the Israeli Army: A 25-yr Struggle-SUMMARY AND CONCLUSIONS

• Stress fractures in Israeli infantry basic training have been reduced from 31% to less than 10% as a result of a systematic study during the past 25 yrs
• Additionally, the severity of stress fractures has been reduced as judged by scintigraphic grading
• Reduction achieved by MODIFIED TRAINING PROGRAM WITH REDUCED CUMULATIVE MARCHING and an ENFORCED SLEEP REGIMEN accompanied by an INCREASED AWARENESS of the problem by the staff
• This reduction has NO ECONOMIC COST

Summary and Conclusions-I

• Stress fractures are NOT traumatic fractures and cannot be treated like traumatic fractures; Applied Load eventually exceeds Bone Strength (over time not momentarily) resulting in a fracture but may result in other stress injuries, e.g., “shin splints” and “stress reactions”
• More time needs to be spent on evaluating and resolving, where possible, the Intrinsic and Extrinsic Risk Factors for better understanding of the pathogenesis and prevention of the injury in individual patients
Summary and Conclusions-II

- The epidemiology of stress fractures is poorly known; the costs to society, to the individual, to the sport, to the team are poorly understood and have never been calculated. (At one US Army training base, recent estimates that over the span of one year, $26 million was lost in training costs for the 749 soldiers who were discharged from training because of stress fractures, an average of over $34,000 per soldier)¹
- The pathogenesis is poorly or incompletely understood
- The role of possible underlying metabolic bone disease is almost never considered (except in amenorrheic females)


Summary and Conclusions-III

- A better understanding of the presence or absence of Secondary Causes of bone disease is needed
- In my view, medical treatment with calcium, vitamin D and presently available (and future) anabolic agents should be tried before surgical intervention; ? NEW PARADIGM
- The exact success of surgical intervention is unknown; no RCT; outcome data on time to return to play, recurrence of the original fracture, occurrence of a new stress fracture, progression to complete fracture, etc., is unknown
Summary and Conclusions-IV

• Most of the data we have is from small case series that have no control groups so we don’t know if rest (partial or non-weight bearing) is better than any other treatment; we have no adequately powered series of rest vs surgery; and, now, no series of rest vs surgery vs medical treatment so the optimal approach to treatment is unclear

• The approach to rehabilitation is POORLY individualized and patients are advanced too quickly and returned to activity too early

• Over the next 10-20 years, the development of newer anabolic agents may make the approach to the treatment of stress fractures radically different than it is today

FRANK and I thank you for this opportunity. We hope your understanding of stress fractures and NEW APPROACHES TO THEIR TREATMENT improves and your use of medical care to assist patient care increases.
Which one do I need to read?

For Your Reading Pleasure

• Bonewald. The Amazing Osteocyte, J Bone Miner Res, 26 (2):229-238, 2011
• Burr and Milgrom, eds., Musculoskeletal Fatigue and Stress Fractures. CRC Press, 2001
• Brukner, Bennett and Matheson. Stress Fractures, Blackwell Science Asia Pty Ltd, 1999
• Bennell K, Bruckner P. How should you treat a stress fracture? Evidence-based Sports Medicine, BMJ Books, 2002
• Rosenthal MD, McMillian DJ. Chapter 11, Comprehensive Evaluation and Management of Stress Fractures in Military Trainees. Recruit Medicine, Textbooks of Military Medicine, Office of the Surgeon General, Department of the Army, United States of America and US Army Medical Department Center and School Fort Sam Houston, Texas 2006