**Arthritis and Joint Pain in (Post)Menopausal Women**

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**Disclosures:**
GSK – consultant
Genetech – consultant

I will reference the off label use of medications for OA and RA.

**Objectives:**

- Discuss influence of menopause and postmenopausal hormone therapy on common rheumatic conditions.
- Review an approach to diagnostic testing and referrals for joint pain in peri/post menopausal women.
On any given day in a rheumatology clinic...

56yo ♀ from Baltimore...

~ 12 months ago new onset joint symptoms
Different from ‘usual’ aches and pains
Started in her feet, difficult to walk to bathroom in am
Worsening stiffness in hands
Also pain in knees, elbows, and back
She feels achy and stiff.

Meds: HCTZ, Naprosyn 220mg daily prn

PMHX: Hyperlipidemia, HTN
Last menstrual period age 51.

FamHX: Granddaughter SLE

SocHX: Lives with husband, 2 kids, 2 dogs. Quit smoking at age 30, occasional whiskey in the evening (and Bailey’s in her coffee). Works as a paralegal in law firm.

Differential Diagnosis:
Osteoarthritis (OA)
Crystalline arthritis (gout)
Systemic autoimmune disease
Osteoarthritis and Estrogen

Osteoarthritis

- ≥ 20 million in the USA
- Present in at least 44% postmenopausal ♀ (WHI)
- 3x more common among ♀ age 45-64 compared to ♂
- Second leading cause of disability in USA
- 400,000 TKR and 600,000 THR per year

Age-Related Prevalence of OA: Changes on X-Ray

ESTROGEN

Tissues in which estrogen receptor subtypes (ERs) are expressed.

<table>
<thead>
<tr>
<th>Type of ER</th>
<th>Tissues in which they are expressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERα</td>
<td>Uterus, placenta, pituitary and cardiovascular system</td>
</tr>
<tr>
<td>ERβ</td>
<td>Ventral prostate, urogenital tract, ovarian follicles, lung and immune system</td>
</tr>
<tr>
<td>ERα and β</td>
<td>Mammary gland, brain and joint tissue: growth plate chondrocytes, articular chondrocytes; subchondral osteocytes, osteoblasts and osteocytes; synovocytes, ligament fibroblasts and myoblasts</td>
</tr>
</tbody>
</table>

Osteoarthritis & Estrogen: Human Data

- Genetic variations in ER genes associated with knee OA in ♀¹
- WHI: 27% decrease THR; 13% decrease TKR in estrogen-treated group²
- Nurses’ Health Study: High BMI and age associated with THR; no association with current/past estrogen supplementation³

¹Riancho JA, et al. Osteoarthritis Cartilage 2010;18:927

56yo ♀ from Baltimore…
OA: Symptoms & Signs

- OA Pain is generally related to use
- Pain gets worse during the day
- Minimal morning stiffness (<20 min) and after inactivity (gelling)
- Range of motion decreases
- Joint instability
- Bony enlargement
- Restricted movement
- Crepitus
- Variable swelling and/or instability

Distribution of primary OA

- Primary OA typically involves variable number of joints in characteristic locations, as shown
- Exceptions may occur, but should trigger consideration of secondary causes of OA

Causes of secondary OA

- Dysplastic
  - chondrodysplasias
  - epiphyseal dysplasias
  - congenital hip dislocation
  - developmental disorders
  - Legg-Perthes
  - Leg-length inequality
- Posttraumatic
  - acute
    - (e.g., fracture through joint)
    - repetitive
    - (e.g., occupational injury)
  - postoperative
    - (e.g., meniscectomy)
- Post inflammatory
  - infection
  - RA/Inflammatory arthritis
- Endocrine, Metabolic
  - acromegaly
  - ochronosis
  - hemochromatosis
  - crystal
  - hyperparathyroidism

Beware…night pain…

Differential Diagnosis:

- Extra articular (bursitis/tendinitis)
- Fracture
- R/O Malignancy
- Severe OA
Is the pain OA?

