Disclosures

• Stryker Foot and Ankle
• Orthofix
• Biomet-Zimmer Subchondroplasty
• NOVADAQ
Charcot Foot and Ankle
A Diagnostic and Treatment Challenge
Objectives

• History
• Pathophysiology
• Diagnosis
• Treatment Principles
• Medical Management
BACKGROUND
Economic Costs of Diabetes in the U.S. in 2012

*Diabetes Care, Volume 36, April 2013*

- Diagnosed Diabetes = 245 B (DMC = 176B)
- Hospital Inpatient Care – 43%
- Medications to treat complications – 18%
- Anti-diabetic meds and supplies – 12%
- Physician office visits – 9%
- Nursing/Residential Facility – 8%
Economic Costs of Diabetes in the U.S. in 2012

*Diabetes Care, Volume 36, April 2013*

- Average medical expenses – **13,700/yr**
- 2.3 x higher than non-diabetics
- 1 in 5 health care dollars
- 20% of *in-patient hospital admissions* = foot related complications = 25% *in-patient dollars*
...the most devastating diabetic foot complication is Charcot Foot and Ankle!!!

- Difficult to diagnose
- Difficult and expensive to treat
- Recurs frequently?
HISTORICAL PERSPECTIVE

1703 – William Musgrave
- Arthropathy of locomotor ataxia – J. M. Charcot 1868 (La Salpetrière, Paris)
- Inflammatory Neuropathy in Tabes dorsalis (Tertiary lues)
- 7th International Medical Congress, London 1881 (James Paget, “Charcot’s Disease”)
First Descriptions of Pedal Osteoarthropathy “Charcot Foot”

- **H. W. Page** described process in foot and speculated etiology of peripheral neuropathy (*7th IMC, London 1881*).
- **William Reily Jordan 1936** - Arch Int Med
  - First reported case in diabetic patient
Etiology

- Diabetes Mellitus
- Tabes Dorsalis
- Alcohol-induced Neuropathy
- Congenital Insensitivity to pain
- Traumatic Denervation
- Leprosy (Paul Brand, MD)
- Syringomyelia
- Lyme Disease
- HIV
Neuropathy

**Tabes Dorsalis**
- Near total loss of pain
- Near total loss of proprioception
- Dorsal column damage
- Proximal joints of lower extremity (knee, hip)

**Diabetic Neuropathy**
- Deep pain sensation relatively intact
- LOPS (5.07 monofil)
- Spinothalamic pathway
- Foot and Ankle joints
“Neurotraumatic” vs “Neurotrophic”

- Charcot neuroarthropathy (CN) is relatively rare but neuropathy affects 30+% of diabetics
- CN usually unilateral but neuropathy is bilateral and symmetrical
- CN recurrence rare? but neuropathy always present

“Inflammation” Theory (Jeffcoate, 2005)
in 2016

- Diabetes Mellitus (Types 1 & 2)
- Profound peripheral neuropathy (Sensory, motor, autonomic)
- Precipitated by trauma
- “Inflammation”
Relative 5-Year Mortality Rates

- Prostate Cancer:
- Hodgkin’s Disease:
- Breast Cancer:
- PAD:
- Colorectal Cancer:
- Charcot Foot:
- Foot Ulcer:
- Amputation:
- Lung Cancer:
- Pancreatic Cancer:

‡Larssen, Apelqvist et al: 1998  
§Moulik et al: 2003  
Van Baal et al 2010
Belch et al: Arch Int Med 2003; 163:884-892
Back to the Future: Charcot, 1881

“Usually, the first phenomenon discernible is extreme tumefaction of the entire member.”

“...the first symptoms of ataxic arthropathy appear suddenly and unexpectedly...”

Lectures on Diseases of the Nervous System. Lecture IV
More than 100 years later.....

Many questions remain

Confusion about Charcot

• Terminology not standard – What do we call it?
• What is it? What causes it?
• Disease or Syndrome?
• How do we diagnose Charcot arthropathy?
• Is there a specific diagnostic marker?
• How is it best treated?
• Is surgery always necessary? If so, when?
The Charcot Foot in Diabetes

**Definition:** The Charcot foot is a rare complication of diabetes that may lead to severe bone and joint destruction. It is characterized by rapid, asymmetrical soft tissue swelling and deformities, often without a history of trauma. The condition is typically associated with peripheral vascular disease and neuropathy.

**Pathogenesis:** The pathogenesis of Charcot foot is not fully understood, but it is thought to involve a combination of factors. Peripheral vascular disease, diabetes mellitus, and neuropathy are all contributing factors. The condition is often associated with peripheral vascular disease and neuropathy.

