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INFLAMMATORY ARTHRITIS

Axial SPONDYLOARTHRITIS (AxSpa)

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that typically affects small and medium-sized joints of the hands and feet, sometimeswith extra articular manifestations.

The primary lesion is synovitis whereby immune cells invade the normally relatively acellular synovium, leading to the formation of inflammatory ‘pannus’.

This hyperplastic, invasive tissue causes cartilage breakdown, bony erosion and, ultimately, loss of function of the affected joint(s).

Systemic involvement—for example, of the respiratory, cardiovascular and haematopoietic systems, may also occur.

The risk of atherosclerosis and lymphoma development is increased.

uncontrolled RA is associated with a reduction in life expectancy, 6–7 years.

epidemiology

RA affects approximately 0.5–1% of European and North American adults, with considerable regional variation.

In some Native American up to 5% of individuals are affected.

Women are about three times more frequently affected than men.

The peak age of incidence for women is between 50 and 60 years and for men is >70 years.

Risk factors

Cigarette smoking, a modifiable risk factor, remains the strongest known environmental risk factor for RA.
Smoking increases the proportion of citrulline-positive cells in the lungs (demonstrated to occur by analysis of bronchoalveolar lavage fluid in smokers and absent in nonsmokers).

Smoking is most strongly associated with ACPA-positive and RF-positive RA.

The risk of RA increases with the intensity (packs per day) and duration of cigarette use.

Risk can remain elevated for up to 20 years after smoking cessation
However, it does decrease with time since quitting.

Risk factors

The human leukocyte antigen (HLA)-DRB1 shared epitope-containing allele IS the strongest known genetic risk factor for RA.

Individuals with the shared epitope may be genetically predisposed to develop ACPAs, which places them at higher risk of developing RA.

(HLA) DRB1 ALLELES THAT CODE A shared epitope (a 5 amino acide sequence motif in residues of 70-74 of the (HLA)DRB1chain), are ssociated with sever rheumatoid arthritis.

Ditary fators

High protein and red meat intake was found to increase the risk of inflammatory arthropathy, but a subsequent study showed no association with protein, iron, or red meat consumption and the risk of developing RA.

Vitamin D is an important modulator of the inflammatory response,Lower intake of vitamin D was associated with an increased risk of RA in one study, but no association was observed in another prospective study.

Medications such as statins have modest anti inflammatory effects in both RA cases and patients without rheumatic disease.

Infectious agents
human parvovirus B19 were also found to be increased in females with RA in one case-control study.
Epstein-Barr virus (EBV) .
no conclusive evidence of association with a number of other putative infectious triggers, including Proteus, cytomegalovirus, retroviruses……

Alcohol consumption may also lower the risk of developing RA, particularly ACPA positive RA.

Socioeconomic status and occupation
an inverse association between socioeconomic status measured by education and occupational class and risk of RA development.

Among the occupational exposures related to increased risk of RA are exposure to silica dust and mineral oil.

Clinical features

-The hallmark of RA is symmetric synovial proliferation and tenderness in multiple joints, particularly the small joints of the hands and feet.

-Most patients experience joint stiffness or gelling for more than an hour in the morning.

-Morning stiffness and swelling in the wrists and proximal interphalangeal and metacarpophalangeal joints are the typical features of rheumatoid arthritis (RA).
-Commonly, patients will have polyarthritis of the small joints of the hands, but monoarticular involvement can occur initially.

- The joint symptoms may occur almost overnight, or they may evolve slowly over a period of several months.

RF and ACPAs have been found in up to half of patients with RA as long as 5 years before the development of clinical disease, thus suggesting the insidious development of disease over time.

- Pain in the joints is universal in patients with RA and the pattern of joint involvement in RA is quite typical in most cases.

- Affected joints include the proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow,shoulder, hip, knee, ankle, and metatarsophalangeal (MTP) joint.

- Stiffness or gelling in the joints is present upon awaking and often takes several hours to abate.

Soft tissue swelling over the knuckles and markedly reduced grip strength.

Discomfort in the feet is generally most prominent in the metatarsal area, patients may complain of the sensation of having a “stone in my shoe.”

- Profound fatigue often accompanies the joint complaints, and anorexia and mild weight loss may occur.

- Typically the patients with RA do not have rash, fever, headache, visual disturbance,or pleuropericardial symptoms at initial evaluation.

The quality of the pain may vary depending on the type of joint involvement for example, the pain associated with chronic inflammatory synovial proliferation may be experienced as a dull ache with little fluctuation in intensity,by contrast, the mechanical pain associated with bone and cartilage damage in the knee or hip, in the absence of inflammation, may be more sharp and acute and be associated with activity and relieved with rest.

Rheumatoid nodules are quite specific for RA and occur in about 20% of patients.

A nodule is a mass of inflammatory tissue with a central focus of necrosis, presumably the consequence of vascular inflammation, surrounded by chronic inflammatory cells.

MCP and PIP joints are almost always involved and typically the index and long fingers are more involved than the others.

The “valleys” between the MCP joints are filled in by synovitis.

The distal interphalangeal (DIP) joints are rarely involved in RA, perhaps because they have less synovium than the MCP and PIP joints.

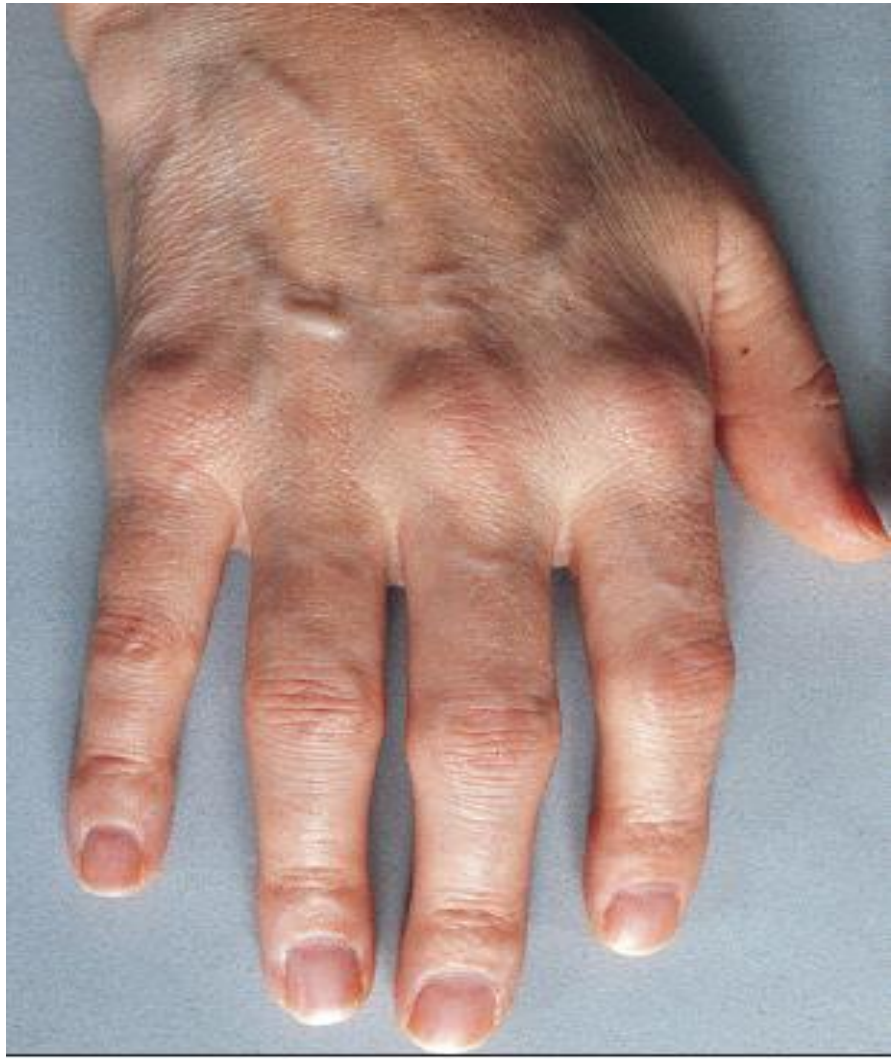
Flexor tenosynovitis is common and may lead to trigger finger (stenosing tenosynovitis)

(painful clicking sound elecited by flexion or extension of the involved digit)

