HIV Infection and Bone Disease

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UCSF Medical Management of HIV/AIDS CME
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- DISCLOSURE -

• Consulting: Merck

HIV and Bone Disease

Osteoporosis/osteopenia *

Osteomalacia *

Osteonecrosis *

* Increased prevalence in HIV+ pts *

Bone disease - most common metabolic complication of HIV infection

TOPICS

• Osteonecrosis of bone

• Osteonecrosis in HIV infected individuals
  – Clinical characteristics
  – Risk factors

• Studies with bisphosphonates

Osteoporosis/osteopenia *

Osteomalacia *

Osteonecrosis *

* Increased prevalence in HIV+ pts *
OSTEONECROSIS

• Cause – impaired delivery of oxygen and nutrients to bone
• Typically affects poorly vascularized fatty bone marrow
• Pathology: areas of ‘dead marrow’ and trabecular bone extending into the subchondral space
• Histology: large bone marrow lesions with edema, hemorrhage, fibro-riticulosis, hypocellularity, fat replaced by eosinophilic debris

"ischemic necrosis"
"avascular necrosis"
"aseptic necrosis"

• 90% of cases involve femoral head – very susceptible –
  – Generally affects the ant-lat aspect of hip just below wt bearing joint space
  – Area of highest mechanical stress in hip
  – Once x-rays positive → collapse of femoral head inevitable (weeks to years)
• NOT a single discrete disease entity but the final common pathway of many involving – -
  – Impaired blood supply to the bone

PROPOSED MECHANISMS

• Small arteries of femoral head occluded by lipid droplets, sickled RBC’s, N2 bubbles
• Structural damage to the vessels
  - TRAUMA
  - VASCULITIS
  - RADIATION
• Release of vasoactive substances locally → ischemia
• Increased intramedullary fat in bone

CLINICAL FEATURES

• True prevalence unknown
• US – 10,000 - 20,000 new cases annually
• Underlying DX in ~10% of all hip replacements
• Location: epiphyses of long bones (femur, humerus, also carpal and tarsal bone, knee)
• Susceptibility: men/women 8:1
• Wide age distribution – most patients are < 50 when diagnosed

Disorder → impaired blood supply → Necrosis

COLLAPSE
CAUSES - Osteonecrosis

- Trauma
- Glucocorticoids
- Excess alcohol

90% of cases in US have these conditions/risk factors associated

All CAUSES & ASSOCIATIONS*

- Trauma
  - Fracture of femoral neck
  - Dislocation or fracture/hip dislocation of hip
  - Other trauma
- Glucocorticoids
- Excess alcohol
- Dysbaric syndromes (i.e., divers)
- Sickle cell disease
- Gaucher disease
- Radiation therapy
  - RHEUMATIC: SLE, antiphospholipid Ab syndrome, vasculitis, other connective tissue diseases; post-transplant
  - Pregnancy
- Infections with HIV
  - Pancreatitis, pancreatic cancer
  - Inherited thrombophilia (maybe)

* Modified from Gansler LA, Current Rheumatology Diagnosis & Treatment, 2013

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>MECHANISM</th>
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<tbody>
<tr>
<td>Trauma</td>
<td>(Femur) within 8 hr of disrupting flow can get ON hip; tenuous blood supply; hematomas increase pressure; displaced fx alters flow; tears of arteries, capsule; certain bones in wrist fx also predisposed to ON</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Dose, duration – imp; &gt;20 mg prednisone; low (&lt;3% if doses &lt;20/d); osteoblast/osteocyte apoptosis (mice)</td>
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<tr>
<td>Alcohol</td>
<td>Dose response with amt consumed, T-bone cell toxicity</td>
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<tr>
<td>Sickle cell disease</td>
<td>Sicking of RBC, marrow hyperplasia</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>Cells with abnl lipid efface marrow</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>Kills bone cells</td>
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<tr>
<td>RHEUM</td>
<td>Steroids + vasculitic disorders cause impaired flow; common post-transplant – due to drugs (pred, CSA, MM)</td>
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<tr>
<td>Pregnancy</td>
<td>- - ? - -</td>
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HIV Multifactorial
**Signs, Symptoms**

- Pathology present for while before symptoms occur
- Pain/aching in the affected joint area
- Hip → groin pain
- Pain may be bilateral
- Exam: decreased ROM due to pain
- Over time: pain, stiffness, decreased ROM progress and can take years
- If LE → may progress to limping
- Lab tests → nothing

