CHAPTER 1

Non-inflammatory joint and soft tissue disorders

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Introduction

Rheumatologists often manage non-inflammatory arthritides and associated soft tissue disorders, including osteoarthritis, carpal tunnel syndrome, and gout. The diagnosis of these conditions as well as recent innovations in treatment will be reviewed here.

Carpal tunnel syndrome

Epidemiology

• One of the most common and frequently diagnosed entrapment neuropathies
  ◦ Accounts for up to 90% of entrapment neuropathies
  ◦ Prevalence in the US population up to 5% of the general population
    ▪ Estimated lifetime risk of 10%
    ▪ Females affected more frequently than men
    ▪ Peak age range 40–60 years
Risk factors include prolonged wrist flexion or extension, repeated use of flexor muscles, and exposure to vibration
- Systemic medical conditions i.e. diabetes, hypothyroidism, obesity, pregnancy, vitamin toxicity or deficiency can predispose
- Many cases remain idiopathic

Pathology
- Median nerve entrapment is caused by chronic pressure at the level of the carpal tunnel
- Compression of the median nerve is secondary to surrounding structures: carpal bones, flexor tendons, and the fibrous transverse carpal ligament leading to median nerve dysfunction
  - Carpal tunnel anatomy (Figure 1.1)
    - Superiorly: transverse carpal ligament
    - Posteriorly: carpal bones
    - Nine flexor tendons: (four) flexor digitorum profundus, (four) flexor digitorum superficialis, flexor pollicis
    - Median nerve
- Repetitive compressive injury to the median nerve leads to demyelination
  - Blood flow may also be interrupted, altering the blood–nerve barrier

Clinical presentation
- Symptoms may include tingling and numbness, in the distribution of the median nerve (first three fingers and radial aspect of the fourth finger); pain involving the entire hand, decreased grip strength, and reduced dexterity

![Figure 1.1 Components of the carpal tunnel (Color plate 1.1).](image)
Symptoms occasionally worse at night (awakenings with paresthesia nocturna: sensation of tingling, burning or numb hand possibly secondary to flexion of wrist at night)

- Patients with carpal tunnel syndrome (CTS) occasionally report subjective swelling of the hands and/or wrists
- Atrophy of the thenar eminence occurs in later stages (this finding is associated with poor response to surgical decompression)

**Diagnosis**

- Combination of the clinical history, examination, provocative tests, electrodiagnostic studies
  - **Phalen’s test** is positive when flexion at the wrist for 60 seconds causes pain and/or paresthesias in median nerve distribution
    - Sensitivity ranges from 67–83%
    - Specificity ranges from 40–98%
  - **Tinel’s test** is positive when tapping over the volar surface of the wrist (course of median nerve) causes pain and/or paresthesias in the distribution of the median nerve
    - Sensitivity ranges from 48–73%
    - Specificity reported as high as 100%
  - Electrodiagnostic studies lack standardized diagnostic criteria currently, making them inadequate as a universally recognized gold standard
    - Nerve conduction studies provide objective information regarding the median nerve across the carpal tunnel
      - Findings include prolonged motor and sensory latencies of median nerve
      - Reduction in median nerve compound motor or sensory action potential amplitude
      - Reductions in sensory and motor conduction velocities
      - Rules out other polyneuropathies included in the differential diagnosis
  - Ultrasonography may reveal flattening of the median nerve within the tunnel and bowing of the flexor retinaculum
    - Cross-sectional area of the median nerve is the most predictive of CTS; it has also been used in the classification of the severity of CTS
  - Magnetic resonance imaging assists in the determination of the severity of nerve compression; it is also helpful in observing anatomical structures that may be contributing to symptoms, i.e. ganglion cysts, bony deformities
Swelling of the median nerve and increased signal intensity on T2-weighted images assist in diagnosing CTS

Treatment

- Mild to moderate symptoms
  - Oral anti-inflammatories
  - Oral corticosteroids may be effective in reducing edema and tenosynovitis associated with CTS
  - Carpal bone mobilization and hand splints are often first-line treatment options
  - Corticosteroid injection along the proximal wrist crease just ulnar to the palmaris longus tendon provides clinical improvement, however benefit beyond 1 month was not shown in a systematic review
  - Ultrasound therapy
- Moderate to severe symptoms
  - Acupuncture therapy has been reported to improve median nerve function
  - Carpal tunnel release (CTR)
    - Surgical procedure to increase space in the carpal tunnel and reduce pressure on the median nerve, via division of the transverse carpal ligament
    - Good to excellent long-term outcomes following CTR in up to 90% of reported cases
    - Surgical treatment has been reported to demonstrate better long-term response when compared to splinting

Differential diagnosis

- Cervical radiculopathy
- Proximal median neuropathy
- Thoracic outlet syndrome
- Central nervous system (CNS) disorders

Osteoarthritis (OA)

Epidemiology

- Most common arthritis
- A leading cause of chronic pain and disability in older adults