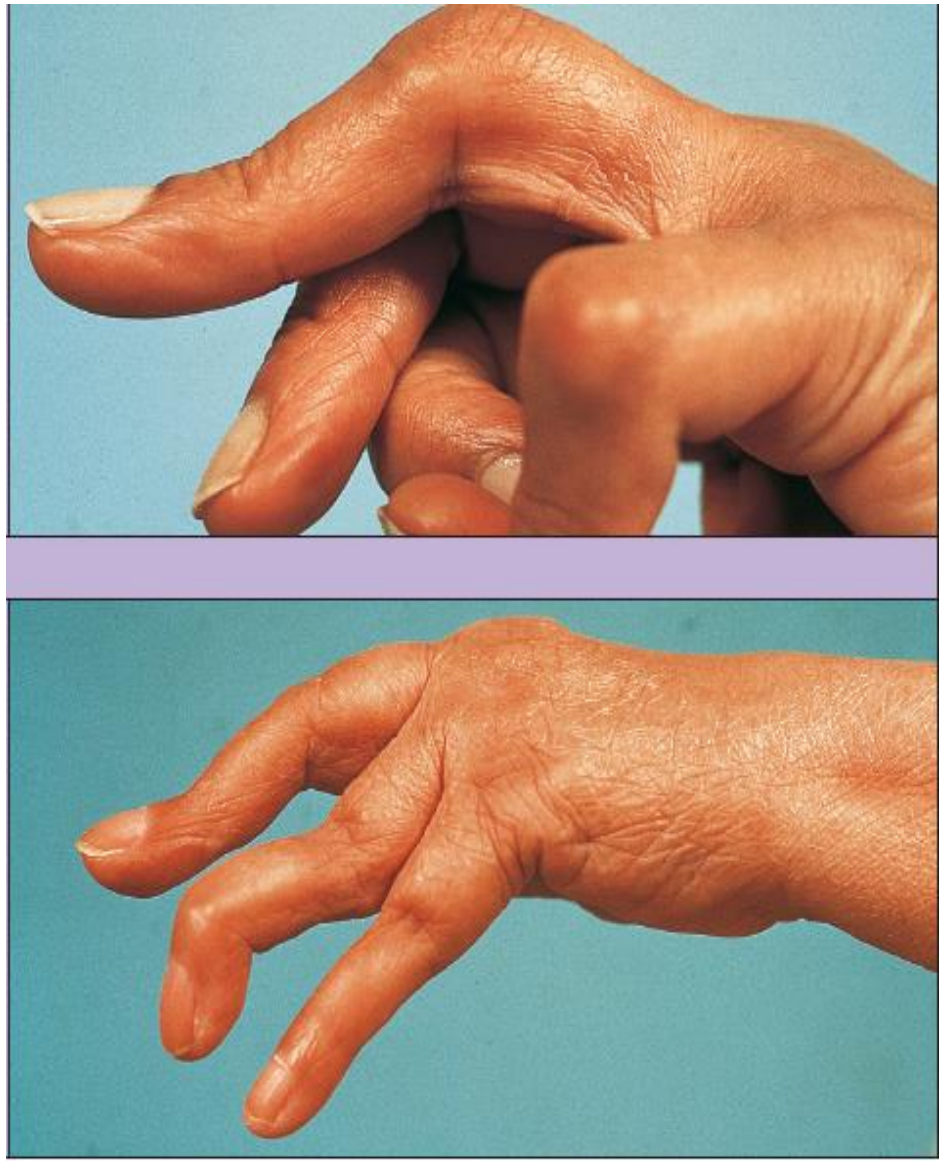
Signs of late disease with irreversible damage include:

- Subluxation of the MCP joints with “ulnar drift often accompanied by atrophy of the intrinsic muscles of the hand.
- The boutonnière deformity entails flexion of the PIP joint and extension of the DIP joint .
- Swan neck is basically the opposite of the boutonnière deformity, with hyperextension of the PIP joint and flexion of the DIP joint .
- At the wrist, synovial proliferation occurs around the ulnar styloid and as the disease progresses, laxity of the radioulnar ligament gives rise to the “piano key” sign as the ulnar styloid moves up and down in response to dorsal pressure from the examiner’s thumb.

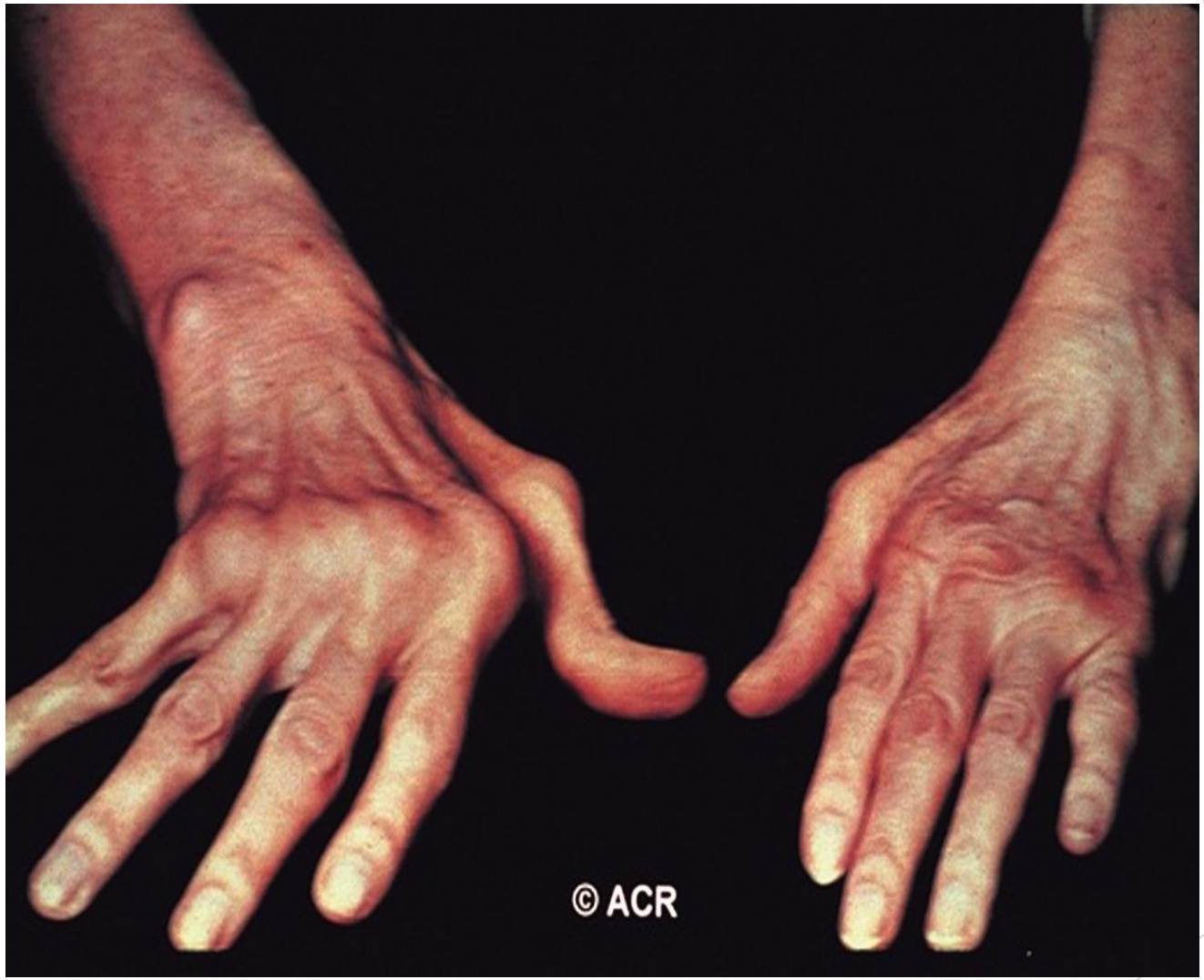
The thumb can be affected by several deformities, the most common has been described as the flail interphalangeal (IP) joint in which case the patient loses the ability to flex that joint,this results in significant functional impairment because of loss of pinch strength,with the patient pinching the index finger against the proximal phalanx.



