The Orthopedic Implications Of Prolonged Bisphosphonate Therapy In Osteoporosis

Orthopedic Implications Of Osteoporosis

**Introduction**

- Osteoporosis Most Common Metabolic Bone Disease Worldwide
- Silent Disease – Bone Loss Occurs Without Symptoms
- Physician Recognition Following Fragility Fractures Is Low (USA)

**Orthopedic Implications Of Osteoporosis**

- Osteoporosis Is The Absolute Reduction In Bone Volume And Mass
- The Bone Is Otherwise Normal
- Loss Of Mechanical Strength
- Leads To Fragility Fractures
Orthopedic Implications Of Osteoporosis

**Introduction**

- High Levels Of Awareness
- Promoted On Television
- News Media Coverage
- 10% Of Women > Age 55 Years In The USA Take "Medication" To Prevent Fractures

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**Burden Of Disease**

- Life Time Risk Of Fragility Fractures In **Women** 40%-50%
- Life Time Risk Of Fragility Fractures In **Men** 13%-22%
- Worldwide 25 Million Fragility Fractures Annually
- Fragility Fractures Result In
  - Increased Morbidity & Mortality
  - Loss Of Quality Of Life

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**Fragility Fractures**

- Pathologic Fx 2° To Weak Bone
- Defined As A Fall From Standing Height Or Less
  - Vertebral Compression Fx
  - Hip Fracture
  - Distal Radius Fracture
  - Proximal Humerus Fracture
### Fragility Fractures
#### Epidemiology > 65 Years

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<tr>
<td>Hip</td>
<td>Distal Radius</td>
<td>Proximal Humerus</td>
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### Orthopedic Implications Of Osteoporosis

#### Demographics
- Yearly Cost Of Fragility Fx’s > $20B
- 400,000 Hip Fractures / Yr USA
  - 25% End Up In Nursing Home
  - 50% Do Not Regain Pre-Injury Activity
  - 25% Die Within One Year
  - $50K In The First 90 Days

### Osteopenia - Osteoporosis
#### Treatment Strategies
- Diet & Exercise
- Calcium & Vitamin D
- Non-Invasive Screening
- Pharmacologic Treatment
Osteopenia - Osteoporosis

Treatment Strategies

- Pharmacological Rx Indicated
  - Metabolic Abnormalities Corrected
  - Dexas Scores < 2.5 (Osteoporosis)
  - Calcium & Vit D Rx Without Success
  - Prior Fragility Fracture

Pharmacologic Treatment Strategies

- Bisphosphonates
  - Cornerstone Of Prevention & Treatment Of Fragility Fractures
  - Effective In Reducing Risk Of Fragility Fractures
  - GI Side Effects
  - Compliance Issues

Pharmacologic Biochemistry

- Bisphosphonates
  - Long Acting Powerful Anti-Resorptive Agents
  - High Affinity For Hydroxyapatite
  - Bone Density Maintaining Drug
  - Normalize Elevated Serum Bone Turnover Markers
Bisphosphonate Therapy
Chemical & Molecular Structure

- Two General Categories
  - Simple Diphosphonates
  - Amino Disphosphonates
- Nitrogen / Amino Form is 10 to 10,000 Times More Potent Than Simple Form

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<thead>
<tr>
<th>Subclass &amp; Generic Name</th>
<th>Brand Name &amp; Manufacturer</th>
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<tr>
<td>Nitrogen Containing Bisphosphonates</td>
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<tr>
<td>Alendronate</td>
<td>Fosamax, Merck</td>
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<td>Boniva, Roche</td>
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<td>Risedronate</td>
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<tr>
<td>Etidronate</td>
<td>Didronel, Proctor &amp; Gamble</td>
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<tr>
<td>Tiludronate</td>
<td>Skelid, Sanofi Avendis</td>
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**Indications**

- Heritable Skeletal Disorders
- Hypercalcemia
- Metastatic Bone Disease
- Multiple Myeloma
- Pagets Disease
- Osteoporosis
Bisphosphonate Therapy
Sales & Marketing