Commonly involved joints

- Hand – most commonly involved in OA – distal interphalangeals (DIPs), proximal interphalangeals (PIPs), first carpometacarpal (CMC)
• Feet – first metatarsophalangeal (MTP), subtalar joint
• Knee
• Hip
• Spine
• Rarely affects elbow, wrist, ankle – look for history of trauma, congenital abnormality, systemic or crystalline disease

Definition
• OA can be defined pathologically, radiographically, or clinically
• Radiographic OA has long been considered the reference standard for epidemiology
  ○ Not all subjects with radiographic OA are symptomatic and not all with symptoms have radiographic OA

Risk factors
• Age – the strongest risk factor, most commonly age >40 years
• Females
• Obesity – the strongest modifiable risk factor
• Previous injury
• Family history (genetic predisposition)
• Joint malalignment (mechanical factors)

Pathogenesis
• Caused by an interplay of multiple factors – joint integrity, genetics, local inflammation, mechanical forces, cellular and biochemical processes
• Abnormal remodeling of joint tissues is driven by a host of inflammatory mediators within the joint
• OA pathogenesis is now thought of as an active response to injury rather than a degenerative process
  ○ Degradation of matrix and articular cartilage
    • Chondrocytes become “activated” and increase production of matrix proteins and matrix-degrading enzymes during inadequate repair response
      → Aggrecanases, collagenases, serine and cysteine proteinases, matrix metalloproteinase (MMP)-3, MMP-13, ADAMTS-5 are all reported to play a role
  ○ Thickening of the subchondral bone
    • Bone remodeling may be initiated at sites of local bone damage resulting from excessive repetitive loading
  ○ Formation of osteophytes
    • At joint margins and enthesal sites – new bone is added by endochondral ossification, leading to osteophyte formation
Variable degrees of inflammation of the synovium
  - Synovial infiltrates have been identified in many OA patients, though lower in grade than in rheumatoid arthritis (RA)
  - Prevalence of synovitis increases with advancing age
  - **Interleukin (IL)-1 beta and tumor necrosis factor (TNF) alpha** suppress matrix synthesis and promote cartilage catabolism, IL-17 induces chemokine production by synovial fibroblasts and chondrocytes
  - Degeneration of ligaments, menisci in the knee, and hypertrophy of the joint capsule, as any meniscal or ligamentous injury predisposes to the development of OA

**Symptoms**
- **Hand**
  - Pain on usage
  - Mild morning or inactivity stiffness, usually lasting <30 minutes
  - Characteristic sites – DIPs, PIPs, base of the thumb
- **Knee and hip**
  - Usage-related pain
  - Often worse toward the end of the day
  - Pain relieved, usually incompletely, with rest
  - Mild morning or inactivity stiffness (gelling)
  - Advanced OA – may have rest or night pain
  - OA symptoms are often episodic or variable in severity and slow to change

**Physical examination**
- **Hand**
  - Heberden’s (DIPs) and Bouchard’s (PIPs) nodes
  - Squared appearance to the first CMC is classic
- **Feet**
  - First MTP involvement may result in hallux valgus or hallux rigidus
- **Knees**
  - Tenderness to palpation of joint
  - Crepitus
  - Joint effusion
    - Synovial fluid in OA typically exhibits
      - Normal viscosity
      - Mild pleocytosis (WBC <2000/mm³)
  - Osteophytes – may have palpable bony enlargements at periphery of joint
  - Restricted movement and range of motion
• Hip
  ○ Hip pain worsened with internal or external rotation
  ○ Anterior and inguinal pain generally indicative of true hip joint involvement
  ○ Check both hips, as ~20% have bilateral OA
  ○ Full exam should also include evaluation for referred pain sources
    ▪ Trochanteric bursitis
    ▪ Lumbosacral spine
    ▪ Knee pathology

Osteoarthritis treatment

Management is primarily symptomatic, as no treatments have been shown to slow or reverse joint damage. Patient education regarding the natural history of the disease is critical. Non-pharmacologic treatments must be balanced with judicious use of pharmacologic treatments.

Non-pharmacologic treatments
• Instruction on joint protection techniques
• Thermal modalities – paraffin wax treatments, heat packs, and heating pads
• Strong recommendation for **weight loss** in patients with hip or knee OA
• Exercise – cardiovascular and/or resistance land-based exercise, aquatic exercise, and manual therapy (physical/occupational therapy) in combination with supervised exercise have all been helpful
• Participation in self-management programs and psychosocial interventions (diet, exercise instruction) can offer significant benefit
• Tai chi programs have been reported to be beneficial in small studies
• Assistive devices, orthotics, and splinting as needed:
  ○ Splints for trapeziometacarpal joint OA
  ○ Medially wedged insoles for lateral compartment knee OA
  ○ Laterally wedged subtalar strapped insoles for medial compartment knee OA
  ○ Medially directed patellar taping for knee OA