**OSTEONECROSIS: Imaging**

- X-ray
- Bone scan
- CT
- MRI

<table>
<thead>
<tr>
<th>STAGE</th>
<th>FEATURES</th>
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<tbody>
<tr>
<td>0</td>
<td>All tests negative – histology positive</td>
</tr>
<tr>
<td>1</td>
<td>MRI positive and +/- symptoms</td>
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<tr>
<td>2</td>
<td>+++ xray abnormalities – linear sclerosis, focal mineralization, cysts in femur; fem head still spherical, NO collapse; +/- symptoms</td>
</tr>
<tr>
<td>3</td>
<td>Joint (hip) begins to fail, &quot;crescent sign&quot; develops (radiolucency); fem head - still spherical; may be able to save joint; intermittent pain, gait normal</td>
</tr>
<tr>
<td>4</td>
<td>Changes in joint → irreversible; femoral head flattened; joint space narrowing; antalgic gait, decr ROM, ++pain</td>
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<tr>
<td>5</td>
<td>ABOVE + osteoarthritis develops (hip) with collapse of fem head; PAIN – significant</td>
</tr>
<tr>
<td>6</td>
<td>Extensive destruction/collapse of femoral head; PAIN – very significant, decreased mobility</td>
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</tbody>
</table>

International Association on Bone Circulation & Bone Necrosis
(Subcommittee on Nomenclature)
OSTEONECROSIS: Imaging

• Frog-leg view/same pt
• Bilateral cystic change and sclerosis
• Collapse of femoral head – joint space not smooth

OSTEONECROSIS: Imaging

• Established ON
• Cystic changes, sclerosis of femoral head + collapse (joint space narrowed)

OSTEONECROSIS: Imaging

• X-ray – generally first test ordered
• Bone scan
• CT
• MRI

OSTEONECROSIS: Imaging

• X-ray – generally first test ordered
• Bone scan – get if want to survey all joints, otherwise not so useful
• CT
• MRI
OSTEONECROSIS: Imaging

- X-ray
- Bone scan
- CT – only slightly better
- MRI
  - Highest degree of sensitivity (95%); $$$
  - Gold standard
  - Most common finding – low signal intensity on T1- & corresponding bright signal on fat-suppressed T2-weighted images
  - Often positive before symptoms

MANAGEMENT

- Conservative measures – pain mgmt, limit wt bearing
- Joint replacement – 50% of pts end up with this
- Core decompression – with or without bone grafting
- Osteotomy - remove diseased bone
- Bisphosphonate (ALN) – small, unblinded studies suggest can delay progression and collapse and may avoid early THA
MANAGEMENT

• Conservative measures
• Joint replacement
• Core decompression
• Osteotomy
• Bisphosphonate (ALN)

**Management is controversial; preserve native joint as long as possible; staging important; age and co-morbidities figure in; prostheses last 10-20 yrs; asymptomatic with 15% fem head involvement should recover; >30% of fem head involvement do not recover

OSTEONECROSIS and HIV

• ON (esp of femur) recognized as complication of (or associated with) HIV since ~1990
• Documented in case reports & case series
• Appears to be increased incidence of “known” clinical risk factors for ON in HIV+ patients
  – Steroids
  – Hypercoagulable state
  – Smoking, alcohol
  – ART (esp PI) (HIV)
  – Presence of lipodystrophy (HIV)
  – Use of megestrol or testosterone (HIV)

What the review articles say…

Morse et al, Clin Inf Dis, 2007

OSTEONECROSIS and HIV

• Rate of symptomatic ON in general population estimated:
  – 0.003-0.006 cases per 100 person years
• Retrospective estimates from case series (HIV infected persons):
  – 0.03-0.37 cases per 100 person years
  – 100 fold greater risk if HIV positive
• Large prospective studies with good control groups
  – not available/rare entity

OSTEONECROSIS and HIV: Estimating Prevalence

• 339 asymptomatic pts with HIV followed at NIH Clinical Center and 118 HIV negative controls (age- and sex-matched) were screened for ON with hip MRI
  – 15 of 339 HIV+ patients had it → 4.4%!!
  – 6 had bilateral hip disease
  – NO CONTROLS had ON (p = 0.015)
• Systematic look at pts with and without ON

Morse et al, Clin Inf Dis, 2007
Miller et al, Ann Int Med, 2002
FINDINGS

- RF’s checked: race, sexual orientation, CD4, viral load, ART, duration of PI use, CBC, chol, TG’s
  - None were significantly different - HIV+ patients with ON vs without

- Risk of ON associated with:
  - ANY lifetime use of corticosteroids (RR 3.8)*
  - Lipid-lowering agents (RR 4.7)*
  - Low testosterone & its use (RR 3.2 & 3.9)*
  - Megesterol use – not significant
  - H/O weightlifting or bodybuilding (RR 3.3)*

*statistically significant  
Miller et al, Ann Int Med, 2002

FINDINGS

- Labs:
  - 14/15 with ON had + anticardiolipin Abs (93%)
  - Compared to 5/50 HIV+ without ON who were positive (10%)
  - 7/14 had titer > 23 IgG phospholipid units (level associated with thrombosis)
  - RR for ON in pts with APA > 23 was 3.9 (CI, 1.7-8.3)
  - 0/15 had lupus anticoagulant **
  - NO other tests for hypercoagulability were positive