- 5 Million Women On Drug In USA
- Bisphosphonate Medication
  - Fosamax
  - Actonel
  - Boniva
- 7.6 Billion Dollars In Worldwide Sales in 2010

Bisphosphonate Therapy
Osteoporosis

- Most Commonly Used Class Of Drugs To Treat Osteoporosis Worldwide
- Prolonged Therapy Alters Normal Bone Remodeling
- Atypical Femur Fractures
- Uncertainty & Debate Regarding Duration Of Rx

Bisphosphonate Therapy
Bone Physiology

- Bone Resorption And Remodeling Are Coupled & Balanced
- Mediated Thru TGF – B
- TGF- B Necessary for Migration Of Stem Cells To Sites Of Resorption
- When Bone Resorption Is Halted, Stem Cells May Not Be Able To Travel To Sites Of Bone Repair
Bisphosphonate Therapy Pharmacokinetics
- Bisphosphonates Bind To HA Crystals In Bone
- Trapped As New HA Crystals Form
- Activated Osteoclasts Take Up Bisphosphonates As They Resorb Bone
- 50% - 75% Of Bisphosphonates Are Cleared
- Remaining 25% - 50% Incorporated Into Bone
- Half Life 5-10 Years

Bisphosphonate Therapy Mechanism Of Action
- Inhibit Osteoclastic Function &
- Induces Osteoclastic Apoptosis By Interfering With Protein Prenylation & Inhibiting The Mevalonate Pathway Of Cholesterol Synthesis

Bisphosphonate Therapy Reduction In Risk Of Osteoporotic Fracture
- Multiple RCT Have Shown Bisphosphonates Increase Bone Mineral Density (BMD) And Decrease The Risk Of Fracture
Bisphosphonate Therapy Literature Review

- Fracture Intervention Trial (FIT)
- Fracture Intervention Trial Long Term Extension (FLEX)
- Health Outcome Reduced Incidence Zoledronic Acid Pivotal Fracture Trial (Horizon)

Fracture Intervention Trial (FIT)

N = 6400 Women

Prospective, Double Blind, Randomized Multi-Center Trial Comparing Alendronate & Calcium To Calcium Alone

Results & Conclusions
- Maintained BMD Throughout The Body
- Decreased The Incidence Of Fragility Fractures
  - Hip 51%, Distal Radius 44%, Vertebral 46%

Lancet 348: 1535-1541, 1996
JAMA 280: 2077-2082, 1998
Arch Intern Med 157: 2617-2624, 1997


1099 Treated With Alendronate For 5 Yrs 5 mg, 10 mg, Placebo (FIT)

Women Who Stopped Rx After 5 Yrs Showed A Moderate Decline In BMD But No Higher Risk Of Fracture Compared To Those Who Continued Treatment

Conclusion: Stopping Therapy For Up To 5 Years Does Not Appear To Significantly Increase Fracture Risk
Health Outcomes & Reduced Incidence Of Fracture With Zoledronic Acid Pivotal Fracture Trial (Horizon)

Randomized Double Blind Placebo Controlled Trial Of 2127 Patients Received Yearly Zoledronic Acid Or Placebo Within 90 Days Of A Hip Fracture

35% Reduction In Incidence Of A Second Fracture
28% Reduction In Death From Any Cause
No Adverse Effects On Fracture Healing


Bisphosphonate Therapy Reduction In Risk Of Osteoporotic Fracture

• These Studies Led To FDA Approval Of Bisphosphonates For The Rx Of Osteoporosis In 1990's
• 10 Year Results Showed Good Safety & Efficacy
• But Wait – The Story Continues

Bisphosphonate Therapy Atypical Femur Fractures

• In 2004-2005 Reports Emerged About A New Fracture Pattern Associated With Prolonged Bisphosphonate Use
• Term Atypical Femur Fracture Was Adopted To Identify This Unique Entity
Bisphosphonate Therapy
Atypical Femur Fractures

- Paradox Of Treatment
- Medication Designed To Prevent Bone Loss & Fractures Has An Apparent Contradictory Effect

Prolonged Bisphosphonate Therapy
Why The Femur?