Pharmacologic therapy
• Acetaminophen
• Topical capsaicin – efficacy is controversial, but some advocate for its use as adjunctive treatment
• Topical non-steroidal anti-inflammatory drugs (NSAIDs), e.g. topical diclofenac, is a safe option especially if age >75 years
• Oral NSAIDs, including non-selective and selective (cyclo-oxygenase (COX)-2 inhibitors) (Table 1.1)
  ◦ Monitor for gastrointestinal (GI) and cardiac adverse effects (GI bleeding, abdominal pain, MI, worsening CHF)
  ◦ Avoid in chronic kidney disease
  ◦ COX-2 selective inhibitors are associated with increased cardiovascular risk and should be avoided in patients with cardiovascular risk factors
• Tramadol can also play a role in pain relief, especially in patients for whom NSAIDs or acetaminophen are contraindicated
• Intra-articular injection of long-acting corticosteroid can be effective for painful flares of OA, especially in trapeziometacarpal joint OA and knee OA

Intra-articular viscosupplementation
• Multiple brands available (Table 1.2)
  ◦ Currently only FDA-approved for knee osteoarthritis
  ◦ Few head-to-head comparisons and generally small studies
• Mechanism
  ◦ Hyaluronic acid (HA) is a constitutive component of the matrix cartilage
    ▪ Plays a key role in maintenance of joint homeostasis
    ▪ Biologically active component secreted by chondrocytes that protects cartilage from degradation by interacting with MMPs and pain mediators
    ▪ In OA, concentration and molecular weight of HA is reduced

Table 1.1 Use of NSAIDs in high-risk populations.

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Recommended regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of GI bleed, but none within the past year</td>
<td>Non-selective NSAID or COX-2 inhibitor + proton-pump inhibitor</td>
</tr>
<tr>
<td>History of GI bleed within the past year</td>
<td>COX-2 inhibitor + proton-pump inhibitor</td>
</tr>
<tr>
<td>Patient taking low-dose aspirin for cardioprotection</td>
<td>Non-selective NSAID other than ibuprofen* + proton-pump inhibitor</td>
</tr>
</tbody>
</table>

*The FDA warns against ibuprofen and low-dose aspirin used in combination, due to a pharmacodynamic interaction causing a decreased cardioprotective effect
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Table 1.2 Comparison of viscosupplementation products.

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosing</th>
<th>Molecular weight (in M Daltons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyalgan (sodium hyaluronate)</td>
<td>Once weekly for 3–5 weeks</td>
<td>0.5–0.73</td>
</tr>
<tr>
<td>Supartz (sodium hyaluronate)</td>
<td>Once weekly for 3–5 weeks</td>
<td>0.6–1.1</td>
</tr>
<tr>
<td>Orthovisc (high molecular weight hyaluronan)</td>
<td>Once weekly for 3–4 weeks</td>
<td>1.0–2.9</td>
</tr>
<tr>
<td>Euflexxa (1% sodium hyaluronate)</td>
<td>Once weekly for 3 weeks</td>
<td>2.4–3.6</td>
</tr>
<tr>
<td>Synvisc (hylan G-F 20)</td>
<td>Once weekly for 3 weeks</td>
<td>6</td>
</tr>
<tr>
<td>Synvisc-One (hylan G-F 20)</td>
<td>Once</td>
<td>6</td>
</tr>
</tbody>
</table>

- Exact mechanism not understood
- Proposed mechanism
  - Biomechanical – improves synovial fluid viscoelasticity, increases joint lubrication, coats articular cartilage surface
  - Analgesic – reduces pain eliciting nerve activity, reduces prostaglandin- or bradykinin-induced pain
  - Anti-inflammatory – reduces levels of inflammatory mediators, decreases leukocyte chemotaxis
  - Antioxidant
  - Chondroprotective – stimulation of endogenous HA and extra matrix component synthesis, protects against chondrocyte apoptosis, inhibits cartilage degradation
- Side effects
  - Generally well tolerated, most side effects related to injection site reactions
  - Rare pseudosepsis reactions, especially with high molecular weight HA
    - Patients present with acute joint swelling, pain, and warmth
    - Care must be taken to distinguish this syndrome from true septic joint
- Clinical use
  - Used in knee OA patients who fail non-pharmacologic treatments, acetaminophen, NSAIDs, and intra-articular steroids
  - Studies have shown improvement in pain scores with viscosupplementation, however:
    - Appropriate patient selection is not well defined
    - Many studies do not control for concomitant pharmacologic therapy
    - Double-blind, placebo-controlled trials report a large placebo effect
Campbell et al. in 2007 reviewed six systematic reviews on viscosupplementation
- Three reviews showed viscosupplementation more effective than placebo
- Three reviews suggested no benefit
- Rutjes et al. in 2012 systematic review and meta-analysis concluded that viscosupplementation is associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events
- Viscosupplementation is not recommended for OA of the hip due to lack of data