**Management:** The management of Charcot foot involves a multidisciplinary approach, including podiatry, vascular surgery, and orthopedic surgery. Early intervention is crucial to prevent further damage and achieve an optimal outcome.

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**La Salpetriere**

Paris, France

January 2011
Definition

- Condition affecting bones, joints and soft tissues of the foot and ankle; characterized by *inflammation* in the earliest phase
- consequence of various *peripheral neuropathies*
  - (DM most common)
- Pain or discomfort a feature in the active (acute) stage, but pain significantly diminished when compared with individuals with normal sensation and equivalent degrees of injury.
- The set of signs and symptoms that occur together with CN qualifies this condition as a syndrome
  - “Charcot foot syndrome.”
- Nomenclature should be standardized to Charcot neuropathic osteoarthropathy (CN) or Charcot foot.

Rogers, Frykberg, Armstrong et al: Diabetes Care 2011
Classification

- Eichenholtz (Temporal)
- Brodsky
- Sanders and Frykberg
- Schon
- Sella
Stages of Natural History

Eichenholtz Classification (Temporal)

**Acute**

**Stage 0**
Prodromal Period
- Swelling
- Local Warmth
- Mild Erythema
- Clinical Instability
- Radiographic Changes
- Are Absent or Minimal

**Stage 1**
Development
- Debris Formation at Articular Margins
- Fragmentation of Subchondral bone
- Subluxation
- Dislocation
- Erosion of Articular Cartilage
- Bone Resorption
- Osteolysis and Osteopenia
- Disorganization and Fragmentation of Bone
- Soft Tissue Edema

**Chronic**

**Stage 2**
Coalescence
- Lessening Of Edema
- Absorption of Fine Debris
- Healing of Fractures
- Fusion and Coalescence of Larger Fragments
- Loss of Vascularity
- Sclerosis of Bone

**Stage 3**
Reconstruction
- Further Repair and Remodeling of Bone
- Fusion & Rounding of Large Fragments
- Revascularization
- Diminution of Sclerosis
- Restoration of Stability
- Increased Bone Density
- Exuberant Ossification
- Deformity

Resorption of Bone

Repair

LJS ‘06

 Sanders and Frykberg, 2007
Schon Classification  
(Midfoot-Anatomic)
• Existing classifications do not provide prognostic value or direct treatment.
• Active or Inactive should be used to describe an inflamed or stable CN, respectively.
• Acute and Chronic can also be used in this regard but there is no accepted measure that defines the transition point.

Rogers, Frykberg, Armstrong et al:2011
Diseases with Potential for Causing Charcot Joints

- Diabetes mellitus
- Tabes dorsalis
- Leprosy
- Syringomyelia
- Alcoholism
- Peripheral Nerve injuries
- Congenital insensitivity to pain
- Lyme Disease
- HIV
Pathogenesis of CF
Combined Theory - Pathogenesis

**Neurotraumatic**

- SensoriMotor Neuropathy
  - Proprioception
  - Pain
  - Vibration

**Diabetes Primary Disease**

- Intrinsic Atrophy
- Crural Atrophy
- Equinus

**Neurovascular**

- Autonomic Neuropathy
  - Sympathetic failure
  - Increased flow
  - A-V shunting

**Trauma**

- Instability
- High Risk Foot

**Spontaneous Dislocation**

- Neuropathic fractures

**OSTEOARTHROPATHY**

- "Viscious cycle"
  - Neuropeptide Dysregulation
  - Edelman 1987

**Acute Inflammation**
The role of proinflammatory cytokines in the cause of neuropathic osteoarthropathy in diabetes


Trauma

- Increased force
- Abnormal Loading

Neuropathy

- Dislocation Fracture
- Pro-inflammatory cytokines (TNF-α, IL 1β)
- Inflammation

Osteopenia

- Osteoclastogenesis
- Inflammatory Theory
- RANK-L NF-κβ

Vicious Cycles of Acute Neuroarthropathy

Neurotraumatic Theory

RGF 2010
The Role of Proinflammatory Cytokines and NF-κB: Is RANK-L the missing link?

- Osteoclastogenesis (osteolysis, osteopenia) is dependent upon activation of nuclear transcription factor κB (NF-κB).
- NF-κB activation is dependent upon the increased expression of a specific transmembrane receptor activator: receptor activator of NF-κB ligand (RANKL) that resides on osteoblasts/stromal cells.
- RANKL binds with the receptor activator of NF-κB (RANK) residing on osteoclast precursor cells.

