Musculoskeletal Diseases in Menopausal Women

Manathip Osiri, MD, MSc
Division of Rheumatology, Department of Medicine, Faculty of Medicine, Chulalongkorn University
Musculoskeletal changes in menopausal women
Immune-aging
Effects of estrogen deprivation on the immune system
Common musculoskeletal disorders in menopausal women
Musculoskeletal changes in menopausal state

- Progressive loss of muscle mass leads to muscle atrophy, weakness, and fall
- Accelerated bone loss that leads to osteopenia, osteoporosis, and fractures
- Associated effects of vasomotor symptoms attributed to menopause, e.g., vertigo, may cause fall and fracture

Effects of sex hormones on the immune system

- Estrogens decrease inflammatory immune responses but enhance immunoglobulin production simultaneously
- Androgens and progesterone are natural immunosuppressors
- Estrogens are important risk factors of autoimmune diseases, e.g. SLE, RA

Estrogens and synovial inflammation in RA

Antibodies

Synovial tissue

16OH and 4OH Estrogen metabolites enhance cell proliferation

E

Macrophage

B cell

Synovial fluid

Androstenedione

Testosterone

Aromatase

Estrone

Estradiol

IL-6

↑ Estrogens

↓ Androgens

Immunosenescence

- As aging progresses, decreased clearance of free radicals causes oxidative stress
- Oxidative stress causes low-level chronic inflammation that leads to several diseases in aging
- A decreased ability of the immune system to respond to foreign antigens, and a decreased ability to maintain tolerance to self-antigens

Effects of menopause on the immune system

- Menopausal state—estrogens deprivation--may affect the immune system in several ways:
  1. Increase in pro-inflammatory cytokines: TNF-α, IL-1, IL-6
  2. Increase in cell responses to these cytokines
  3. Decrease in CD4+ T and B lymphocytes, NK cells cytotoxic activity

Common musculoskeletal diseases in menopause women

- **Non-inflammatory musculoskeletal diseases**
  - Perimenopausal polyarthralgia/arthritis
  - Osteoarthritis
  - Spondylosis
  - Osteoporosis
  - Hypothyroidism
  - Myofascial pain
  - Fibromyalgia

- **Inflammatory musculoskeletal diseases**
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Crystal-induced arthritis
    - Gouty arthritis
    - CPPD arthropathy
  - Polymyalgia rheumatica/giant cell arteritis
Perimenopausal polyarthralgia/arthritis (1)

- Joint pain, joint stiffness were reported in approximately 50% of menopausal women
- Decline in estrogen levels may relate to increase inflammatory responses and pain processing pathways
- Polyarthralgia usually involve PIP joints of hands, sometimes true arthritis is also presented, which may mimic RA

Perimenopausal polyarthralgia/arthritis

- Polyarthralgia/arthritis in menopausal women is usually mild in severity, self-limited, and does not result in joint destruction or deformity.
- Other possible causes of polyarthralgia/arthritis should be excluded.
- Treatment included reassurance, NSAIDs, or a short course of antimalarial agents.

Magliano M. Maturitas 2010;67:29-33.
Degenerative joint diseases: osteoarthritis and spondylosis

- DJDs are characterized by progressive loss of articular cartilage associated with bone hypertrophy (osteophytes and subchondral bone sclerosis)
- OA is a disease of synovial joints
- Spondylosis is common at cervical and lumbar spine, involves intervertebral disc joints
- DJDs are the most common joint disease worldwide, impose the major burden to the patients, society, and healthcare systems

Knee OA

Lumbar spondylosis
Menopause and osteoarthritis

- Incidence of OA increases with age, especially in female population age > 50 years
- Obesity, trauma and joint overuse are other risk factors
- Knee and hand OA are more prevalent in menopausal women
- Estrogen deficiency plays a major role in initiating OA and accelerating disease progression
- HRT may prevent the onset or reduce the progression of knee OA

Hand OA

Heberden’s node

Bouchard’s node

Shelf sign
Erosive (inflammatory) OA of hands
Knee OA
Osteoporosis *(1)*

- Disease characterized by low bone mass and a microarchitectural deterioration of bone tissue
- Results in increased bone fragility and fracture
- Definitions of osteoporosis and osteopenia are based on the bone mineral density related to the mean BMD of young adults (T-score)
- Risk of fracture increases with age in post-menopausal women
Osteoporosis

- Risk factors of osteoporosis: estrogen deficiency (menopausal state), aging, low body weight (BMI<19 kg/m²), previous fracture, FH of fracture, use of glucocorticoids, etc.
- Several autoimmune diseases definitely increase the risk of osteoporosis and fractures, esp. SLE and RA
- Assessment of fracture risk may be performed using data from BMD testing or fracture prediction algorithms (e.g. FRAX)
Osteoporotic fracture
Rheumatoid arthritis (1)