**Glucosamine and chondroitin sulfate**
- Both are labeled as supplements in the United States and are therefore do not need to be approved by the FDA before they are marketed; therefore variations in dosage among the marketed supplements exist, making comparisons difficult
- The GAIT trial for knee OA demonstrated that response to glucosamine and chondroitin alone or in combination were not different from placebo
  - A small subgroup analysis of patients with moderate-to-severe knee OA did show statistically significant improvement with combination therapy
  - 2-year follow up did not demonstrate clinically significant differences between the treatment groups
- Other studies have shown efficacy with these agents but were criticized for flaws, including failure to adhere to intention to treat, small numbers of patients, potential bias related to sponsorship of the study, and inadequate masking of the study agent
- As a result, recommendations from leading organizations differ:
  - American College of Rheumatology (ACR) 2012 statement recommends against the use of glucosamine and chondroitin
  - European League against Rheumatism (EULAR) recommendations include glucosamine and chondroitin as viable treatment option for knee OA
  - OARSI (Osteoarthritis Research Society International) recommends a trial for 6 months, followed by reassessment and discontinuation if ineffective at that time

**Surgery for osteoarthritis**
- Joint replacement for the knee and hip should be considered in patients with radiographic evidence of OA along with chronic pain and disability
that is refractory to treatment with non-pharmacologic and pharmacologic interventions

- Surgical intervention should be performed before the development of significant deformities, contractures, functional loss, or muscle atrophy for optimal result

Knee surgical options include arthroscopy, osteotomy, and total knee arthroplasty. The type of surgical procedure is dependent on the location and stage of OA, comorbidities, age and physical activity level, and the degree of patient symptoms.

- Arthroscopic lavage and debridement
  - Role in knee OA is controversial
  - Lack of evidence to show significant benefit

- Unloading osteotomy
  - Can be used in young and active patients with unicompartmental OA
  - Aim to unload damaged compartment and transfer weight by slightly overcorrecting into a valgus or varus axis
  - Must have appropriate patient selection for satisfactory outcome
  - Typically good results in the first few years, however, satisfaction decreases thereafter

- Arthroplasty
  - Unicompartmental knee arthroplasty
    - Indicated when OA involves only one compartment of the knee
    - Appropriate for younger patients with less severe disease
    - More rapid recovery
    - Provides preservation of bone stock, more normal knee kinematics, greater physiologic function
    - Poorer long-term survival of prosthetic than total knee arthroplasty
  - Total knee arthroplasty (TKA)
    - Indicated in advanced OA with more than one compartment involved
    - Durability of prosthetic components is approximately 15–20 years, therefore it is typically avoided in patients <60 years old
    - Main complications – femoropatellar problems, loosening of components, infections, residual stiffness
Hip surgical options are less varied than knee surgical options. Hip resurfacing is an option for young, more active patients who have an interest in a bone-conserving replacement procedure. Total hip arthroplasty (THA) has excellent long-term results in the treatment of late, symptomatic OA. Complications for THA are similar to those for TKA.

Secondary osteoarthritis

Secondary osteoarthritis is caused by previous injury or disease of the target joint, due to conditions that adversely alter the articular cartilage or subchondral bone. Conditions that predispose to the development of secondary OA include trauma, infections, prior surgery, mineral deposition, and autoimmune disorders. Several of these conditions will be discussed further in this section.

Etiologies

- Metabolic
  - **Crystal-associated arthritis** (gout, pseudogout)
    - Both monosodium urate (MSU) and calcium-containing crystals (calcium pyrophosphate dihydrate [CPPD], basic calcium phosphate crystals) may contribute to inflammation in OA tissues through direct interactions with components of the innate immune system and the amplification of other inflammatory signals
    - Calcium-containing crystals are frequently found in tissues from patients with end-stage OA
  - **Ochronosis** (hereditary alkaptonuria)
    - A rare hereditary autosomal recessive disease characterized by a defect in the gene coding for homogentisate 1,2-dioxygenase leading to accumulation of homogentisic acid
    - Black pigment produced by oxidation and polymerization of homogentisic acid deposits in connective tissues and binds irreversibly to them, causing ochronosis
    - Clinical manifestations
      - Arthropathy causing degeneration of major joints and intervertebral discs
      - Can also affect skin and sclera
      - Patients tend to be asymptomatic until approximately 30 years of age, when sequelae of ochronosis becomes apparent
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- Ochronotic arthritis may begin in the late 30s with low back pain and stiffness; knee symptoms resemble typical osteoarthritis
- Symptoms simulate degenerative joint disease – articular space narrowing, bone sclerosis, effusion
- Cartilage tends to be more easily damaged, promoting rapid progression to end-stage disease

- Radiographic findings
  - Spine
    - Plain film and computed tomography (CT) scans of the spine show multilevel narrowing of intervertebral spaces, calcification, and vacuum phenomenon of intervertebral discs
  - Peripheral joints
    - Primarily affects weight-bearing joints (frequently knees, but also can involve hips, shoulders)
    - Joint space narrowing and subchondral sclerosis with cyst formation are apparent with minimal osteophytes
- Treatment is primarily symptomatic for early-stage disease, with many patients progressing to total joint replacement as end-stage joint disease develops

- Hemochromatosis
  - A relatively prevalent genetic disease characterized by tissue iron overload
  - Most frequent mutation is the homozygous C282Y gene mutation
  - Patients can develop life-threatening organ damage – liver cirrhosis, carcinoma, diabetes, and heart failure
  - Other complications include arthropathy and osteoporosis; pseudogout is also commonly seen in patients with hemochromatosis