Jeffcoate et al: Lancet, 2005
Mabilleau et al: Diabetologia 2008
Genetic Predisposition

- Two recent Genetic Studies have shown that Charcot patients have a significant association with certain single nucleotide polymorphisms (SNP) for **OPG** gene
  - Pitocco et al: Diabetes Care September 2009 32:1694-1697
    - Charcot risk 6 x lower for those with CC/TT homozygosis (1/OR TT + CC)
    - In a multivariate logistic backward regression model, only weight and the lack of CC and TT genotypes were independently associated with Charcot neuroarthropathy. (P=0.001, P=0.015, P=0.002)
    - Linkage with the G allele of both genes with Ch group
    - TT genotype at 1217 residue of OPG: 8.5-fold higher risk of Charcot vs TC or CC
    - TT genotype at 245 residue of OPG: 11.5-fold higher risk of Charcot vs TC or CC
Clinical Presentation: Making the Diagnosis
The Keys to Early Diagnosis

- CLINICAL SUSPICION
- PATIENT HISTORY
- CLINICAL FINDINGS
- RADIOGRAPHIC STUDIES

Charcot Consensus 2011

Rogers, Frykberg, Armstrong et al: 2011
Diagnosis

Primarily a *clinical* diagnosis

- **Red, hot swollen foot** in the presence of neuropathy
- **Inflammation** is the earliest (and key) finding
- At inception (after an often subtle injury) radiographs frequently remain normal despite “bone stress injury”
  - Stage “0” – prodromal- Charcot “in-situ” (Shibata 1990)
- **Midfoot collapse “rocker-bottom”** foot is the hallmark deformity although a later finding in most cases

*Joint Task Force 2011*
A Red Hot Swollen Foot (in a neuropathic patient) should be considered a Charcot foot until proven otherwise!

Charcot Consensus 2011
Diagnostic Recommendations for Active CN

- The occurrence of acute foot/ankle *fractures* or *dislocations* in neuropathic individuals is considered *active CN* (inflammatory process of bone healing) *even in the absence of deformity*
- **X-rays** initial imaging performed - look for subtle fractures or subluxations (if no obvious pathology is visible)
- **MRI or nuclear imaging** can confirm clinical suspicions

Charcot Consensus 2011
Rogers, Frykberg, Armstrong et al:2011
If Negative: MRI (Stage 0)
“Silent” Bone Stress Injuries
Stage 0

- Prodromal Stage without Radiographic changes
  - Usually follows minor “trigger injury”
- Clinically inflamed foot
  - Relatively painless edema (usually no ulcer)
- Precursor to Eichenholtz Stage I
- MRI is most sensitive modality to detect
  - Bone marrow edema, periosteal edema

Shibata 1990
Chantelau 2006, 2007
Schlossbauer 2008
Wukich 2010, 2011
Imaging

• X-Ray

• MRI (STI – Abscess, bone edema)

• CT Scan (wt. bearing)

• Nuclear Imaging (Tri-phasic, wbc, sulphur colloid)
TREATMENT
Treatment Goals

• Convert from Active to Inactive stage
• Prevent further deformity
• Provide protected ambulation
• Prevent recurrent ulcerations
Parameters

- Ulcer
- STI
- Osteomyelitis
- Deformity
- Active vs Inactive
- Stable vs Unstable
Management Strategies

Acute Onset

Acceptable Alignment
- Halt Process
- Jones Cast

Dislocation
- Open Reduction with Arthrodesis
- Closed Reduction with or without Percutaneous Pins

NWB Cast Immobilization 12-20 weeks
TREATMENT OBJECTIVES
Convert from Active to Inactive Stage

• **Non weightbearing is recommended**
  – bedrest, crutches, wheelchair
  – Weight-bearing TCC acceptable
    • Pinzur 2006, de Souza 2008

• **Immobilization**
  – ace bandage, Jones dressing
  – Total contact cast, bi-valve cast, cast walker, CROW brace

• **Adjunctive**
  – Pharmacologic
    • Bisphosphonates, Calcitonin, etc
    • Bone Stimulation – electric, US

Frykberg, Eneroth 2010
Chantelau 2006, 2007
Petrova, Edmonds 2008
Management Strategies

Chronic Deformity

- Stable
  - Exostectomy
- Stable
  - Bracing and Shoe Therapy
- Unstable
  - Reconstruction
    - Acute
    - Gradual
Management of Chronic Charcot Foot

Non-ulcerated
- Therapeutic footwear
- Bracing – PTBB, CROW, Muenster, etc.
- Surgery for severe instability

Ulcerated
- Offloading: TCC, Cast walker, etc.
- Surgery: Exostectomy, Realignment Arthrodesis
  » Debridement/Rx Osteomyelitis

Frykberg, Eneroth: In “The Diabetic Charcot Foot” 2010
56 yo retired teacher…..