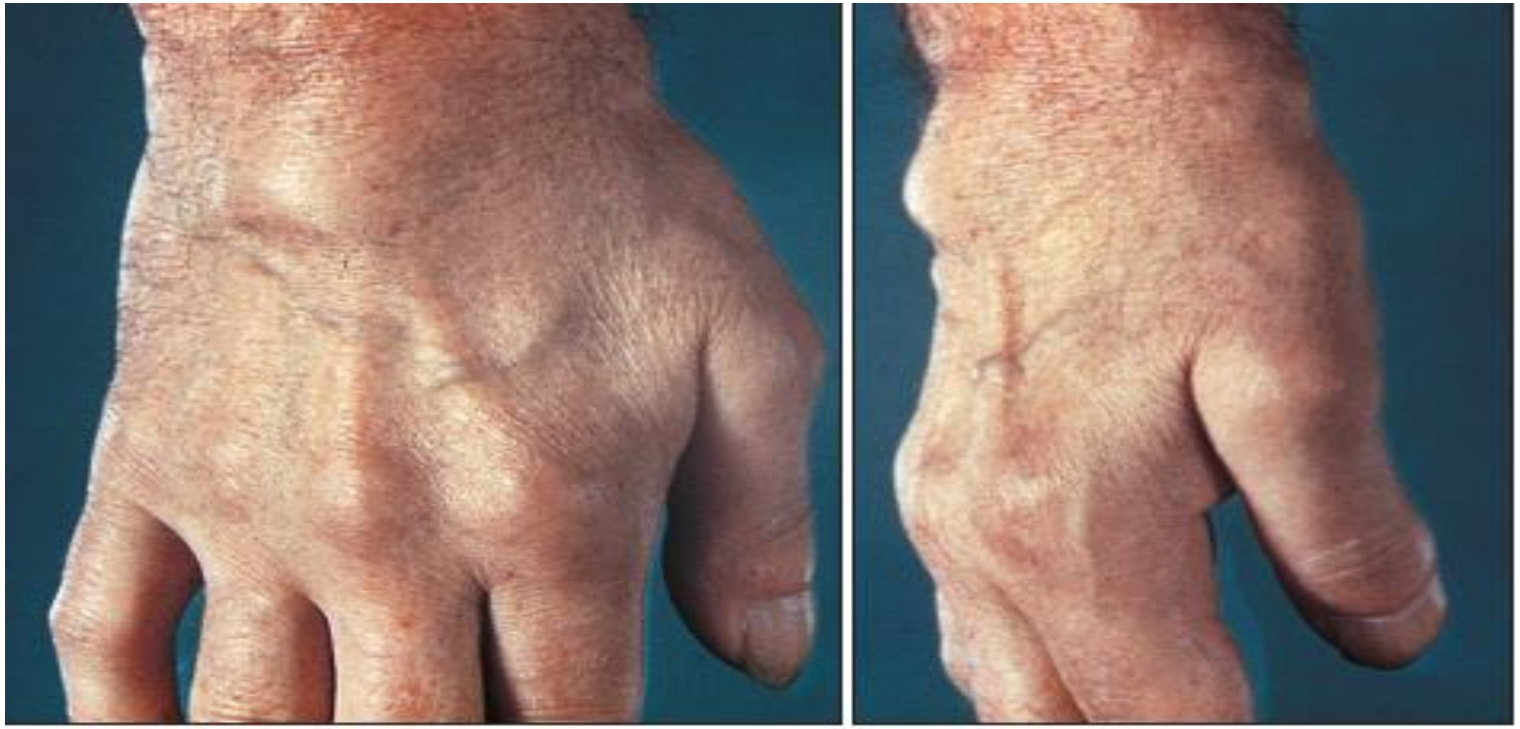
swelling of the metacarpophalangeal and proximal interphalangeal (PIP) joints.



The boutonnière deformity—flexion of the proximal interphalangeal (PIP) joint and hyperextension of the distal interphalangeal (DIP) joint.
The swan neck deformity—flexion of the metacarpophalangeal(MCP) joint, hyperextension of the PIP joint, and flexion of the DIP joint.

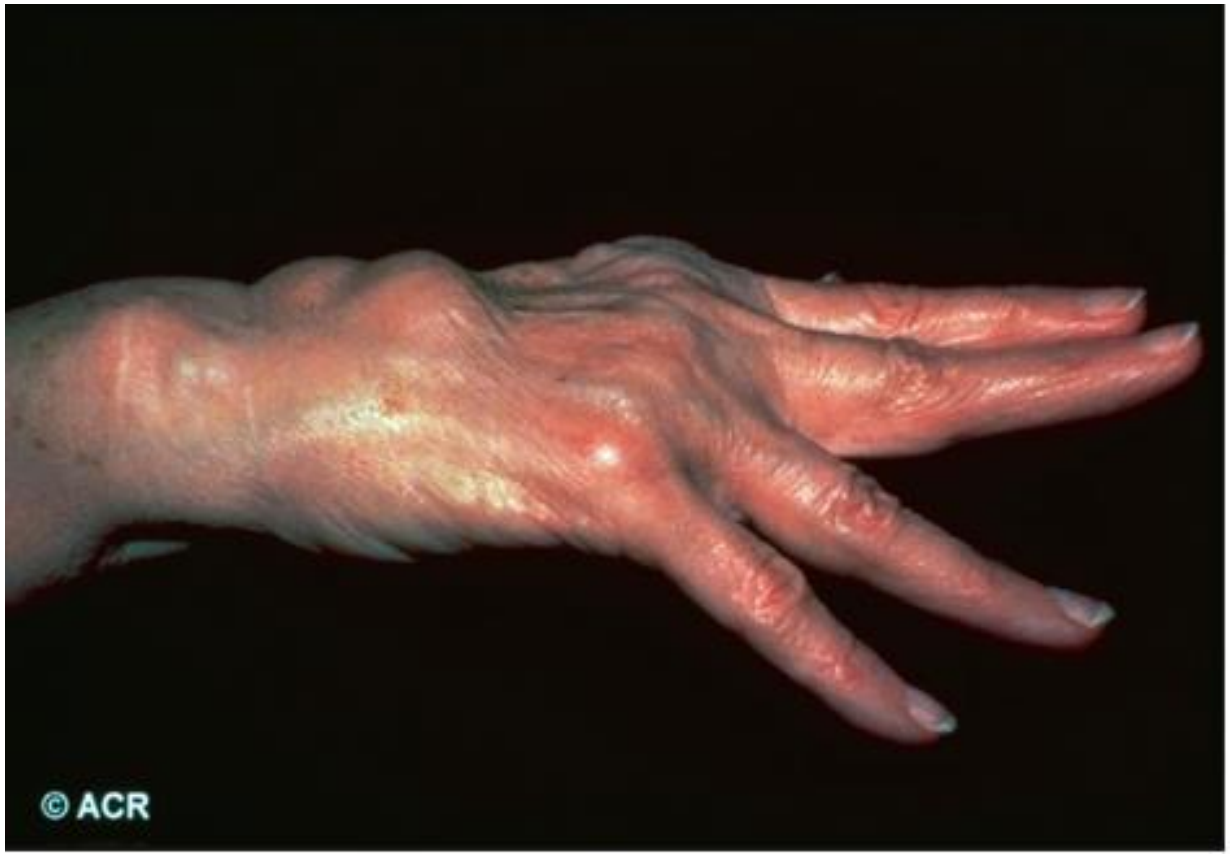


Hyperextension of the interphalangeal joint of the right hand illustrates a “flail thumb.” also subluxation of the right fifth metacarpophalangeal joint, the prominent ulnar styloid, and ulnar drift.



Tenosynovial swelling as a result of tenosynovitis—the “tuck” sign.

- Inflammation and swelling of the extensor tendons and their sheaths may cause the tuck sign as painless swelling bunches up on the dorsum of the wrist with active finger extension. Bulging becomes accentuated with full extension of all the fingers of the hand.
- Persistent tenosynovitis over the dorsum of the wrist may lead to extensor tendon erosion and rupture, particularly of the tendons of the fourth and fifth fingers.



Subluxation of the wrist in severe disease associated with extensor tenosynovitis and extensor tendon rupture.

Patterns of onset

- Gradual onset: the most common early finding is a gradual or insidious onset in which small peripheral joints such as the wrist, MCP, PIP, ankle, or MTP joints are affected.(It is defined as one that the patient can date only to the nearest month).

It is usually symmetric, with considerable morning stiffness, difficulty making a fist, and poor grip strength.
The morning stiffness may last minutes to hours.

- Slow, monoarticular onset:

Less common is a slow monoarticular process affecting larger joints such as shoulders or knees.
The symptoms may remain confined to one or two joints but frequently spread over the ensuing days and weeks additively to affect the wrists, fingers, ankles, or feet in widespread fashion.

- **Abrupt, acute polyarthritis:**

Less frequently, RA is manifested as an abrupt acute polyarthritis of the shoulders, elbows, wrists, fingers, hips, knees, ankles, and feet, with intense joint pain, diffuse swelling, and limitation leading to incapacitation.

Sudden onset is defined as one for which the patient can give a specific date.

Spine involvement

- Is limited mostly to the cervical spine, particularly the upper portion

- More than half of all patients with RA experiencing involvement in the course of their disease.
  - The most common abnormality is atlantoaxial subluxation(anterior,posterior,and vertical,
  - lateral and rotational), followed by basilar invagination.