- Diagnosis
  - Clinical symptoms
    - Chronic weakness
    - Arthralgias/arthritis
    - Chondrocalcinosis
    - Bronze skin pigmentation
    - Unexplained liver disease or hepatomegaly
    - Type 1 diabetes
    - Early onset osteopenia/osteoporosis
    - Cardiac symptoms (rhythm disturbances, cardiac failure)
  - Laboratory abnormalities
    - Plasma transferrin saturation and ferritin are increased
    - Must rule out increased ferritin from non-hemochromatosis causes – alcohol, inflammation, cell necrosis, dysmetabolic iron overload syndrome
Joint manifestations
- Arthritis is common
  - If present, symptoms often precede diagnosis by up to 9 years
  - Two thirds of patients report joint symptoms as a major cause of impaired quality of life
  - One third of hemochromatosis cases are revealed through the workup of isolated articular pain
- Symptoms can begin before 30 years of age in men but usually after menopause in women
- Joint location
  - Classic joints involved – second and third metacarpophalangeals (MCPs)
    - Bony enlargement over second and third MCPs is common
  - Other common joint involvement – wrists, PIPs, hips, knees, ankles
  - Less frequent locations – shoulders, elbows, spine
- Can have either a monoarthritis or polyarthritis and pain crises
- Synovial fluid and laboratory studies may show either a degenerative or inflammatory profile

Radiological manifestations:
- Most often seen in second and third MCPs
- Hook-shaped osteophytes of the MCPs is very characteristic with associated joint space narrowing
- Wrist and distal radioulnar joints are frequently affected
- Can sometimes lead to erosive arthritis which can mimic RA
- Chondrocalcinosis may also be seen, indicating concomitant CPPD

Treatment:
- Iron removal by phlebotomy is often not helpful for joint symptoms
- No evidence based treatment to date
- NSAIDs and intra-articular glucocorticosteroids can be effective
- Treatment for pseudogout, if present, can also alleviate symptoms

Wilson’s disease
- A rare autosomal recessive disorder characterized by release of free copper and accumulation of intracellular hepatic copper with subsequent hepatic and central nervous system abnormalities
- Associated with mutations of ATP7B gene
• Peripheral joint manifestations – described in small open studies and case reports
  → Often spontaneous or mechanical type arthralgias
  → Patients report mono- or polyarthritis, generalized arthralgias, and low back pain
  → Involves mainly large joints – especially knees
  → Hip, wrist, hand, shoulder, and ankle are less frequently affected
• Diagnosis
  → Psychiatric, neurologic, and hepatic disturbances are suggestive of the diagnosis
  → Serum copper levels are elevated; ceruloplasmin levels are low
  → 24-hour urine collection shows elevated copper excretion
  → Genetic testing or liver biopsy is sometimes indicated
• Radiological manifestations
  → Early OA changes – especially at knee, hip, and wrist joints
  → Bone fragmentation and osteochondritis, especially at knee joint
  → Chondrocalcinosis is also described
• Treatment
  → Diet low in copper-containing foods – avoidance of mushrooms, nuts, dark chocolate, dried fruit, and shellfish
  → D-penicillamine for copper chelation is the first described treatment
  → Tetrathiomolybdate is employed as initial therapy to reduce free copper levels in the serum
  → Zinc is now the mainstay of maintenance due to improved side-effect profile; it works by preventing the intestinal absorption of copper from dietary sources

• Anatomic causes of secondary OA
  ○ Act by causing abnormal load distribution within the joint
  ○ Angular misalignment is the most potent risk factor for deterioration of the joint structure because it increases the degree of focal loading
  ○ Common anatomic abnormalities in secondary OA
    • Slipped femoral epiphysis
    • Epiphyseal dysplasias
    • Blount’s disease
    • Legg–Calvé–Perthes disease
    • Congenital dislocation of the hip
    • Unequal leg lengths
    • Hypermobility syndromes
• **Trauma and secondary OA**
  - **Major joint trauma**
    - Patients who have had an acute knee injury are seven times more likely to develop knee OA than are those who have not had a previous knee injury
    - Combined effect of the injury and its biomechanical consequences alter load distribution on the joint, hastening OA development
    - Anterior cruciate ligament (ACL) or meniscus tear is highly associated with knee osteoarthritis and its progression
    - Meniscus damage may play an important role in OA pathophysiology
      - Torn meniscus and extrusion seem to be strong risk factors for the development and progression of knee OA
      - Meniscectomy increases the risk of knee OA two-fold, more if combined with ACL damage or injury
      - Mixed patellofemoral and tibiofemoral OA is common in individuals who have undergone a meniscectomy

**Inflammatory/erosive hand osteoarthritis**

There is controversy about inflammatory/erosive hand osteoarthritis (IE-HOA) as a separate disease entity from osteoarthritis (OA). Some characterize it as a variant of OA, a subset of OA, or an inflammatory phase of OA, while others find it an entity that is entirely distinct from OA. As a result, there is no general consensus on the definition. Typically seen in postmenopausal women, this condition poses significant diagnostic and therapeutic challenges.