** 3 tests: Ab to cardiolipin (ELISA), Ab to B2 glycoprotein (ELISA), lupus anticoagulant test (functional); more that are positive assoc with greater chance of APLS but still need “syndrome” – prothrombotic state – osteonecrosis does not meet that criteria

FINAL POINTS – NIH Series

- MRI is better than x-ray but can’t do in everyone – target those with pain
- No association with PI’s - ON in HIV pts occurred before PI’s used
- Lipid lowering agents – marker for those with severe dyslipidemia
- Steroids: important
  - Don’t need long courses
  - Even short courses implicated (several days to weeks) – only 1/15 pts was on steroids for ~2 yrs

Miller et al, Ann Int Med, 2002
Asymptomatic pts who has MRI screening for osteonecrosis (L) and cohort of patients with osteonecrosis and clinical symptoms (R).

Asymptomatic cohort (asx)

- 9/18 had bilateral disease
- With f/u only 2 had THR (5.7 years) and 3 died (unrelated)
- 16/18 were radiographically stable or even improved

Symptomatic cohort

- 18/22 had bilateral hip disease
- 7 with symptomatic ON of other bones (5 shoulders, 3 knees, 1 ankle)
- With f/u of 2 years → 13/18 (59%) had THR
- 4 lost to f/u and 2 died
- 87% of pts in sx group had > 50% involvement of fem head

Comparison: Asymptomatic (18) vs Symptomatic (22) Patients

• Asymptomatic group:
  - 9/18 had bilateral disease
  - With f/u only 2 had THR (5.7 years) and 3 died (unrelated)
  - 16/18 were radiographically stable or even improved

• Symptomatic group:
  - 18/22 had bilateral hip disease
  - 7 with symptomatic ON of other bones (5 shoulders, 3 knees, 1 ankle)
  - With f/u of 2 years → 13/18 (59%) had THR
  - 4 lost to f/u and 2 died
  - 87% of pts in sx group had > 50% involvement of fem head

Summary

• Incidence of:
  - Asymptomatic ON in HIV+ 0.65 cases/100 PY
  - Symptomatic ON in HIV+ 0.26 cases/100 PY
  - ON in general population 0.004 cases/100 PY
  ~100 times more common in HIV+ patients

• Osteonecrosis can progress rapidly – use steroids judiciously, avoid risk factors if possible
**ALENDRONATE: Osteonecrosis**

(Agarwala et al, Rheum, 2005 - Mumbai, India)

- Observational study: 60 pts (100 hips) with ON
- All treated: ALN (10 mg/d) + Ca/vit D3
- Monitored clinical & functional parameters, pain, ROM, xray, MRI
- F/U: >1 yr (41 pts), 2 yrs (24 pts), > 2 yrs (21 pts)
- Functional: decreased pain at 1 yr, improved walking/standing, less NSAIDs
- Xray: hips stabilized or progressed only 1 grade; MRI → decreased marrow edema - at 1 yr
- Only 6 pts had surgery (more predicted)

CONCLUSION: ALN reduces pain, improves fct, retards progression, avoids early surgery

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**CONCLUSION**

ALN reduces pain, improves function, retards progression, avoids early surgery.

**Reasoning:**

- Without RX, >70% of femoral heads with ON collapse & require THA in 3-4 yrs of DX. ALN reduces turnover & path turnover involved in bone loss → collapse (hypothetical).

**Goal:**

- Prevent early collapse of fem head in pts with non-traumatic ON

- Randomized 40 pts with Stage 2 or 3 ON with necrotic area > 30% - 20 pts to 70 mg ALN/wk, 20 pts to nothing X 24 wks with f/u for 24 mos by xray and clinically (NO MRI done: no HIV pts)

- Study – unblinded clinically, single-blinded (xray)

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**ALN may prevent collapse – many caveats**
CONCLUSIONS*

- HIV+ pts have many of the classical risk factors – unlikely ART or HIV infection itself predisposes.
- Data on role of lipid-lowering therapy & testosterone (as risks) – suspect!
- Uncertain what role is for bisphosphonates – could consider, studies – not strong, all done before.
- OSTEONECROSIS of jaw (!) reported with bisphosphonate.
- Maintain high degree of awareness in patients who develop joint pain – esp if h/o glucocorticoid rx.
- Consider screening pt with ON for osteoporosis – many RF’s are the same.

# have & document informed consent  * includes opinions

MANAGEMENT

- Conservative measures
- Joint replacement
- Core decompression
- Osteotomy
- Bisphosphonate (ALN)