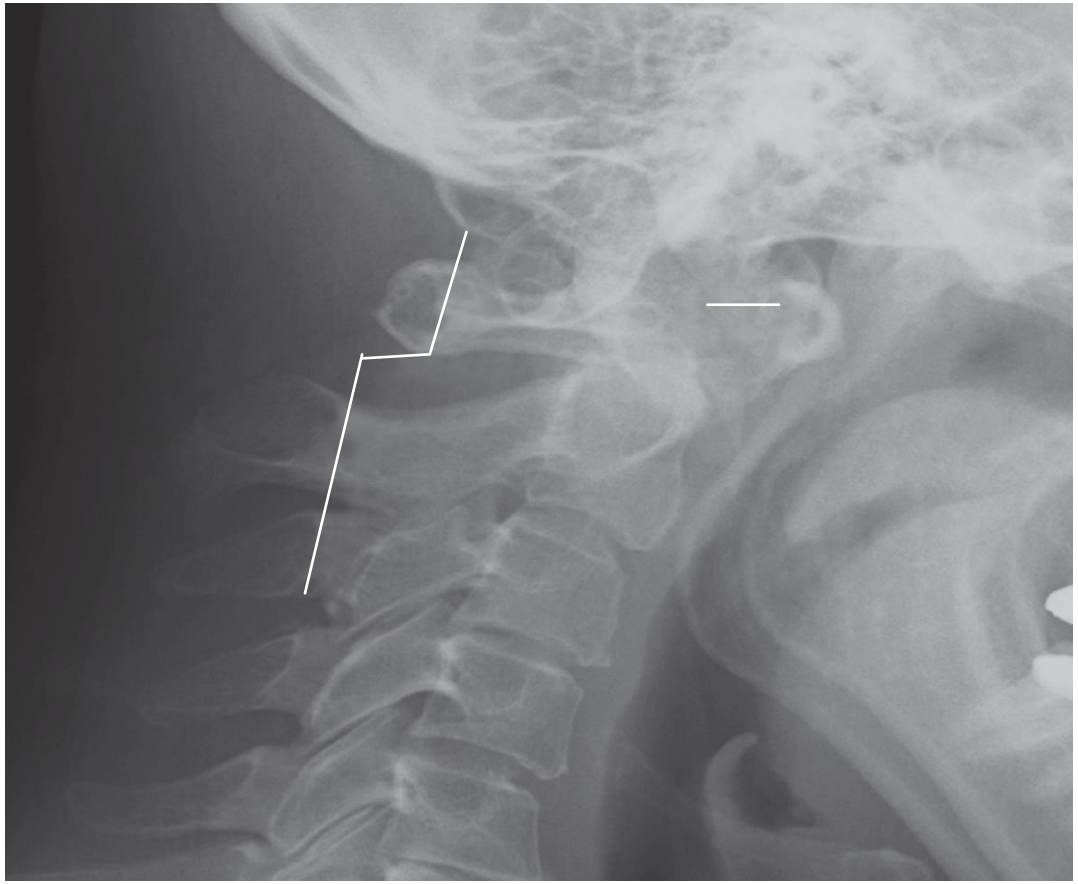
- Atlantoaxial subluxation is defined when the space between odontoid process from C2 and arch of the atlas (C1) exceeds more than 3 mm in adult and more than 5 mm in children.

- Subluxation greater than 8 mm usually requires surgical intervention.

- The most critical involvement occurs at the atlantoaxial joint, where the ring of C1 pivots on the odontoid peg of C2 the transverse ligament of the axis courses around the posterior portion of the odontoid, which prevents subluxation of C1 on C2.

- Tenosynovitis here can decrease the space available for the upper cervical cord as it passes through the bony spinal canal posterior to the odontoid.

- This can also lead to laxity of the transverse ligament or erosion of the odontoid, in which case the ring of C1 can move forward on neck flexion (atlantoaxial subluxation)and reduce the diameter of the spinal canal and compress the upper cervical cord .



Atlantoaxial subluxation,The anterior arch of C1 is displaced 8 mm anterior to the dens.
This is confirmed by the abnormal posterior cervical line,a radiographic line drawn between the spinal lamina of C1, C2, and C3 and should be straight.
Anterior subluxation of the C1 lamina reflects the same degree of anterior subluxation of the atlantoaxial articulation.

- The subluxation exacerbated by cervical flexion and reduced by cervical extension.

- Cranial settling describes caudal migration of the cranium on the spinal column, which results in movement of the odontoid into the foramen magnum, where it compresses vital structures .

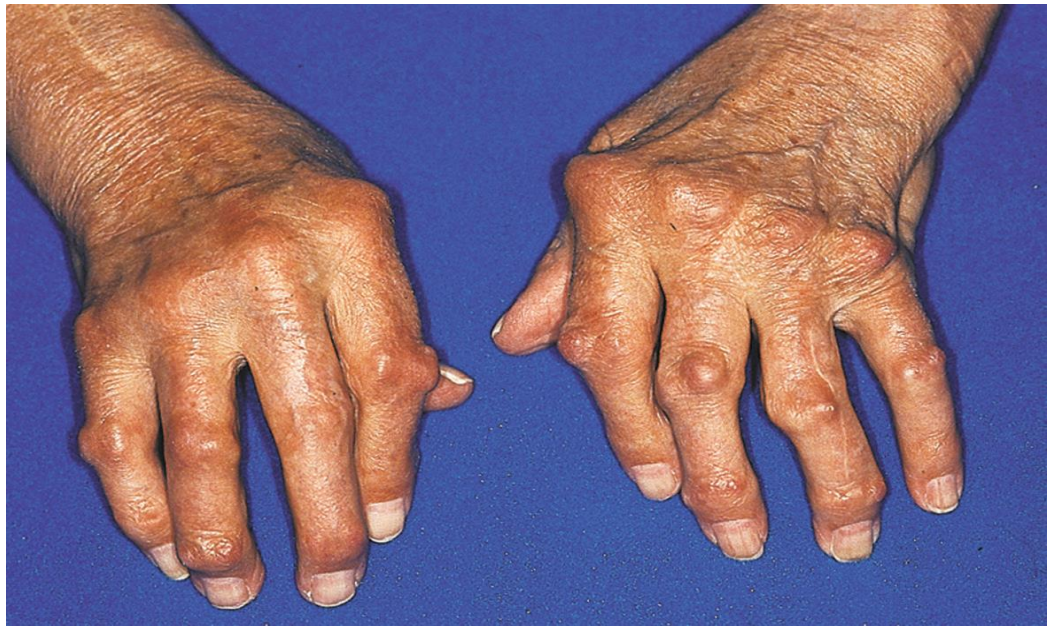
- Sub axial subluxation represents unstable movement of one vertebral body on another below C1-C2.

Extraarticular features and systemic

SKIN DISEASE

- Subcutaneous nodules mainly in patients who are RF positive and rarely in seronegative patients.
- Patients with rheumatoid nodules are at an increased risk for the development of severe extraarticular manifestations
- Nodules develop most commonly on pressure areas.
- Subcutaneous nodules may regress during treatment with disease modifying drugs.

- methotrexate may increase nodules, particularly over finger tendons .



Rheumatoid nodules in a patient with long-standing rheumatoid arthritis treated with low-dose methotrexate weekly.

- Other skin lesions include neutrophilic dermatoses such as Sweet syndrome pyoderma gangrenosum.
  Skin ulcers may be the result of vasculitis or Felty syndrome,venous or arterial insufficiency.

HEMATOLOGIC ABNORMALITIES

- Anemia : commonly normochromic and normocytic.
- Thrombocytosis: frequent finding in active RA.
- Thrombocytopenia: rare in RA, except when related to drug treatment or Felty syndrome.

Lymphadenopathy : frequent in active RA(Histologic examination usually reveals benign follicular hyperplasia).

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FELTY SYNDROME

defined as RA in combination with splenomegaly and leukopenia.

The syndrome characteristically occurs in patients with longstanding, seropositive,nodular, deforming RA.

Many of these patients have indolent lower extremity ulcerations, hyperpigmentation,and antinuclear antibodies.

Thrombocytopenia also occurs in Felty syndrome.

Risk for the development of lymphoproliferative and other malignancies is increased in patients with RA, particularly in those with Felty syndrome.

Bacterial infections are common in felty syndrome and correlate with a polymorphonuclear leukocyte count lower than 100/mm3, and they account for substantial mortality in this condition.

Treatment strategies for felty syndrome may include methotrexate, parenteral gold , glucocorticoids, granulocyte colony-stimulating factor, and splenectomy.

HEPATIC ABNORMALITIES

hepatomegaly, may be present in up to 65%of patients with Felty syndrome.

PULMONARY INVOLVEMENT

involvement of the pleura is reported in up to 50% of individuals with RA but detected clinically in only about 7% to 10% of such cases.

Rheumatoid pleural effusions are usually exudate .
Parenchymal pulmonary nodules found in seropositive RA patients with widespread synovitis.

tend to be peripheral in location and can measure less than 1 cm or up to 6 to 8 cm in diameter. They can cavitate and cause pleural effusions and bronchopleural fistulas.

Pathologic examination of the nodules reveals a central necrotic zone surrounded by a cellular area of proliferating fibroblast.

Differential diagnosis of pulmonary rheumatoid nodules includes:
Neoplasms
tuberculosis
and fungal infections.

In the case of a solitary rheumatoid nodule in the lung, excisional biopsy may be necessary to confirm the diagnosis.

Treatment of the underlying rheumatoid disease frequently results in improvement in the pulmonary nodules.

Pulmonary nodulosis and pneumoconiosis in patients with RA (Caplan syndrome) is characterized by several nodules greater than 1 cm in diameter scattered throughout the peripheral lung field.

Caplan syndrome is seen in individuals with extensive exposure to coal dust, exposure to silica and asbestos may also lead to pulmonary nodulosis in these patients.

interstitial lung disease (ILD):
non specific interstitial pneumonitis or usual interstitial pneumonitis.

CARDIAC DISEASE

pericarditis is the most common cardiac manifestation of RA .

myocarditis ,Valvular lesions, aortic root abnormalities, and coronary arteritis can also occur
RA itself is an independent risk factor for coronary artery disease.