**Diagnosis**

- Combination of clinical and radiological features
- Some research studies use the **ACR criteria for hand OA** along with the presence of **characteristic erosions on radiography**
- **EULAR description of IE-HOA**
  - Characterized by an abrupt onset, marked pain and functional impairment, inflammatory symptoms and signs, including stiffness, soft tissue swelling, erythema, paresthesia, mildly elevated C-reactive protein and worse outcome than non-erosive hand OA osteoarthritis
  - Radiographically defined by subchondral erosions, cortical destruction and subsequent reparative change, which may include bony ankylosis
Clinical features
- Abrupt onset
- Targets interphalangeal (IP) joints
  - DIPs more commonly involved than PIPs
  - Second and third fingers more commonly involved than fourth and fifth fingers, often in symmetrical fashion
- Swelling, redness, warmth, stiffness, and limited function of IP joints
- Throbbing paresthesias in finger tips
- Typically polyarticular and may persist for several years
- Accelerated progression of symptoms compared to non-erosive hand osteoarthritis
- Frequently leads to joint deformities
  - Lateral subluxations
  - Heberden’s and Bouchard’s nodes
  - Instability and ankylosis of DIP and PIP joints

Radiological features
- Combination of bony proliferation and erosions seen in both DIPs and PIPs
- Joint space narrowing and erosions are seen early in the course of disease
- Later in the course – margins affected by bony proliferation lead to Heberden’s and Bouchard’s nodes
- Central erosions in subchondral bone at the articular surface are most common
  - “Seagull-wing” – classic appearance due to marginal sclerosis and osteophytes on the distal side of the joints while the proximal side is centrally eroded or collapsed and thinned
  - “Saw-tooth” – seen in PIPs

Differential diagnosis for IE-HOA
- Nodal generalized hand OA
  - Flares mainly at onset of involvement of each joint, followed by relatively quiet disease in each individual joint
  - A stuttering pattern of polyarthropathy of DIPs and PIPs
- Psoriatic arthritis
  - Joint erosions are located more marginally, where the synovial tissue is more concentrated
  - Frequent involvement of other sites in the body (i.e. sacroiliac (SI) joints)
  - Periostitis is common in psoriatic arthritis but rare in EOA
Rheumatoid arthritis
  - Typically involves MCPs and PIPs, sparing DIPs
  - Joint erosions are also typically more marginal

Treatment
  - To date, there is no definitive therapeutic approach to IE-HOA
  - Treatments recommended for non-erosive hand osteoarthritis are frequently ineffective
    - Acetaminophen frequently inadequate, NSAIDs with limited efficacy
  - Intra-articular steroid injections can provide symptomatic relief
  - Hydroxychloroquine
    - Small pilot studies suggest symptomatic improvement
  - Anakinra
    - Small case series with three patients suggests improvement

Diffuse idiopathic skeletal hyperostosis (DISH)

Introduction
  - A non-inflammatory disorder, also known as Forestier’s disease or ankylosing hyperostosis
  - Characterized by calcification and ossification of soft tissues, mainly ligaments and where tendons and ligaments attach to bones (entheses)
    - Hallmark of the disease – calcification of the anterolateral aspect of the thoracic spine
  - More common in people over 50 years old and men
  - Etiology unknown

Metabolic conditions associated with DISH:
  - Hyperinsulinemia with or without diabetes
  - Obesity, especially with large waist circumference
  - Hyperuricemia
  - Dyslipidemia
  - Hypertension
  - Coronary artery disease

Clinical findings
  - Asymptomatic condition in many individuals
  - Most common symptoms are stiffness and decreased range of spinal motion
  - Mild back pain (commonly in thoracic region)
• Painful enthesopathy
• Increased susceptibility to unstable spinal fractures after trivial trauma
• Cervical spine
  ○ Dysphagia
  ○ Odynophagia and otalgia
  ○ Hoarseness
  ○ Atlantoaxial complications
  ○ Stridor – rare, results from large anterior osteophytes at C2–C3
  ○ Myelopathy – due to spinal cord compression from the posterior longitudinal ligament
• Lumbar spine
  ○ Radiculopathy
  ○ Spinal stenosis

Radiologic findings (see also Chapter 11, Review of musculoskeletal radiology)
• Preference for axial skeleton
  ○ Classically involves the thoracic spine (especially the middle and lower part), but can be seen in cervical and lumbosacral spine
  ○ “Flowing” ossification along the anterolateral margins of vertebral bodies over four contiguous levels
    • Radiolucent line usually separates the ossified anterior longitudinal ligament from the anterior aspect of the adjacent vertebral bodies
    • Findings more prominent on right side of thoracic spine
      → Pulsation of the aorta may influence location of ossification
  ○ Cervical spine
    • Hyperostosis initially occurs along the anterior surface of the vertebral body
    • More common in the lower cervical spine
    • Ossification of the posterior longitudinal ligament less common, but occurs almost exclusively in the cervical spine
• Extraspinal involvement is less common, but can occur
  ○ Radiographic changes are often symmetric
  ○ Pelvis radiographs
    • Hypertrophic whiskering (bone proliferation) can involve the iliac crest, ischial tuberosity, trochanter
    • Ligament ossification
    • Periarticular osteophytes
  ○ Peripheral joints
    • New bone formation is prominent in the enthesial areas, particularly around the heels, knees, and elbows
• Hand – phalangeal tufting, increased cortical thickness of tubular bones of the hand, increase in the size of sesamoid bones