The Proximal Femur Is Subjected To The Highest Stresses In The Body & One Of The Adaptations To Such Forces Is The High Concentration Of Cortical Bone In The Region

Prolonged Bisphosphonate Therapy
Key Point

Long Term Suppression Of Normal Bone Remodeling Increases The Risk Of Fracture Particularly In The Areas Of Greatest Tensile Strength ie Femur (800psi)
Prolonged Bisphosphonate Therapy
Atypical Femur Fracture

A Bisphosphonate Related Lesion
Represents A Brittle Stress Fracture
In The Femur With No Plastic Deformation Prior To Failure

This Stress Fracture Is The Result Of
• Increased Mineralization
• Heterogeneity Of Mineralization
• Altered Rates Of Bone Turnover
• Microdamage Accumulation
• Altered Collagen Cross-Linking

Unique Clinical And Radiographic Features
New Onset Hip Or Thigh Pain In Patients On Bisphosphonates Mandates Imaging Of The Hip & Femur
Bisphosphonate Therapy
Femur Fractures

**Clinical Presentation**
- Hip, Groin, Thigh Pain
- Pain In Absence Of Trauma
- Bilateral Symptoms Common
- Prodromal Pain 50% - 70%
- Younger Than Typical Hip Fracture Patient

**Clinical Presentation**
- Virtually All In Women
- More Common In Caucasians And Asians
- Higher BMI's
- Often On Steroids Or Statins
- T-Scores -1.5 to -2.0 Range

**Differential Diagnosis**
- Osteoarthritis Of The Hip
- Trochanteric Bursitis
- Atypical Sciatic
- Spinal Stenosis
- Myositis
- Tumor
Prolonged Bisphosphonate Therapy

Radiographic Findings

• **Stage 1**
  • Cortical Thickening Lateral > Medial
  • Flaring (Beaking) Of The Lateral Cortex
  • Increased Bowing Of The Femur

• **Stage 2**
  • Lucent Line (Stress Fracture)
  • Uni-Cortical Vs Bi-Cortical (Dreaded Black Line)

• **Stage 3**
  • Complete Fracture

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Prolonged Bisphosphonate Therapy

Stage 1  Stage 2  Stage 3
Cortical thickening  Incomplete Fracture  Complete Fracture

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Typical Proximal Femur Fracture In Elderly

• Slightly Older Age Group
• Spiral Fracture Pattern
• Some Comminution
• Cortical Thinning
Atypical Proximal Femur Fracture In Elderly

- Slightly Younger Age Group
- Transverse Or Short Oblique Fracture Pattern
- Little Or No Comminution
- Cortical Thickening

Prolonged Bisphosphonate Therapy
Treatment Stage 1

- Stop Bisphosphonates!
- Protective Wt. Bearing
- Correct Calcium & Vitamin D
- Warn Pts Of Risk Of Fracture!
- Consider Forteo (PTH)
- If No Improvement In 2-3 Months Consider IM Nailing
Prolonged Bisphosphonate Therapy  
Treatment Stage 2

- Incomplete Stress Fracture
- Almost All Very Symptomatic
- High Risk Of Fracture
- Prophylactic Nailing !!!
- Switch To PTH (Forteo)

79 Year Old Asian Female: 8 Yrs On Alendronate

Prolonged Bisphosphonate Therapy  
Treatment Stage 3

- Complete Fracture
- Surgical Urgency
- Medical Co-Morbidities
- Intra-Medullary Nailing
- Technical Issues
Prolonged Bisphosphonate Therapy

**Treatment Stage 3**

- IM Nailing Treatment Of Choice
- Slower Healing
- Higher Incidence Of Non-Union
- Technical Issues
  - Femoral Bowing
  - Thickened Cortices
  - Narrow Canal

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Prolonged Bisphosphonate Therapy

**Technical Challenges**

- Technical Issues
  - Femoral Bowing
  - Thickened Cortices
  - Narrow Canal
  - Special Reamers
  - Slow Healing

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Park-Wyllie et al: Bisphosphonate Use And The Risk Of Subtrochanteric Or Femoral Shaft Fractures In Older Women