• 4 year history of ulcer
• Previous 5th Ray amputation
• Wound care center for two years, q2 weeks
• 105 HBO dives, 7 skin grafts
• Surgeons won’t consider reconstruction until osteomyelitis is “cured” – recommend BK Amputation.
• No MRI, nuclear scan, bone biopsy
Grade 3 Ulcer
Rockerbottom Deformity
Soft Tissue Infection?
Osteomyelitis?
Fracture / Dislocation heel
Comminution
Unstable
Type 1 Diabetes Mellitus
Peripheral Neuropathy
Peripheral Vascular Disease?
No Osteomyelitis!
4-7 Months
1000+ Reconstructions at G-CMC since 1994
Ankle Charcot Algorithm

Active ulcer/Infection?

Talus Salvageable?

Yes ➔ Ankle/TTC with Blade Plate/IM Nail

No ➔ Talecctomy with TC Fusion +/- Leg Lengthening

Talus Salvageable?

Yes ➔ Ankle/TTC External Fixation

No ➔ Talecctomy with TC Fusion External Fixation

Talus Salvageable?

No ➔ Talecctomy with Intercallary Bone Block
Medical Management
Medical Management of Charcot Foot

Alexandra Jirkovská, Robert Bém

Institute for clinical and Experimental Medicine, Prague,

Czech Republic
Objectives

• Decreasing BMD may be involved in the pathogenesis of traumatic foot fractures and the development of CNO.
• The management of CNO is currently inadequate - no specific pharmacological treatment available.
• Only bisphosphonates and intra-nasal calcitonin have been demonstrated to have some benefit in patients with CNO, but the evidence is not sufficient to become standard therapy.“

Jirkovska et al, Diab Med, 2001
Jude et al, Diabetologia, 2001
Bém et al, Diabetes Care, 2006
Jeffcoate, Lancet, 2005
Charcot Foot and Bone Disease

- Jirkovská A. et al., Diabetic Med 18, 2001, 495-500

# Osteoporosis in Charcot Patients and Healthy Controls

<table>
<thead>
<tr>
<th>Místo</th>
<th>T-scóre*</th>
<th>Osteoporosis (T-skóre -2,5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>Stiffness of calcaneus</td>
<td>Charcot foot n = 16</td>
<td>-3,0 ± 1,4</td>
</tr>
<tr>
<td></td>
<td>Non-Charcot n = 16</td>
<td>-2,4 ± 1,1</td>
</tr>
<tr>
<td>BMD spine</td>
<td>n = 14</td>
<td>-0,6 ± 1,3</td>
</tr>
<tr>
<td>BMD hip</td>
<td>n = 14</td>
<td>-1,6 ± 1,2</td>
</tr>
</tbody>
</table>

Jirkovská A.et al., Diabetic Med 18, 2001, 495-500
Calcaneal ultrasonometry in Charcot and non-Charcot foot (Jirkovská A. et al., Diabetic Med 18, 2001, 495-500)

- Dual-energy X-ray absorptiometry (Young, Marshall, Adams, Selby, and Boulton, 1995) - BMD of Charcot lower extremities significantly less than non-Charcot diabetic patients.
Classen, 2000) did not show differences between diabetic patients with Charcot arthropathy and diabetic patients without Charcot arthropathy.

Young et al.'s findings were in line with those of others who observed bone resorption in up to 81% of Charcot arthropathy patients (Brower & Allman, 1981; Cundy, Edmonds, & Watkins, 1985).
All of the patients with Charcot arthropathy were qualitatively diagnosed with cardiovascular autonomic neuropathy and demonstrated significantly reduced BMD in the afflicted feet.
There was no difference in lumbar spine BMD values. Nevertheless, Young et al. concluded that their findings supported the assertions of Edmonds et al. (1985). “Reduced BMD in Charcot arthropathy patients results in reduced bone strength, predisposing patients to the development of fractures“.


Not all Charcot arthropathy patients had reduced BMD. Those within the fracture-pattern group had significantly lower BMD compared to the dislocation group and the combination group.

Conclusion:
- Reduced BMD in the lower extremity was a specific risk factor for patients developing the fracture pattern, especially in the ankle.
- Those with normal BMD were more likely to develop a dislocation or combination pattern.
*Fracture significantly lower than dislocation (p < 0.005)

Fig. 6

Variation of the DXA-derived BMD t-score between the fracture, the dislocation, and the combined fracture-dislocation patterns of Charcot arthropathy.
Table 2  BMD and bone markers values in the different groups of diabetes patients.