- “Hip” pain
  - Trochanteric bursitis
  - PMR
  - Iliotibial band syndrome
  - AVN
  - meralgia paresthetica
  - psoas/piriformis syndromes
  - neuropathic

- Knee Pain
  - Patellofemoral syndrome
  - Chondromalacia patella
  - referred hip
  - pes anserine bursitis
  - AVN
  - FM tender points

Differential Diagnosis:

- Osteoarthritis (OA)
- Crystalline arthritis (gout)
- Systemic autoimmune disease

Women and Gout

Gout

- Overall prevalence ~4% in USA
- 5.9% prevalence ♂
- 2% prevalence ♀
- Major risk factors: hyperuricemia, age, BMI (obesity)

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Gout & Women

• Obesity in early-mid adulthood is associated with 2.8 fold increased risk gout among ♀\(^1\)
• Age, not menopause status, was associated with gout\(^2\)
• Use of opposed estrogens decreased risk incident gout (OR 0.69, 95% CI 0.56-0.86) ♀ >45yo (w/o renal failure)\(^3\)

\(^2\)Krishnan E, et al. Menopause 2014;21(11):1311
\(^3\)Bruderer SG, et al. Menopause 2015;22(12):1335

56yo ♀ from Baltimore…

Differential Diagnosis:

• Osteoarthritis (OA)
• Crystalline arthritis (gout)
• Systemic autoimmune disease
Almost all autoimmune/rheumatic diseases are more common in women:

- ↓ Estrogen & DHEA
- ↓ IFN-gamma
- ↑ IL1, IL6, TNFα

Almost all autoimmune/rheumatic diseases are more common in women:

- SLE/Lupus (SELENA; HRT-SELENA)
- Sjogren’s syndrome
- Giant cell arteritis/polymyalgia rheumatic
- Rheumatoid arthritis

**RA: Epidemiology**

- Prevalence ~ 1% of the general population
- Peak incidence between 35 - 60 years of age
- Incidence 2-4x greater in women than in men

**RA: Who cares?**

- If untreated, 20-30% of RA pts become permanently unable to work within 3 years of diagnosis
- Lifetime cost approaches that of cardiovascular diseases
- Associated with an increased mortality risk (infection risk with disease activity)
- Early diagnosis and appropriate therapy reduces joint damage and comorbidities
Premature Mortality in Patients with RA

- Control Women
- Control Men
- RA Women
- RA Men

Major Cause of Excess Deaths is Cardiovascular Disease

N = 886
SMR = 3.08

SMR = standardized mortality ratio for patients with RA compared with non-RA controls.


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2010 Rheumatoid Arthritis Classification Criteria

Target population: (Who should be tested?). Patients who:
1) have at least 1 joint with definite clinical synovitis (swelling)
2) with the synovitis not better explained by another disease

Classification criteria for RA (non-tender joint) add score of categories A-D

A. Joint involvement
   1. large joint
   2. 10 large joints
   3. 1-3 small joints with or without involvement of large joints
   4. 10 small joints with or without involvement of large joints
   5. >10 joints (at least 1 small joint)

B. Serology (at least 3 test result is needed for classification)
   1. Negative RF and negative ACPA
   2. Low-positive RF or low-positive ACPA
   3. High-positive RF or high-positive ACPA

C. Anti-nucleolar antibodies (at least 1 test result is needed for classification)
   1. Normal CRP and normal ESR
   2. Abnormal CRP and abnormal ESR

D. Duration of symptoms
   1. <6 weeks
   2. >6 weeks

No DIP, CMC, 1st MTP

The Clinical Spectrum of RA

Early PIP swelling
Active with some deformity
Late-stage deformities
RA: Clinical Features

SYMPTOMS:
- Joint swelling
- Joint pain
- Joint redness and warmth
- SIGNIFICANT Morning Stiffness (>30min)