OCULAR INVOLVEMENT

The most common ocular involvement in RA is keratoconjunctivitis sicca(10% of patients).
Episcleritis usually correlates with the activity of RA .
Scleritis is less common than episcleritis.
unusual ocular findings in RA include uveitis, episcleral nodulosis,
ulcerative keratitis (corneal melt).

NEUROLOGIC IMPAIRMENT

Peripheral entrapment neuropathy, when the nerve is compressed by the inflamed synovium against a fixed structure.
Atlantoaxial subluxation may cause neurologic impairment in patients with RA.

Peripheral neuropathy manifested as diffuse sensorimotor neuropathy,or mononeuritis multiplex occurs in a small subset of patients with RA.
Involvement of the central nervous system in RA is rare.

MUSCULAR INVOLVEMENT

Muscle weakness in RA is usually due to muscle atrophy secondary to joint inflammation.
RA may coexist with idiopathic inflammatory myopathy without other signs of systemic disease.

RENAL ABNORMALITIES

RA is risk for all causes of chronic kidney disease.
Low-grade membranous nephropathy, glomerulitis, vasculitis, and nephrotic syndrome as a result of secondary reactive amyloidosis have all been described.

AMYLOIDOSIS

Amyloidosis may rarely complicate long-standing RA

RHEUMATOID VASCULITIS

Systemic vasculitis is uncommon in RA but often occurs in rheumatoid patients with long-standing disease of more than 10 years' duration.

Small-vessel vasculitis commonly involves the skin and causes nail fold infarcts , digital gangrene , and leg ulcers.

Autoantibodies in rheumatoid arthritis

IgM-RF can be detected in 60% to 80% of RA patients with established disease, whereas its prevalence in patients with early RA ranges between 50% and 60%.

RFs of all subtypes may already be present in the earliest stages of the disease and can precede the onset of RA by several years.

IgM-RF shows only moderate specificity for RA, but specificity is considerably increased at higher titer.

high-titer IgM-RF, as well as IgA-RF, also has considerable prognostic value because it is associated with the severity of RA, such as erosiveness ,more rapid disease progression, poor outcome, and extraarticular manifestations.

ANTI–CITRULLINATED PROTEIN/ PEPTIDE ANTIBODIES(ACPAs)

ACPAs are generally present early in the disease course and can even be detected years before joint symptoms develop.

high disease specificity (>95%).
Sensetivity 55%-80%

Radiographic progression as well as extraarticular Manifestations such as ischemic heart disease and lung pathology, is more common in ACPA-positive patients.

RF, and ACPA antibodies are independent predictors of erosive Disease .

RF and ACPA tests are positive in about 80% of patients with RA.

However, RF may be negative early in RA, and positive RF may be seen with many other conditions, hepatitis C infection

DIAGNOSIS

RA is a clinical diagnosis for which no single physical finding or laboratory test result is pathognomonic.
As a practical matter, a patient older than 18 years who has symmetric joint pain, swelling in the hands and feet, and morning stiffness is likely to have RA, especially if RF or ACPA is positive.

The 2010 RA classification criteria are very helpful in this regard.

Radiographs of the hands and feet are sometimes diagnostic at initial evaluation, and musculoskeletal ultrasound and magnetic resonance imaging can detect early evidence of synovitis and erosions not seen on radiographs.

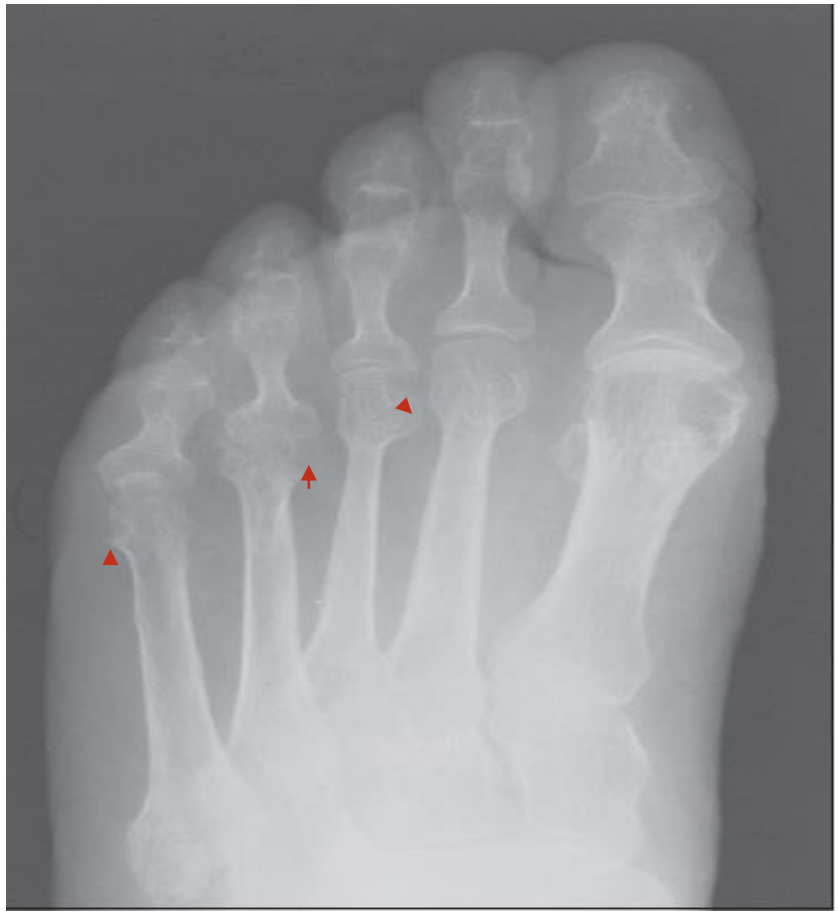
2010 ACR/EULAR classification criteria for RA

Joint involvement	score
1- large joint†	0
2-10 large joints	1
1-3 small joints‡	2
4-10 small joints	3
>10 joints (at least 1 small joint)	5
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute-phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	
<6 wk	0
≥6 wk	1

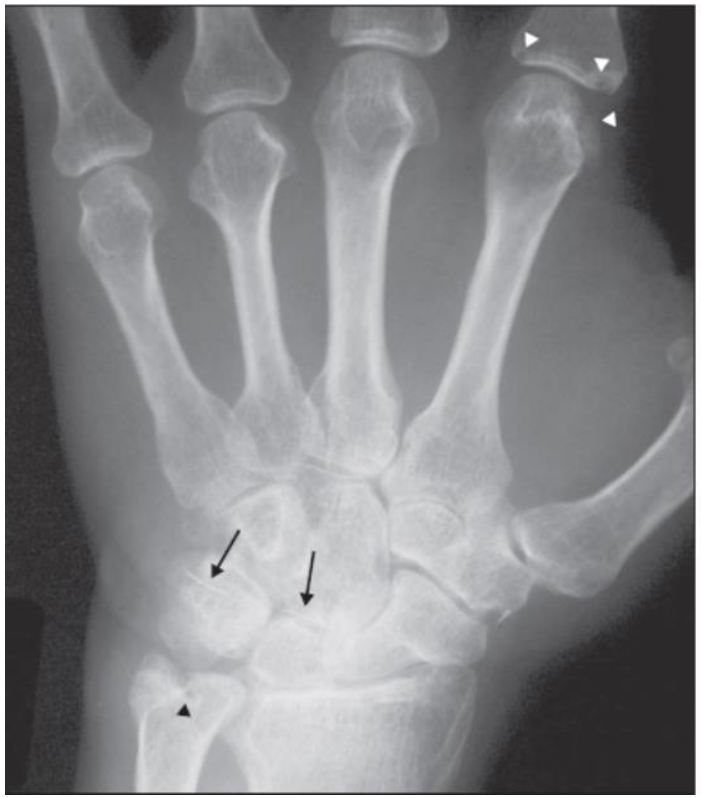
The target population should have at least one joint with definite synovitis that is not better explained by another diagnosis.
A score of 6 of 10 or greater is needed for classification of definite RA.
Large joints: shoulders, elbows, hips, knees, and ankles.
Small joints: second to fifth metacarpophalangeal (MCP), proximal interphalangeal (PIP), thumb interphalangeal, and wrists. ACPA, anti-citrullinated peptide antibody; ACR, American College of Rheumatology; CRP,C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis; RF, rheumatoid factor

Erosions are an important imaging finding that helps confirm the diagnosis of RA and demonstrate the severity of disease.

Erosions initially appear at the edge of the joint where cartilage is thinnest and synovium Attaches, this is referred to as the “bare area.” Such erosions are also called marginal erosions.



Radiograph of the foot demonstrating erosions of the third through fifth metatarsal heads with associated narrowing of the metatarsophalangeal joint space. There is also narrowing of the first interphalangeal joint space with bare area erosions.



Erosive disease is present at the ulnar styloid and bare areas of the second metacarpophalangeal joint (arrowheads). Note the erosive changes of the radial aspect of the second metacarpal head with interruption of the white cortical line as opposed to the intact third metacarpal head. This is a Korean patient who used acupuncture to treat her rheumatoid arthritis.