<table>
<thead>
<tr>
<th>BMD (g cm⁻²)</th>
<th>Without neuropathy n = 11</th>
<th>Neuropathy n = 9</th>
<th>First toe amputated n = 5</th>
<th>Acute Charcot n = 17</th>
<th>Chronic Charcot n = 7</th>
<th>ANOVA P&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body</td>
<td>1·19 ± 0·03</td>
<td>1·28 ± 0·05</td>
<td>1·19 ± 0·08</td>
<td>1·17 ± 0·03</td>
<td>1·25 ± 0·03</td>
<td>0·24</td>
</tr>
<tr>
<td>AP-spine L2–L4</td>
<td>1·14 ± 0·06</td>
<td>1·30 ± 0·07</td>
<td>1·20 ± 0·05</td>
<td>1·24 ± 0·06</td>
<td>1·39 ± 0·06</td>
<td>0·14</td>
</tr>
<tr>
<td>Hip total dual</td>
<td>1·00 ± 0·04</td>
<td>1·15 ± 0·08</td>
<td>0·92 ± 0·06</td>
<td>0·99 ± 0·04</td>
<td>1·07 ± 0·05</td>
<td>0·09</td>
</tr>
<tr>
<td>Calcaneus healthy foot</td>
<td>0·75 ± 0·04</td>
<td>0·84 ± 0·06</td>
<td>0·73 ± 0·08</td>
<td>0·72 ± 0·02</td>
<td>0·80 ± 0·05a</td>
<td>0·47</td>
</tr>
<tr>
<td>Calcaneus affected foot</td>
<td>0·74 ± 0·03</td>
<td>0·82 ± 0·06</td>
<td>0·73 ± 0·09</td>
<td>0·71 ± 0·03</td>
<td>0·75 ± 0·05a</td>
<td>0·45</td>
</tr>
<tr>
<td>CTX (ng mL⁻¹)</td>
<td>0·36 ± 0·16</td>
<td>0·33 ± 0·24</td>
<td>0·71 ± 0·77</td>
<td>0·47 ± 0·19</td>
<td>0·34 ± 0·15</td>
<td>0·19</td>
</tr>
<tr>
<td>N-MID (ng mL⁻¹)</td>
<td>12·27 ± 5·06b</td>
<td>13·89 ± 9·20</td>
<td>26·58 ± 33·51</td>
<td>19·76 ± 5·75b</td>
<td>16·71 ± 6·42</td>
<td>0·02</td>
</tr>
</tbody>
</table>

Values given as mean ± SEM.

*P < 0·01, paired t-test used, comparison between healthy and affected foot in chronic Charcot group.

bStatistical difference between without neuropathy and acute CA (P = 0·03).

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Bone mineral density in diabetes mellitus patients with and without a Charcot foot

Tomas M. Christensen¹, Jens Bülow², Lene Simonsen², Per E. Holstein³,⁴ and Ole L. Svendsen¹

¹Endocrine Research Unit, ²Department of Clinical Physiology, ³Copenhagen Wound Healing Centre, Bispebjerg Hospital, University of Copenhagen, Copenhagen, and ⁴Steno Diabetic Centre, Gentofte, Denmark
Research into the relationship between reduced BMD and the pathogenesis of Charcot arthropathy has led to the investigation of bone resorption mediators.

Increases in certain proinflammatory cytokines, which are known mediators of bone resorption, are a contributing factor to increased osteoclastic activity in ACA patients (Baumhauer, O'Keefe, Schon, & Pinzur, 2006).
Autonomic neuropathy

(Small fibre diabetic neuropathy)

Loss of cholinergic inflammatory reflex

- Injury
  - Fracture + dislocation
    - Osteopenia
      - Increased intravascular pressure in bone
        - Increased blood flow
          - RANKL, TNFα, IL-1, IL-6, IGF, TGF, MCSF, NF-kappa β...

- Overactivation of inflammatory cells
  - Fracture + dislocation
    - Osteoclast activation
Secondary osteoporosis is defined as bone loss, micro-architectural alterations, and fragility fractures due to an underlying disease or concurrent medication (1). Secondary osteoporosis remains a diagnostic and therapeutic challenge as it frequently affects patient populations, e.g. premenopausal women or younger men who are usually not target populations for routine screening for osteoporosis. In addition, the underlying conditions are diverse and rare, and require specific diagnostic tests (1). Moreover, response to osteoporosis therapy may be limited if the underlying disorder
**Approach to the patient with secondary osteoporosis**

Lorenz C Hofbauer\(^1,3\), Christine Hamann\(^2\) and Peter R Ebeling\(^4\)

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**Table 1** Common causes for secondary osteoporosis.