N = 209,466 Women > 68 Years Treated With Bisphosphonate

Conclusions

1. Bisphosphonate Therapy Significantly Decreases The Risk For Femoral Neck Or Intertrochanteric Hip Fractures
2. Only In Patients Taking Bisphosphonates > 5 Years Do Atypical Fractures Substantially Increase. In The Two Years Following Five Years Of Treatment; One in 500 May Sustain A Fracture
3. Atypical Fractures Are Uncommon & Data Supports Bisphosphonate Therapy

JAMA 305: 783-789, 2011
Prolonged Bisphosphonate Therapy
Kaiser California Experience

1,835,115 Patients Rx Bisphosphonates 2007-2011

142 Atypical Femur Fractures Of Whom 128 On Bisphosphonate

Age Adjusted Incidence
1.78 / 100,000 Years With Exposure Up To Two Years
113 / 100,000 Years With Exposure Between 8 – 10 Years

Incidence Of Hip Fractures Declined By 30% And The Benefits Of Bisphosphonate Therapy Is 100 fold Greater Than The Risk Of Atypical Femur Fracture

Bawa HS, Weick J, Dirschl D: Anti-Osteoporotic Therapy After Fragility Fracture Lowers The Rate Of Subsequent Fracture JBJS 97: 1555-1562, 2015

Database Analysis Of 31,069 Patients Who Sustained A Fragility Fracture

10.6% Of Patients Were Place On Anti-Osteoporotic Therapy Following Their Index Fracture

3 Year Fracture Rate Was 7.5% in The Treatment Group & 9.7% In The Non-Treatment Group

Conclusion: Anti-Osteoporotic Rx Reduces The 3 Yr Risk Of A Subsequent Fracture By 40% & Can Prevent A Subsequent Fracture In One Of Every Twenty-Seven Patients Treated

Clinical Cases

Acute Cases
71 Yr Old Asian Female With 5 Month History Of Thigh Pain

On Alendronate 7 Years

On Alendronate 8 Years

X-Ray 10 Months Later No Diagnosis. No Treatment

Low Energy Proximal Femur Fracture

Rx: Intra-Medullary Nailing

Missed Diagnosis!

Long Term Bisphosphonate Use. Open Femur Fracture S/P Ground Level Fall

Courtesy Richard Dell MD Kaiser Permanate

Courtesy Charles Moon MD
83 Yr Female On Fosamax For 10 Years. Missed Step & Fell  Classic Atypical Femur Fracture
Post-Op Closed Intra-Medullary Nailing

Distracted?

2 Year Follow-Up; Healed; Asymptomatic

Reconstructive Cases

Atypical Femur Fractures

Delayed Healing In 10%-25% Of Cases
Initial Treatment Usually Very Good
Intra-Medullary Nail Usually In Place

Now What?
Post-Operative Outcomes Of Femoral Subtrochanteric Fractures In Patients On Bisphosphonate Therapy: A Prospective Study

N = 33

Mean Age 67.5 Years   Mean Duration Of Bisphosphonates 5 Years

Extramedullary Devices In 23 Patients (70%); IM Nails in 10 (30%)

30 % Of Patients Required Revision Surgery
23% Incidence Implant Failure
Average Healing Time With Extramedullary Devices 11 Mos
Average Time To Healing With IM Nails 7.7 Months

Teo et al  Poster Exhibit 27th Annual Meeting OTA San Antonio, Texas 2011

Failed ORIF Atypical Femur Fracture

Complex Hardware Removal & Intra-Medullary Nailing
71 Yr Female Referred For Rx Of A Tibial Non-Union; No History Of Injury To Her Lower Leg. However The Patient Had An 8 Yr History Of Bisphosphonate Use & A Previous Atypical Femur Fx Nailed 3 Yrs Ago

Sequential IM Nailing Of The Tibia & Impending Pathologic Fx Femur
Closed Reamed Proximal Dynamic Interlocking Nailing

Could The Tibia Be A Bisphosphonate Fracture / Non-union?