- A systemic disease characterized by chronic inflammatory polyarthritis involved mainly synovial joints
- RA results in functional disability, joint damage and deformity, premature death
- Common age group at disease onset is 40-50 years, female: male ratio = 4-4.5:1
- Prevalence of RA varies between 0.3-1% and increases with age

Rheumatoid arthritis

- Elderly-onset RA (EORA) or late-onset RA (LORA) occurs in patients aged > 60 years (postmenopausal state)
- Prevalence of EORA is ~2%, female:male ratio = 1.5-2:1
- Different clinical features:
  - Classic RA
  - RS3PE
  - PMR-like

Hormonal replacement therapy and rheumatoid arthritis

• HRT has no significant effect on the risk of RA or disease activity in postmenopausal women
  

• HRT may help prevent the onset of RA in women with HLA-DRB1 *01 and/or *04 alleles
  

• HRT helps improve BMD in patients with EORA without increasing cardiovascular risks
  
Systemic lupus erythematosus

- A systemic autoimmune disease characterized by multi-organ involvement from immune complexes
- Immune complexes in SLE = self antigens + autoantibodies
- Ratio of child-bearing aged women: men = 9:1
- After menopause, the female: male ratio is 3-4 :1
SLE in postmenopausal women (1)

- Use of HRT in postmenopausal women increased the risk of developing SLE (RR ~2)
- Compared with patients with SLE in their childbearing ages, patients with disease onset after menopause had
  - More atypical features
  - Less disease severity
    - Common features: polyarthritis, weight loss, myalgia
    - Fewer typical features or major organ events: malar rash, lupus nephritis, leukopenia
  - Better prognosis

SLE in postmenopausal women

- Disease activity in SLE patients diagnosed in the postmenopausal years was lower than that in premenopausal patients
  - Fewer events of vasculitis, proteinuria, rash, pericarditis and positive anti-DNA Ab
- Higher damage index in postmenopausal group at any time points after the diagnosis
- No association between disease activity, flares, damage and menopausal status

Postmenopausal patients with SLE and HRT (1)

- Postmenopausal lupus patients taking HRT had a small risk of SLE flare compared to placebo
- Flares of SLE were mostly mild to moderate in severity
- HRT did not demonstrate to increase cardiovascular risk in patients with SLE

Postmenopausal patients with SLE and HRT (2)

- However, HRT clearly increased the risk of invasive breast cancer and thromboembolism.
- In lupus patients with antiphospholipid antibodies/syndrome, HRT may increase the risk of vascular thrombosis.
- The benefits of HRT on prevention of osteoporotic fracture should be balanced with the risks of HRT.

Gouty arthritis

Definition

- **Gouty arthritis**
  - Arthritis caused by monosodium urate (MSU) deposition in and around the joint tissues

- **Gout**
  - Hyperuricemia plus
    - Gouty arthritis
    - Gouty nephropathy and renal stone
    - Tophaceous gout
Serum uric acid, gout and menopause

- Serum uric acid levels in women gradually increase throughout early adulthood but do not reach the maximum level until after menopause.
- First attacks of gouty arthritis in women occur ~7-12 years later than in men, usually after menopause.
- An important factor that hastens the onset and/or modifies the clinical symptoms of gouty arthritis in menopausal women is the medications used.
## Difference between women and men with acute gouty arthritis

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation</td>
<td>Older (50s-60s)</td>
<td>Younger (40s)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>More (~28%)</td>
<td>Less (~16%)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Family history</td>
<td>More</td>
<td>Less</td>
</tr>
<tr>
<td>Pre-existing joint disease</td>
<td>More (~50%)</td>
<td>Less (~25%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>More (~30%)</td>
<td>Less (~13%)</td>
</tr>
<tr>
<td>Upper limb involvement</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Polyarticular gout</td>
<td>More</td>
<td>Less</td>
</tr>
</tbody>
</table>

Hyperuricemia, gout and menopause, HRT

- Compared to premenopausal women, postmenopausal women had:
  1. Higher levels of serum uric acid
  2. Higher incidence of acute gouty arthritis

- Postmenopausal women who used HRT had:
  1. Lower levels of serum uric acid
  2. Lower incidence of acute gouty arthritis than those not taking HRT

Polymyalgia rheumatica (PMR) / giant cell arteritis (temporal arteritis)

- PMR is a syndrome characterized by abrupt, symmetrical pain at shoulders, neck and hips with stiffness and limitation of ROM of shoulder and pelvic girdles
- PMR is common in individuals age $\geq 50$ years
- Other symptoms include anorexia, weight loss, malaise, prolonged fever, periarthritis
- High ESR or CRP
PMR / GCA (TA)

- PMR may be associated with giant cell arteritis (GCA) or temporal arteritis (TA)
- Clinical features of GCA include prolonged fever, headache, jaw claudication, CNS ischemia, ischemic optic neuropathy
- PMR should be differential diagnosed from other inflammatory polyarthritis
- Screening for malignancies should be performed if no response to proper treatment