<table>
<thead>
<tr>
<th>Endocrine diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>GH deficiency (rare)</td>
</tr>
<tr>
<td>Acromegaly (rare)</td>
</tr>
<tr>
<td>Hypercortisolism</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Premature menopause</td>
</tr>
<tr>
<td>Male hypogonadism</td>
</tr>
</tbody>
</table>

*Diabetes mellitus type 1* The risk of osteoporotic fractures is increased by 12-fold in patients with type 1 diabetes (4). Lack of the bone anabolic actions of insulin and other β-cell-derived proteins such as amylin have been postulated to contribute to low BMD and impaired fracture risk (3). In long-standing disease, diabetic complications, such as retinopathy, polyneuropathy, and nephropathy, are the major determinants of low bone mass and increased fracture risk, in part due to the enhanced propensity of falls (3). Data from the Women's Health Initiative Observational Study also indicate a 20% higher risk for fractures after adjustment for frequent falls and increased BMD (4–5% higher at the hip) in women with type 2 diabetes mellitus (29). An important additional risk factor for fractures in postmenopausal women with type 2 diabetes mellitus is the use of a TZD type insulin sensitizer, associated with fractures of the hip, humerus, and small bones of the hands and feet (30).
REVIEW

Approach to the patient with secondary osteoporosis

Lorenz C Hofbauer¹,², Christine Hamann¹ and Peter R Ebeling³

Table 2 Drugs known to cause osteoporosis and/or fragility fractures.

<table>
<thead>
<tr>
<th>Drug class¹</th>
<th>Examples</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids¹,²</td>
<td>Prednisolone, Cyclosporine A</td>
<td>Autoimmune diseases, Allogeneic organ transplantation</td>
</tr>
<tr>
<td>Calcineurin inhibitors¹,²</td>
<td>Methotrexate, ifosfamide</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Chemotherapeutic drugs</td>
<td>Imatinib</td>
<td>Chronic myelogenous leukemia</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>Rosiglitazone, pioglitazone</td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Thiazolidinediones¹,²</td>
<td>Goserelin, buserelin, flutamide</td>
<td>Prostate cancer, endometriosis</td>
</tr>
<tr>
<td>GnRH agonists¹,²</td>
<td>Anastrozole, letrozole, exemestane</td>
<td>ER-positive breast cancer</td>
</tr>
<tr>
<td>Aromatase inhibitors¹,²</td>
<td>Depot-medroxyprogesterone acetate</td>
<td>Contraception</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Omeprazole and pantoprazole</td>
<td>Peptic ulcer and reflux diseases</td>
</tr>
<tr>
<td>Proton pump inhibitor¹,²</td>
<td></td>
<td>Thromboembolic diseases</td>
</tr>
<tr>
<td>Unfractionated heparins¹,²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase inhibitors</td>
<td>Orlistat</td>
<td>Morbid obesity</td>
</tr>
<tr>
<td>Thyroid hormone²</td>
<td>L-thyroxine</td>
<td>Replacement therapy for hypothyroidism, thyroid cancer</td>
</tr>
<tr>
<td>Anticonvulsants¹</td>
<td>Valproic acid</td>
<td>Chronic seizure disorders</td>
</tr>
<tr>
<td>Antidepressants¹,²</td>
<td>Selective serotonin re-uptake inhibitors</td>
<td>Chronic depression</td>
</tr>
<tr>
<td>Anti-retroviral drugs</td>
<td>Tenofovir</td>
<td>HIV disease</td>
</tr>
</tbody>
</table>

¹Strong evidence.
²Drug is associated with increased fractures.
REVIEW

Approach to the patient with secondary osteoporosis
Lorenz C Hofbauer¹,³, Christine Hamann² and Peter R Ebeling⁴