**Diagnosis**

- Resnick and Niwayama diagnostic criteria
  - Presence of flowing calcification and ossification along the anterolateral aspects of at least four contiguous vertebral bodies
  - Preservation of the intervertebral disc spaces
  - Absence of apophyseal joint space narrowing or sacroiliac inflammatory changes

**Differential diagnosis**

- Ankylosing spondylitis (AS)
  - Shared features between DISH and AS
    - Involvement of the axial skeleton and peripheral entheses
    - Bone proliferations in the latter phases of their courses
    - Both can have severe limitation of spinal mobility and postural abnormalities
  - Sacroiliac joint involvement in DISH is typically the upper, ligamentous portion
    - In AS the lower, synovial portion of the sacroiliac joint is involved
  - Peripheral enthesopathy in DISH is not as painful as in AS
  - AS begins at a younger age; it is rare for DISH to occur in patients <40 years old
  - AS is associated with inflammatory back pain symptoms
  - No SI joint erosions or bony ankylosis are noted in DISH
  - DISH has not been associated with HLA-B27

- Osteoarthritis
  - Both seen in similar age groups – both conditions may coexist
  - Distinctive features that differentiate DISH
    - Involvement of joints usually unaffected by primary OA (elbows, wrists, ankles, shoulders)
    - Increased hypertrophic changes compared with primary OA
    - Prominent enthesopathies at sites adjacent to peripheral joints
    - Calcification and ossification of entheses in sites other than joints

**Treatment**

- Aimed at symptomatic relief of pain and stiffness
- Similar to OA
  - Acetaminophen
  - NSAIDs
○ Local applications
○ Physiotherapy
○ Weight loss
• Control of associated constitutional and metabolic disorders
• Surgery is rarely needed but can be helpful in the following settings:
  ○ When dysphagia results from large anterior cervical osteophytes
  ○ When progressive myelopathy results from the ossification of posterior longitudinal ligament
  ○ In the setting of nerve root compression and thoracic outlet syndrome

**Gout**

Gout is a relatively common crystalline arthropathy that causes episodic flares of arthritis that over time may become debilitating. Deposition of excess serum uric acid crystals into an affected joint induces a subsequent local inflammatory reaction that results in characteristic pain, warmth, and swelling. This section will focus on hereditary causes of gout, as well as newer therapies in the treatment of gout.

### Causes of early-onset gout

• HGPRT (hypoxanthine-guanine phosphoribosyltransferase) deficiency
  ○ HGPRT is a transferase enzyme that is part of the purine salvage pathway; deficiency leads to uric acid excess
  ○ Total HGPRT deficiency => Lesch–Nyhan syndrome (X-linked recessive syndrome, mental retardation, self-mutilation, gout, nephrolithiasis)
  ○ Partial deficiency => Kelley–Seegmiller syndrome (gout and nephrolithiasis only)

• PRPP synthetase hyperactivity
  ○ PRPP synthetase is an enzyme necessary for de novo synthesis of purine and pyrimidine nucleotides; superactivity induces excess purine formation; subsequent catabolism of excess purines induces hyperuricemia
  ○ Glucose-6-phosphatase (G6P) deficiency (Von Gierke’s disease) is a type 1 glycogen storage disease which also induces hyperuricemia via hyperactivity of PRPP synthetase

• Polycystic kidney disease
• Familial juvenile hyperuricemic nephropathy: renal tubular disorder leads to end-stage renal disease (ESRD) by age 40 years

**Drugs causing hyperuricemia**

- Thiazides
- Cyclosporine
- Ethanol
- Azathioprine: *be aware that azathioprine is metabolized by xanthine oxidase; when used in combination with allopurinol, severe leukopenia can result*
  - Tacrolimus
  - Nicotinic acid
  - Ethambutol
  - Pyrazinamide
  - Warfarin
  - Levodopa
  - Theophylline
  - Didanosine
  - Loop diuretics

**Gout treatments**

See Table 1.3.