Bone mineralization is usually normal in all arthropathies except RA (periarticular osteopenia).

Joint space narrowing in RA is diffuse, unlike that in osteoarthritis, in which narrowing occurs along biomechanical vectors of use.

Symmetric swelling about joints in the hands as a result of a combination of effusion, synovial proliferation, and periarticular soft tissue edema is an early finding on conventional radiography

Atlantoaxial subluxation and basilar invagination are frequently present and the lateral cervical spine in flexion is the best way to evaluate patients
for atlantoaxial subluxation ,Basilar invagination is best appreciated on magnetic resonance imaging and computed tomography.

Other imaging
MRI
CT SCAN
US

Management of rheumatoid arthritis

Complete remission of (RA) disease activity should be the ultimate goal of treatment for all RA patients.

Early, aggressive treatment of synovitis is desirable to have the greatest impact in preventing damage and disability.

- Patients with risk factors for poor prognosis warrant the most aggressive suppression of synovitis,

- Presence and titer of autoantibodies (RF and anti-CCP antibodies)
- Genetic factors (the presence of HLA-DRB1
"shared epitope" alleles, especially HLA-DRB1*0401 and HLA-DRB1*0404)
- Radiographic factors (the presence of erosive disease on plain radiographs
at presentation)
- inflammatory markers (elevated CRP level and ESR) and degree of functional
disability (measured using the Health Assessment Questionnaire))

Step-up combination approaches, beginning with rapidly titrated methotrexate, are the best studied and most commonly used strategies in clinical practice.

In most cases, except when there are specific contraindications or high disease activity with poor prognostic features, a nonbiologic DMARD is recommended as the initial therapy in a Disease-modifying antirheumatic drugs (DMARD)-naive patient with early disease.

In DMARD-naive patients with early RA (disease duration of less than 6 months), the ACR 2012 panel recommends starting DMARD monotherapy for disease of all degrees of severity in the absence of poor prognostic factors.

In the presence of poor prognostic features and moderate or high disease activity, double- or triple-DMARD combination therapy or an anti-TNF agent (with or without methotrexate) is recommended.

In DMARD-naive patients with longer disease duration (6 months or more), low disease activity, and no features of poor prognosis, DMARD monotherapy is recommended.

For those with poor prognostic factors and/or moderate to high disease activity, methotrexate monotherapy or DMARD double or triple therapy is recommended as initial treatment.

Pharmacological therapy

NSAIDs.
Glucocorticoids.
(DMARDs) and biologic agents.
DMARDs:
Methotrexate
Sulfasalazine
Leflunomide
Hydroxychloroquine
Minocycline

Biologic agents

- Tumor necrosis factor inhibitors

- Etanercept (Dimeric fusion protein consisting of the extracellular ligand binding portion of the human tumor necrosis factor receptor linked to the fc portion of the human IgG1).
- Infliximab (Chimeric anti-TNF-α antibody).
- Adalimumab, Golimumab(Human anti-TNF-α antibody).
- Certolizumab (Pegylated human anti-TNF-α antibody).

❑ Other biologics

- Abatacept (Cytotoxic T Lymphocyte Associated antigen 4–immunoglobulin) Inhibits T-cell co stimulat

Fusion protein composed of the Fc region of the IgG1 fused to the extracellular domain of CTLA4.

- Rituximab(Anti-CD20 monoclonal antibody) depletes B cells.
- Tocilizumab(Humanized anti-IL-6 receptor antibody; inhibits IL-6).
- Anakinra (Recombinant IL1 receptor antagonist).

psoriatic arthritis

chronic inflammatory disease of both the skin and joints, as well as extraarticular features such as enthesitis and dactylitis.

Five different subtypes are generally recognized

- Distal interphalangeal joint–predominant arthritis (10%).
- Asymmetric oligoarticular arthritis (70-80%)
- Symmetric polyarticular arthritis(5-20%).
- Axial disease predominant with spondylitis, sacroiliitis, and hip and shoulder involvement (5-20%).
- Arthritis mutilans - rare.

- The onset of PsA symptoms may vary in patients with psoriasis, In the majority, skin changes occur before the involvement of joints, However, this is not always a consistent feature.

- A subset of patients can have skin and joint symptoms concurrently, More rarely inflammatory joint symptoms occur before skin changes.

- Typically, PsA is initially a mild, oligoarticular disease but can become polyarticular with time and progresses to a severe, erosive condition in at least 20% of patients.
- The aggressive form is seen more commonly in patients who exhibit polyarticular or erosive PsA at initial evaluation.

EPIDEMIOLOGY

The exact prevalence of PsA is unknown, estimates vary from 0.3% to 1% of the U.S. population, with a reported prevalence of 7% to 42% in patients with psoriasis.

PsA can develop at any age, in most people it appears between the ages of 30 and 50 years.

PsA seems to affect men equally or even at a slightly higher rate than women.

Clinical features

Psoriatic arthritis is an inflammatory arthritis associated with psoriasis, tests for rheumatoid factor are usually negative.

Among patients with psoriasis, arthritis develops in 7% to 42%.

■ In 15% of patients psoriasis develops after the onset of arthritis.
■ Nail changes have the strongest association with arthropathy, the distal interphalangeal joints are particularly affected.
■ Typical clinical features include the following
- Distal interphalangeal joint involvement
- Asymmetric sacroiliitis/spondylitis
- Dactylitis
- Enthesitis

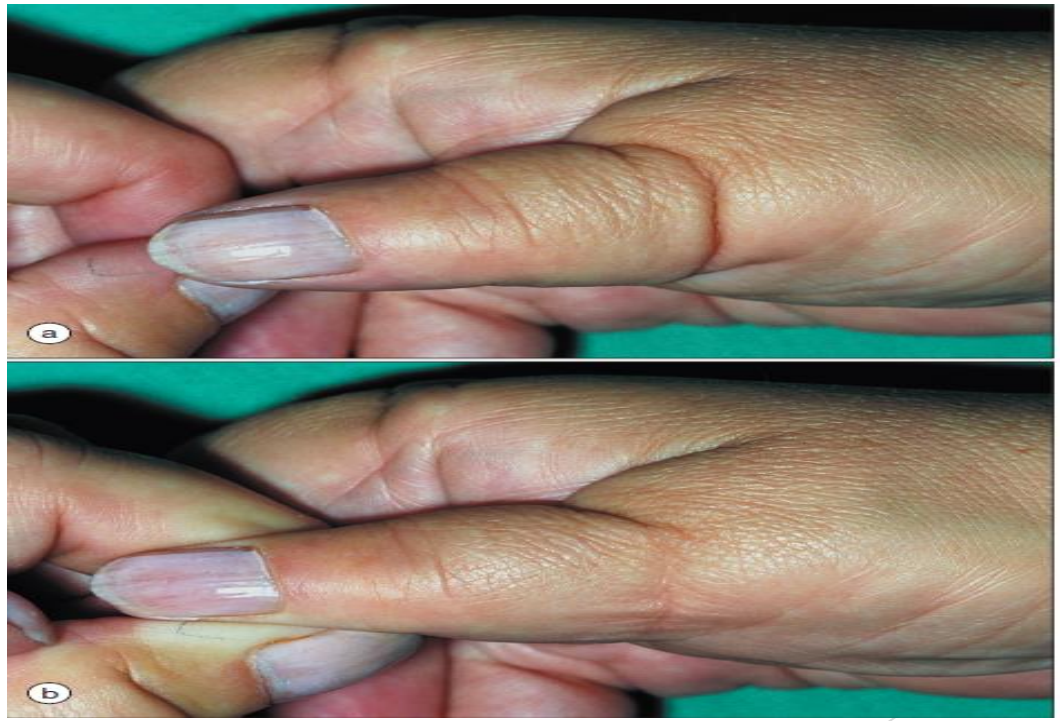
- The number of joints involved can increase with disease duration.
- Patients with polyarticular involvement tend to have poorer long-term outcomes.

- asymmetry is a common feature of psoriatic arthritis, particularly with the oligoarticular pattern.