**Table 3** Diagnostic tests in the work-up of secondary osteoporosis.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical exam</td>
<td>To identify risk factors for fractures, the underlying disease, and potential drugs</td>
</tr>
<tr>
<td>Dual-energy X-ray absorptiometry (lumbar spine and hip)</td>
<td>To quantify bone mineral density</td>
</tr>
<tr>
<td>Spinal X-rays</td>
<td>To detect prevalent vertebral fractures</td>
</tr>
<tr>
<td></td>
<td>To exclude osteolytic lesions or tumors</td>
</tr>
<tr>
<td><strong>Diagnostic test</strong></td>
<td></td>
</tr>
<tr>
<td>Complete blood count</td>
<td><strong>To detect or exclude</strong></td>
</tr>
<tr>
<td></td>
<td>Anemia as in myeloma/celiac disease</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis in leukemia</td>
</tr>
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<td>Renal or liver failure, alcohol abuse</td>
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<td>Primary hyperparathyroidism, myeloma</td>
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<td>Chronic infection/inflammation</td>
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<td>Paget’s disease; osteomalacia</td>
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<td>Vitamin D deficiency, osteomalacia</td>
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<td>Hyperparathyroidism</td>
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<td>Male hypogonadism</td>
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<td>Diabetes mellitus</td>
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<td>Primary hyperparathyroidism</td>
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<td>MGUS, myeloma</td>
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<td>Hypercalcemia</td>
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<td>Celiac disease</td>
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<td>HIV disease, AIDS</td>
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<td>Cushing’s syndrome</td>
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<td>Systemic mastocytosis</td>
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<td>Osteogenesis imperfect</td>
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<td>Systemic mastocytosis, MGUS/myeloma, osteomalacia, lymphoma/leukemia</td>
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AP, alkaline phosphatase.
Therapies for Osteoporosis and Metabolic Bone Disease

- **Antiresorptive agents**
  - bisphosphonates
    - ibandronate, alendronate, zolendronic acid, risedronate
  - calcitonin (nasal, oral, parenteral)

- **Selective estrogen response modulators (SERMs)** - tamoxifen, raloxifen

- **Anabolic therapies** – teriparatide (PTH)

- **Strontium ranelate** – both anabolic and antiresorptive properties

- **Denosumab** – MAb directed against RANK-L that binds to it with high affinity and blocks its actions on osteoclastogenesis.

- **Vitamin D and calcium**

- **Calcimimetics** (cinalcacet) – modulators of calcium receptors by binding to these receptors on parathyroid cells and mimicking the action of high CA to inhibit PTH secretion

*Shoback D., J Clin Endocrinol Metab 92: 747-753, 2007
Cranney A. et al. Endocrine Reviews 23: 540-551, 2002*
**Specific osteoporosis treatment**

**Vitamin D and calcium** An adequate intake of calcium (800–1200 mg/day) via dietary intake or supplements is recommended. Vitamin D supplementation (at least 800 IU/day) is recommended as vitamin D deficiency has a high prevalence and, in addition to various adverse extraskeletal effects, may contribute to low bone mass and increase the propensity to falls (68). In addition, the efficacy of anti-osteoporotic drugs has only been demonstrated in the presence of vitamin D and calcium supplementation. Therapy should be titrated with doses that result in normocalcemia and serum 25-hydroxyvitamin D concentrations of at least 30 ng/ml. In patients with normal renal function, a decrease in serum PTH levels from elevated to normal levels indicates that 25-hydroxyvitamin D deficiency has been corrected. Some anti-epileptic drugs, e.g. phenytoin, phenobarbitone, primidone, and carbamazepine, increase hepatic metabolism of vitamin D, requiring higher vitamin D doses (56).
REVIEW

Approach to the patient with secondary osteoporosis
Lorenz C Hofbauer, Christine Hamann and Peter R Ebeling

Specific osteoporosis treatment

Bisphosphonates Both oral and i.v. bisphosphonates have been used in the treatment of secondary osteoporosis. In general, alendronate (70 mg/week) and risedronate (35 mg/week) are reasonable anti-osteoporotic drugs for secondary osteoporosis. However, many patients with osteoporosis secondary to gastrointestinal diseases or concurrent medications not tolerating, or adhering to, oral bisphosphonates and those in whom oral bisphosphonates are contraindicated may benefit from treatment with i.v. ibandronate or zoledronic acid. I.v. bisphosphonates are also favorable to oral bisphosphonates which are poorly absorbed in malabsorption. Because of its potency and convenient administration, zoledronic acid (4 or 5 mg/year) has recently been evaluated in various forms of secondary osteoporosis. It is important to note that the evidence for an anti-fracture effect of bisphosphonates is limited for most forms of secondary osteoporosis, except for women and men with GIO, men with hypogonadism, and men after cardiac transplantation. In addition, most studies were not powered to assess fracture risk reduction.

The use of bisphosphonates in patients with renal insufficiency has been a concern. However, a post-hoc analysis of the fracture intervention trial (FIT) demonstrated that alendronate reduced fractures in postmenopausal women with osteoporosis and impaired renal function (glomerular filtration rate, GFR <45 ml/min) (72). A small study conducted in patients with osteopenia on regular hemodialysis demonstrated an increase in the spinal BMD with ibandronate (2 mg every 4 weeks over 48 weeks) by 5.1%, although no fracture risk reduction was assessed (73).
Specific osteoporosis treatment

Teriparatide Bone formation is severely impaired in GIO and in many men with osteoporosis, thus providing a rationale to use the bone anabolic teriparatide.