Intra-Medullary Reamings Sent To Pathology: Lymphoma
9 Month Follow-Up; Femur Healed

1 Yr Follow-Up Tibia Healed

16 Months S/P IM Nailing Of Atypical Femur Fracture

Dynamized

Revision ORIF With Compression, Lag Screw, & BMP
12 Months Post-Op; Mild Residual Pain; Healed

78 Yr Female with 6 Yr Hx of Fosamax Use Who Sustained An Atypical Femur Fracture Following Low Energy Fall

10 Month S/P Cephalo-Medullary Nailing With A Painful Nonunion

Exchange Nailing 6 Months Follow-Up 12 Month Follow-Up
67 Yr Female Fell On Alaskan Cruise Sustaining A Femur Fracture

5.5 Year History Of Bisphosphonate Use

Emergency Surgery In A Small Town In Alaska With Trochanteric Entry Nail Supine On A Fracture Table
Interim History

- Returns To Los Angeles At 3 Weeks
- Seen By Her Family Doctor
- Wound Clean & Dry, Sutures Removed
- Diagnosed With DVT & Placed On Coumadin
- Physical Therapy & Ortho On Hold

Referred At 9 Weeks Post-Op With These Radiographs

15° Varus
40° Anterior Angulation

How Would You Manage This Problem Now?

1. Revision Nailing
2. Blade Plate
3. Prox Femur Locking Plate
68 Yr Female Presents With 3 Month History of Hip & Groin Pain

1 Year Follow-Up Healed

Lateral Decubitus On A Fracture Table
Reamed Piriformis Entry Reconstruction Nailing

Pre-Op
Post-Op
Leg Gave Out Descending Stairs At Home

Classic Atypical Femur Fracture Secondary To Prolonged Bisphosphonate Therapy

Closed Intra-Medullary Nailing: Poor Reduction & Distracted

At 4 Months Proximal Screw Breaks; Little Evidence Of Healing
Revised To A Synthes Cephalomedullary Nail With Bank Bone Graft

Persistent Painful Nonunion 18 Months After Exchange Nailing

I Performed A 95 Degree AO Blade Plate; Surgical Sequence
X-Rays At 7 Months Show Healing

Walking The Dog & Leg Gave Out

Calcar Replacement Total Hip Arthroplasty

Courtesy Chris Allison MD
6 Months Post-Op; Walks With A Cane

Classic Atypical Femur Fracture In A 73 Yr Old Asian Female

Poor Reduction With Anterior & Lateral Starting Point
Referred At 6 Months With Fixation Failure & Non-Union

Removal Of Broken Hardware Which Was Difficult!

Fibular Allograft To Block Original Nail Portal Entry
Restoration Of Length & Temporary Unicortical Plate
Revision Fixation With A Reconstruction Nail & BMP-2

9 Month Follow-Up The Fracture Is Healed; Patient Uses A Cane

7 Mos S/P Nailing Of An Atypical Femur Fracture In 71 Yr Old Female
Revision Nailing With Deformity Correction

Original Start Point Was To Lateral & Anterior

Correction Of Entry Portal Allows Restoration Of Hip Biomechanics
Revision With A Reconstruction Nail; Unicortical Plate & BMP-2

3 Months Post-Op

6 Mos Post-Op Healed

Prolonged Bisphosphonate Therapy
Conclusions

- Very Strong Relationship Between Bisphosphonates & Atypical Femur Fractures
- Cephalomedullary Nailing Rx Of Choice
- Delays In Healing 10%-25%
- Duration Of Treatment Remains Controversial
- Current Protocol 5 Yrs Than Drug Holiday
Prolonged Bisphosphonate Therapy

Conclusions

- Solicit Info On Hip Or Thigh Pain
- Is Patient On Bisphosphonates?
- X-Rays Are Mandatory
  - Early Changes Are Subtle
  - Cortical Thickening / Beaking
  - MRI Very Sensitive
  - X-Ray Contra-Lateral Side

- Flawed Perception That These Drugs Are "Health Supplements" With Minimal Adverse Effects
- Long Term Retention In Bone
- Persistence Of Their Effect After Stopping Therapy
- Drug "Holiday" For Low To Moderate Risk Patients

It Is Not Enough To Stare Up The Steps; We Must Step Up The Stairs

Donald.Wiss@cshs.org