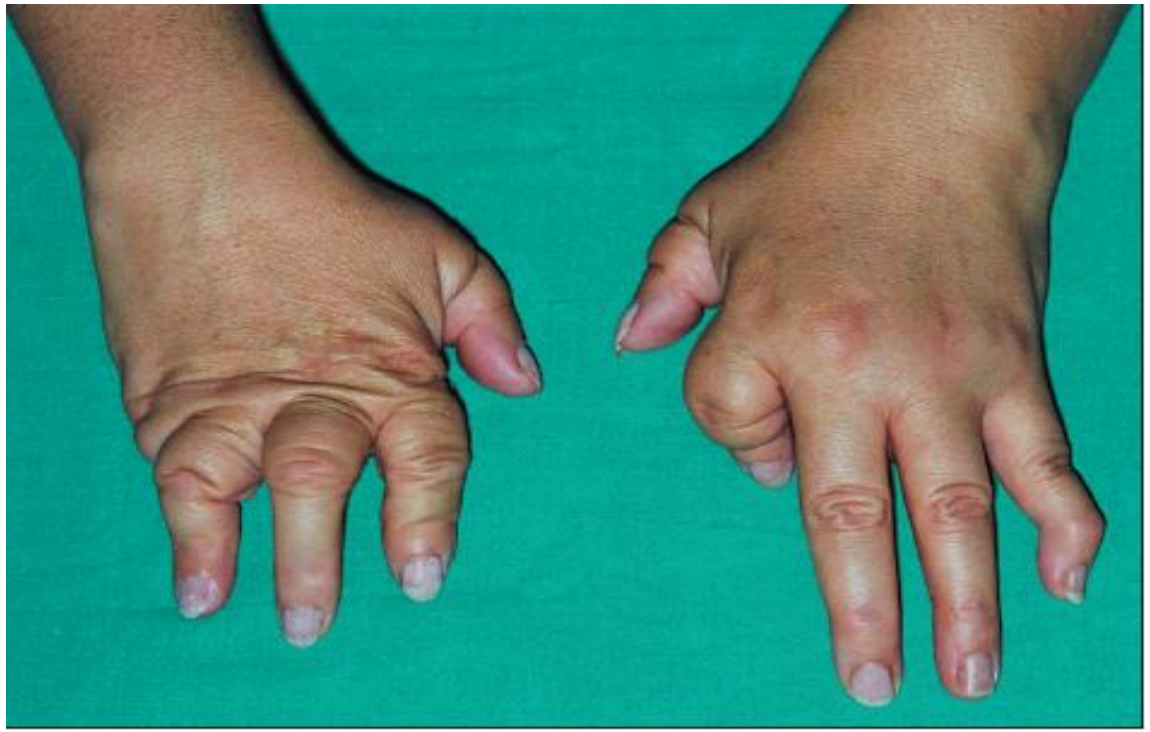
- In contrast, the majority of patients with polyarticular disease have symmetric involvement.
- Involvement of the DIP joints in up to 54% of patients as part of polyarthritis, whereas the DIP-predominant subgroup represented a much smaller proportion of cases (1% to 16%) .

Arthritis mutilans

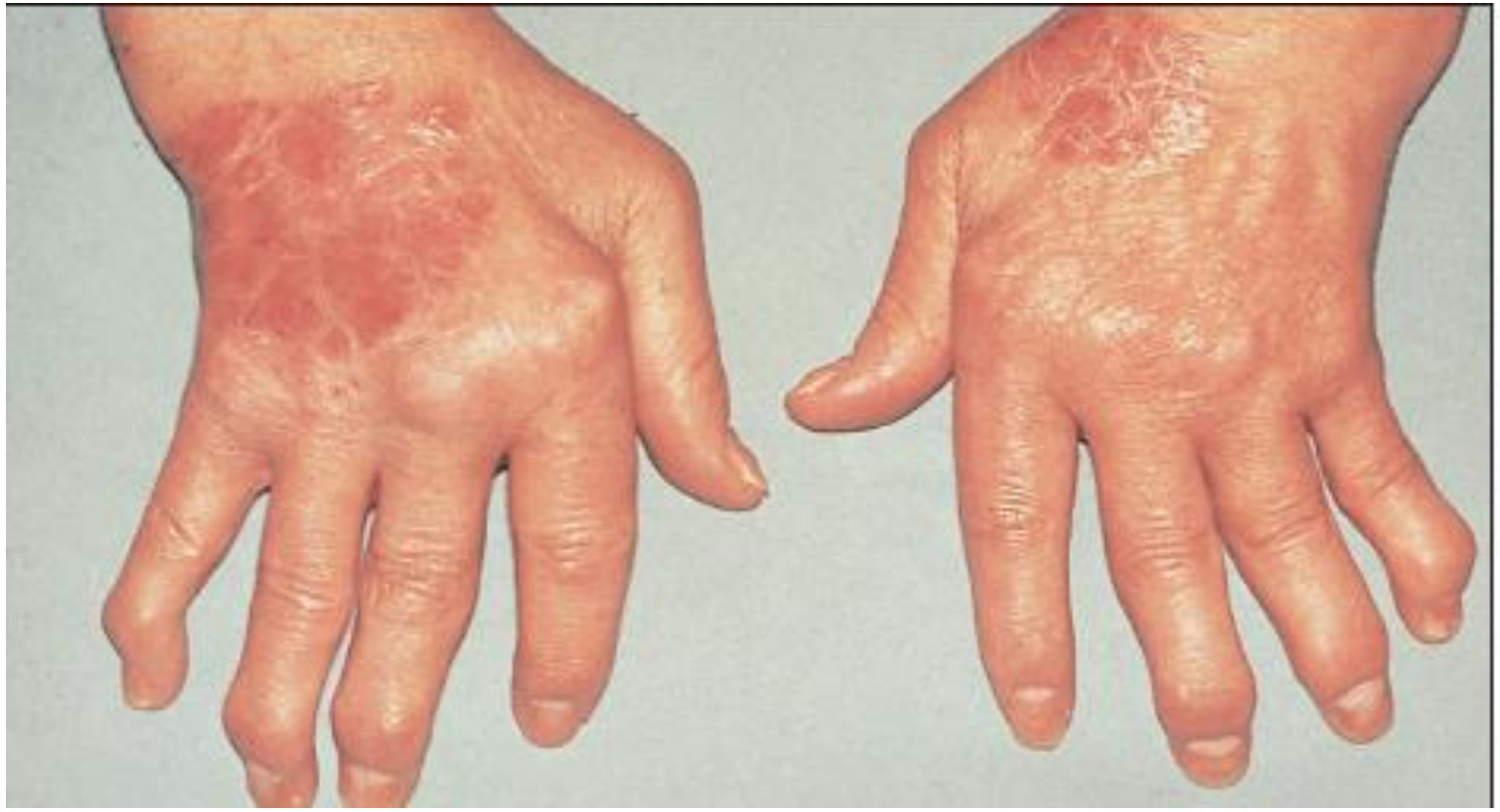
describes the end stage of a destructive erosive arthritis, with disorganization of joints leading to subluxation, “flail” joints, and digital telescoping (opera glass finger).
its prevalence is lower than 5%,Arthritis mutilans is associated with long-standing disease and a female preponderance.



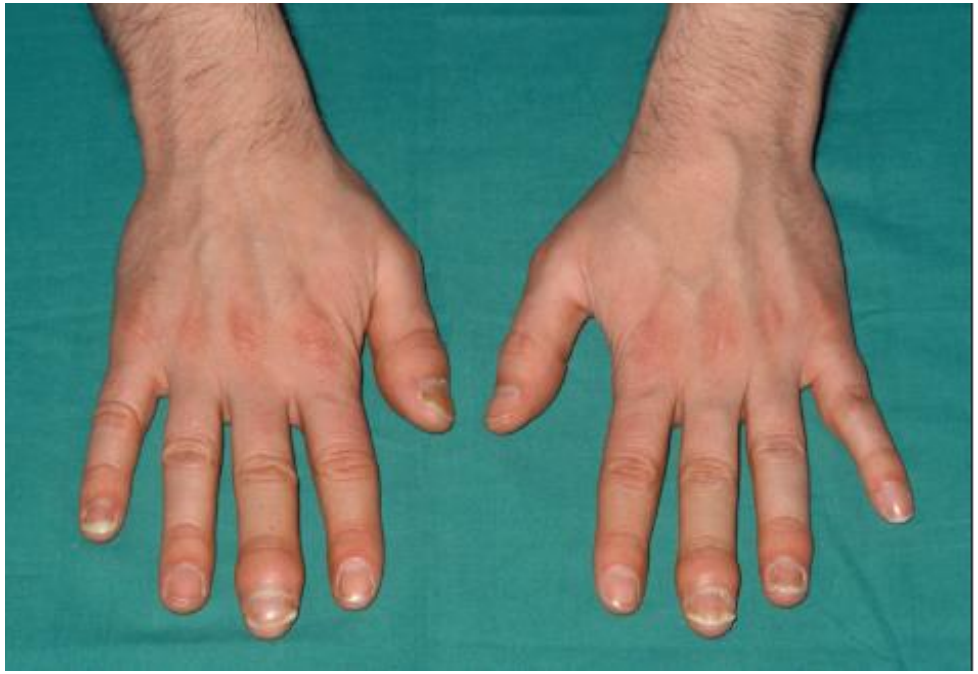
Digital telescoping in arthritis mutilans.



Arthritis mutilans, Note the shortening of the thumbs and the left index finger (the right fifth finger has been amputated).