Osteoporosis in men.

Glucocorticoid-induced osteoporosis. I

therapy is warranted. New therapies are currently under investigation, including denosumab, a human antibody against RANKL, odanacatib, a specific cathepsin K inhibitor, and third-generation selective estrogen receptor modulators.

Denosumab Denosumab is a human MAB directed against RANKL, an essential cytokine for osteoclastogenesis (103). In men receiving androgen-deprivation therapy for prostate cancer, denosumab (60 mg s.c. every 6 months for 2 years) increased spinal BMD by 7% and reduced vertebral fractures by 62% (104). Similarly, in women on AI therapy for breast cancer, denosumab increased BMD at the spine and the femoral neck (105), although this study was not powered to assess fractures. Denosumab has not been approved for primary or secondary osteoporosis, but may expand our armamentarium to treat bone loss conditions.
Objectives

- **Vitamine D, Bisphosphonates, Calcitonin and Denosumab** may affect bone metabolism by way of many overall and local factors and may directly influence pathogenetic defects in Charcot disease.

  - proinflammatory cytokines regulation (TNFα, IGF, TGF, TGFα,β, M-CSF)

  - RANKL/OPG system, down regulation of nuclear factor kappa-B and genes encoding proinflammatory cytokines
Objectives

• It is logical to treat Charcot disease analogous to the treatment of osteoporosis (e.g. postmenopausal) and high-turnover metabolic bone disease (e.g. renal osteodystrophy)
Advantages of Selected Therapeutic Agents
Vitamine D, Bisphosphonates, Calcitonin and Denosumab

- improvement in systemic inflammation
- decreased osteolysis
- without serious adverse events
- proved in studies with osteoporosis and/or metabolic bone diseases
Bisphosphonates in the treatment of Charcot neuroarthropathy: a doubleblind randomised controlled trial

Markers of bone turnover were high at baseline and significantly decreased in treated subjects in comparison with controls

*Jude et al, Diabetologia, 2001*
Objectives

Intranasal Calcitonin in the Treatment of Acute Charcot Neuroosteoarthropathy

The calcitonin group had significantly greater reduction in 1CTP and BALP in comparison with the control group

*Bém et al, Diabetes Care, 2006*
Objectives

Long-term effects of intra-nasal calcitonin on healing times and recurrence of acute Charcot foot: a randomized controlled trial.

- Calcitonin group had significantly shorter healing time and a tendency of decreasing recurrence rates in comparison with controls during 15 months after cessation of casting.

*Bem R. et al., EASD, 2006*
Objectives

Denosumab in Postmenopausal Women with Low Bone Mineral Density

- A randomized, placebo-controlled, dose-ranging study included eight double-blind groups and one open-label treatment group
- Denosumab treatment for 12 months resulted:
  a) in an increase in bone mineral density at the lumbar spine, at the total hip and at the distal third of the radius
  b) in a near-maximal reductions in mean levels of serum C-telopeptide from baseline

McClung et al, NEJM, 2006
Comparison of vitamin D insufficiency (25(OH)D \( \leq 20 \) ng/mL) between patients with acute Charcot foot (n = 38) during 1 year follow-up period and controls.

\[ \text{Jirkovská A. et al., ADA 2007} \]
Correlation between area under the curve (AUC) of vitamin D and osteoclastic activity (ICTP) in patients with Charcot foot during 1 year follow-up period

\[ r = -0.40 \]
\[ p < 0.02 \]

Jirkovská A. et al., ADA 2007
• Red, hot, swollen foot in a patient with peripheral neuropathy should be considered Charcot Neuroarthropathy until proven otherwise.

• Patient with ulcer (history of previous ulcer) should be aggressively worked-up for osteomyelitis.
Take-Home Points...

• The most effective treatment for acute onset CN is non-weightbearing followed by a weightbearing TCC changed weekly.

• Medical treatment with Bisphosphonates and other anti-RANKL medications may shorten the inflammatory period and prevent deformity.
Take-Home Points...

• Non-healing or recurrent ulcers, osteomyelitis, or instability may require surgical intervention for limb salvage. (HBO will not cure “rocker-bottom” deformity)

• Ankle Charcot is primarily a surgical problem.
Take-Home Points...

• Charcot disease is a multi-specialty problem involving endocrinology, podiatry, orthopedics, vascular surgery, plastic surgery and physical therapy.
Questions?
Literature


Literature
15. Machin D., Campbell M. Design of studies for medical research. John Wiley and sons, Chichester, 2005