SIGNS
- ARTHRITIS: symmetric, polyarticular (>3 joints)
  - Symmetry may not be present at disease onset!
- MCP/PIP/Wrist/MTP Involvement
- "Row" Pattern
- Cervical spine
- Sparing of T/L spine

Joint Involvement in Early RA

<table>
<thead>
<tr>
<th>Joint</th>
<th>% Patients</th>
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<tbody>
<tr>
<td>MCP, PIP</td>
<td>90</td>
</tr>
<tr>
<td>Wrists</td>
<td>80</td>
</tr>
<tr>
<td>Knees</td>
<td>65</td>
</tr>
<tr>
<td>Shoulders</td>
<td>65</td>
</tr>
<tr>
<td>Ankles</td>
<td>50</td>
</tr>
<tr>
<td>Feet</td>
<td>45</td>
</tr>
<tr>
<td>Elbows</td>
<td>40</td>
</tr>
<tr>
<td>Hips</td>
<td>20</td>
</tr>
</tbody>
</table>

RA: Catch the Warning Signs
Refer to a rheumatologist if a patient shows any of these symptoms:
- ≥ 3 swollen joints (do not have to be symmetric!)
- Positive "squeeze" test
- Morning stiffness ≥ 30 minutes
- Persistence of symptoms > 6 weeks
- Positive Anti-CCP/ACPA

RA: Laboratory Characteristics

MCP Squeeze Test
Squeeze test indicates pain across second to fifth metacarpals (MCP), metatarsals (MTP)

IgM RF
IgG RF
Fc
Fab
IgG
IgG
Fc
Fab

© ACR
**What is ‘Rheumatoid Factor (RF)’?**

- Autoantibodies to the Fc portion of IgG
- *Primarily* IgM (IgG, IgA also possible)
- Pathogenic role unclear

**How common is RF?**

- 60-80% of patients with established RA
- Frequently absent early in disease course
- HIGH titer = poor prognosis (erosions, vasculitis, severe dz)

**BEWARE: +RF DOES NOT ALWAYS +RA**

- Acute phase reactant
- Infections (chronic, endocarditis), inflammation (Stills, Sjogrens)
- Paraproteinemias, cryoglobulinemia

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**Anti-Citrullinated Peptide Antibodies (ACPA)**

**Anti-CCP Antibodies**

- High Specificity for RA\(^1\),\(^2\)
- High Positive Predictive Value for RA\(^3\)
- May be especially useful in HCV and Sjogren's\(^4\)
- Detectable earlier than RF (predate clinical disease)\(^5\)
- Found in up to 40% of patients who are RF negative especially early in disease\(^6\)
- Predictive of erosive disease and joint damage\(^7\)

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**Anti-PAD3/4 antibodies**

- Antibodies activate enzymes that generate citrullinated autoantigens
- Hypothesis is this provides a feed-forward loop which may drive the erosive outcome observed in RA patients with these autoantibodies
- Associated with ILD
- Highly correlated with anti-CCP, but may identify subset of patients with HIGHLY erosive, aggressive disease
- May be future treatment target

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**Rheumatoid arthritis, Estrogen and Menopause**

Estrogen & RA Observations

- Incidence of new RA and RA flare are low during pregnancy.
- Post-partum (3-24 months) incidence of RA and RA flare are high.
- Peak age of RA onset is peri- post-menopausal period (age 45-65 years).

Menopause & RA

- Swedish population case/control study, postmenopausal hormone use decreased risk of seropositive (CCP) but not seronegative RA
- WHI: 105 incident, 63 prevalent RA. Trend toward protective effect estrogen alone. No difference in “RA severity” or SF-36
- NHS: Highest risk (HR 2.4; 95%CI 1.5-4.0) seronegative RA early age menopause (<44 years); menopausal status did not influence seropositive RA