- **Febuxostat** (Uloric) for the treatment of gout
  - As a xanthine oxidase inhibitor similar to allopurinol, febuxostat blocks the conversion of xanthine to uric acid in purine metabolism
  - Does not need dose adjustment in mild to moderate renal failure (CrCl >30 mL/min)
  - Three phase 3 randomized-controlled trials comparing febuxostat to allopurinol showed better efficacy at lowering the serum uric acid level below 6 mg/dL. Patients receiving febuxostat had an increased number of gout flares in the first 8 weeks of the medication compared to allopurinol; this equalized between groups after 8 weeks and became less frequent
  - Adverse events related to febuxostat in the trials included increased liver function tests (LFTs), diarrhea and dizziness
  - Open-label extensions of the studies found a small but increased risk of cardiovascular events in patients receiving febuxostat (2.7%) vs allopurinol (1.1%), with patients with a history of coronary atherosclerotic heart disease (CASHD) or congestive heart failure (CHF) at highest risk; therefore **febuxostat should be used in cardiac patients with caution**
**Table 1.3 Role of gout treatments for various phases of gout.**

<table>
<thead>
<tr>
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<th>Treatment of acute gouty arthritis</th>
<th>Anti-inflammatory prophylaxis during intercritical periods</th>
<th>Uric acid-lowering therapy for prevention of future attacks</th>
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<tr>
<td>NSAIDS</td>
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<tr>
<td>Corticosteroids</td>
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<td>In rare cases of gout with severe renal failure</td>
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<td>Colchicine</td>
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<td>Rilonacept</td>
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</table>

- **Pegloticase** (Krystexxa) for the treatment of gout
  - Pegloticase is a recombinant form of uricase that induces conversion of uric acid to allantoin, a metabolite that is more easily excreted by the kidney
  - Dosing is 8mg IV q2weeks, with no optimal duration of therapy defined
  - Limitations
    - May precipitate gout flares due to rapid lowering of uric acid
    - Infusion reactions were common, and 5% of patients had anaphylactic reactions to the drug (vs 0 in placebo groups)
    - Must use with caution in patients with CHF, as it may precipitate CHF exacerbation
    - Study patients receiving pegloticase developed antibodies to the drug, and antibody titers were associated with decreased half-life and efficacy of drug and increased risk of infusion reactions and anaphylaxis
    - Contraindicated in patients with G6PD deficiency as pegloticase may precipitate hemolytic anemia
Clinical utility
- Utility is limited as duration of therapy has not been defined, and immunogenicity limits long-term use
- At this point, the consensus is to reserve pegloticase for patients with tophaceous gout, damaging arthropathy, and persistent gout attacks who cannot tolerate conventional treatment with allopurinol or febuxostat, or patients who do not respond to these treatments
- Anecdotal evidence shows success with using pegloticase as adjunctive therapy for 1–3 months, followed by conventional treatment with allopurinol or febuxostat, but this has not been studied
- The ACR recommends checking a serum uric acid level prior to each pegloticase infusion; if the uric acid level during treatment rises to above 6 mg/dL, consider discontinuing pegloticase as this may predict risk of infusion reactions and anaphylaxis
- Antibodies to pegloticase may be checked as well to follow immunogenicity, but this testing is expensive and not widely available

• Rasburicase for the treatment of gout
  - Although it is useful in preventing renal failure in hyperuricemia due to tumor lysis syndrome, its use in treatment in non-oncologic indications is limited
  - Rasburicase has a short half-life (less than 24 hours) and may induce severe hypersensitivity reactions in as many as 5% of patients
  - Immunogenicity is also a concern that limits long-term efficacy
  - One study from 2002 randomized gout patients that could not receive allopurinol treatment to rasburicase once monthly for 6 months or once daily for 5 days
    - Methylprednisolone was infused as a pretreatment for every infusion of rasburicase
    - Patients receiving monthly rasburicase had lower serum uric acid levels and 2/5 patients had reduction in tophi size
    - Patients receiving daily rasburicase did not have improvements in either serum uric acid concentrations or tophi
    - Patients still had increased gout attacks during the study period; adverse events including hypersensitivity reactions were common
  - Given hypersensitivity, immunogenicity, and short half-life, rasburicase remains a drug with primarily oncologic indications

• Anakinra for the treatment of gout
  - Anakinra is an IL-1 inhibitor approved for the treatment of rheumatoid arthritis
  - It is a recombinant human IL-1 receptor antagonist that inhibits both membrane-bound and circulating IL-1 isoforms
The basis for IL-1 inhibition in the treatment of acute gout stems from animal data showing uric acid as a key trigger of inflammasome activity and production of IL-1B, making acute gout a disease potentially mediated by IL-1B

- Anakinra and gout open-label pilot study:
  - Patients with acute gout who failed conventional treatment received daily anakinra for 3 days
  - Nine of ten patients had complete resolution of acute gout by day 3
- The bottom line: further studies need to be done to confirm the results of the initial study; additionally, although rapid response to anakinra may warrant its use in some cases, at this point its cost limits regular use in all patients

- Rilonacept for the treatment of gout
  - Building on data for inflammasome and IL-1B activity in gout, rilonacept as an alternate IL-1 inhibitor to anakinra is gaining attention
  - Rilonacept was originally produced and recently approved for treatment of CAPS (cryopyrin-associated periodic syndromes); it is a recombinant protein that binds IL-1A and IL-1B preventing their binding and activation to the IL-1 receptor complex
  - A pilot study of 10 patients with chronic gout receiving weekly rilonacept for 6 weeks showed improvement in pain scores and inflammatory markers at 2, 4, and 6 weeks of follow up
  - Further study is warranted to determine if IL-1 inhibition will be a valid and effective additional gout treatment strategy

**Further reading**