Symmetric polyarthritis resembling rheumatoid arthritis

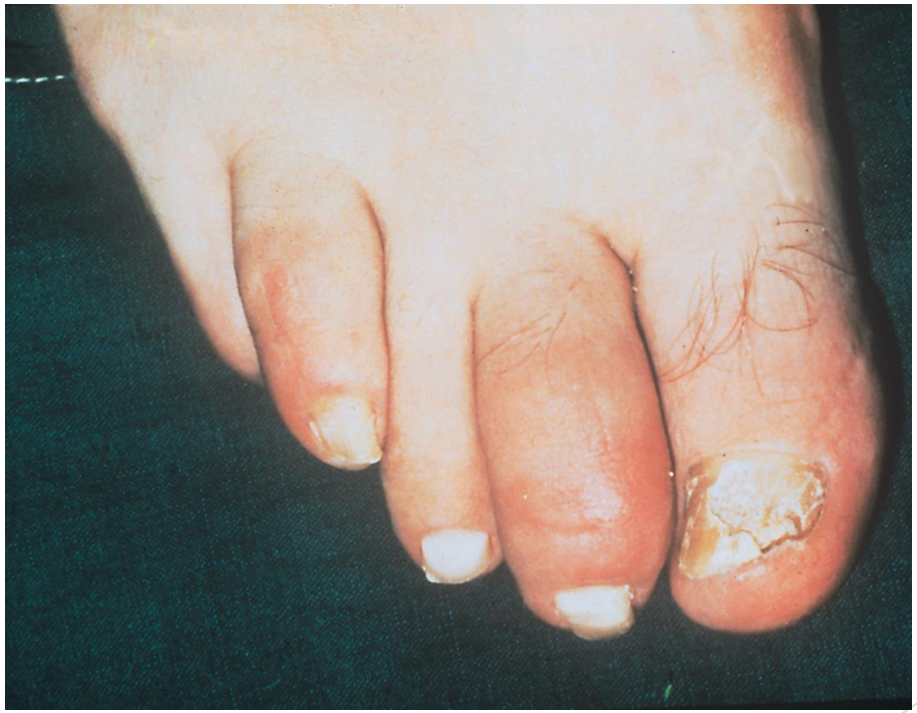


Psoriatic arthritis with predominant involvement of the distal interphalangeal joints.

Other musculoskeletal features

Dactylitis or “sausage digit,” represents complete swelling of a single digit in the hand or foot.

Dactylitis occurs in 30% to 40% of patients during the course of their disease, feet are affected more commonly than the hands.



Dactylitis of the second toe.

Enthesitis

Inflammatory lesions at the insertion of tendon into bone are a hallmark clinical feature of spondyloarthritis,it has been postulated that this inflammatory lesion is the key central pathogenic process in all forms of seronegative spondyloarthritis.

Symptomatic enthesitis occurs in 20%to 40% of patients with psoriatic arthritis.

Common sites of enthesitis include the Achilles tendon, the plantar fascia insertion into the calcaneus, and ligamentous insertions into the pelvic bones.

nail and skin changes

Skin changes

most patients with psoriatic arthritis have only mild to moderate skin disease.
no correlation between the extent of skin disease and total joint scores in patients with psoriatic arthritis.

30% to 40% of patients with psoriatic arthritis report synchronicity of flares of their joint and skin disease, although the validity of this observation has not been formally tested.

- Nail involvement is a risk factor for the future development of psoriatic arthritis

although onset of the skin disease may precede onset of the arthropathy by an average of 7 to 10 years, onset of the nail changes often occurs only 1 to 2 years
before the onset of arthropathy.

- Nail involvement occurs in 20% to 40% of patients with uncomplicated psoriasis whereas 60% to 80% of patients with psoriatic arthritis have nail involvement.

diagnosis

Laboratory investigation

No laboratory tests are diagnostic of psoriatic arthritis.
The following abnormalities can be seen

- Anemia of chronic disease
- Hypoalbuminemia
- Iincreased erythrocyte sedimentation rate (ESR) andC-reactive protein (CRP) and fibrinogen levels Hypergammaglobulinemia.

RF-positive status has been reported in 5% to 10% of patients.

Anti–citrullinated peptide antibodies(ACPAs) 6% to 10% in psoriatic arthritis.
Like RF positivity, there is an association with female gender and polyarticular disease.

Classifications of psoriatic arthritis

Moll and Wright[12]	CASPAR[13] (ClASsification criteria for Psoriatic ARthritis)*		
	Points	Category	Description
Presence of psoriasis and an inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis) The (usual) absence of serologic tests for rheumatoid factor (RF)	2	Current psoriasis	Psoriatic skin or scalp disease confirmed by a dermatologist or rheumatologist; history of psoriasis from the patient, family physician, dermatologist, rheumatologist, or other qualified practitioner; patient-reported history of psoriasis in a first- or second-degree relative
	1	Personal or family history of psoriasis	
	1	Psoriatic nail dystrophy on current physical examination	Includes onycholysis, pitting, and hyperkeratosis
	1	Negative test for RF	Enzyme-linked immunosorbent assay or nephelometry preferred (no latex) using the local laboratory reference range
	1	Current dactylitis or history of dactylitis documented by a rheumatologist	Swelling of the entire digit
	1	Radiographic evidence of juxtaarticular new bone formation	Ill-defined ossification near joint margins in the hand or foot, excluding osteophyte formation on plain radiographs

**Psoriatic arthritis is diagnosed when 3 or more points are assigned in the presence of inflammatory articular disease (joint, spine, or entheseal).*

Radiographic changes

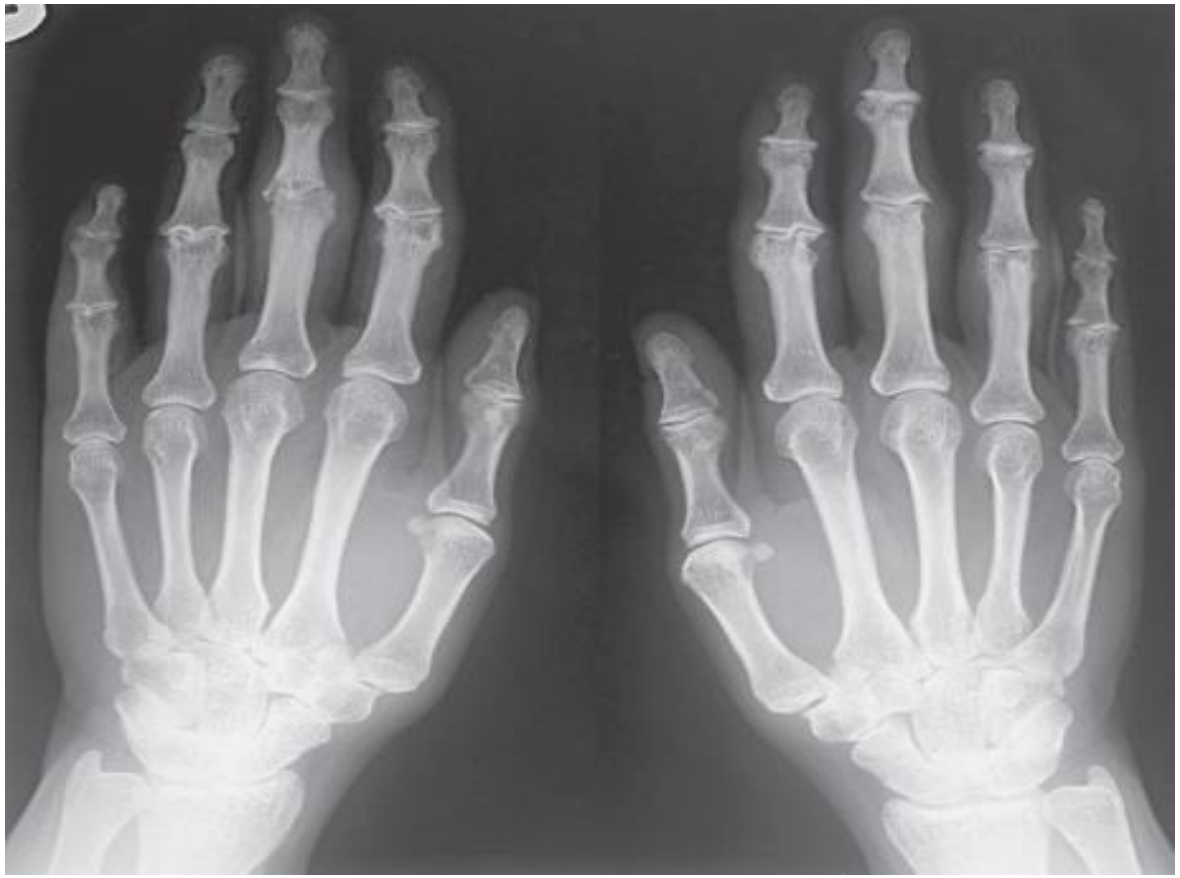
- involvement of the DIP joints and an asymmetric distribution when few joints are affected are well described.
- involvement of entheseal sites can result in proliferative new bone formation at sites such as the plantar fascia and Achilles
- Erosions are most frequent in patients with polyarthritis and in those with a longer disease duration, as well as in those with dactylitis.
- In addition to erosions, soft tissue swelling can be seen around sites of active inflammation, although periarticular osteopenia is not a feature of psoriatic arthritis.

- Destructive changes

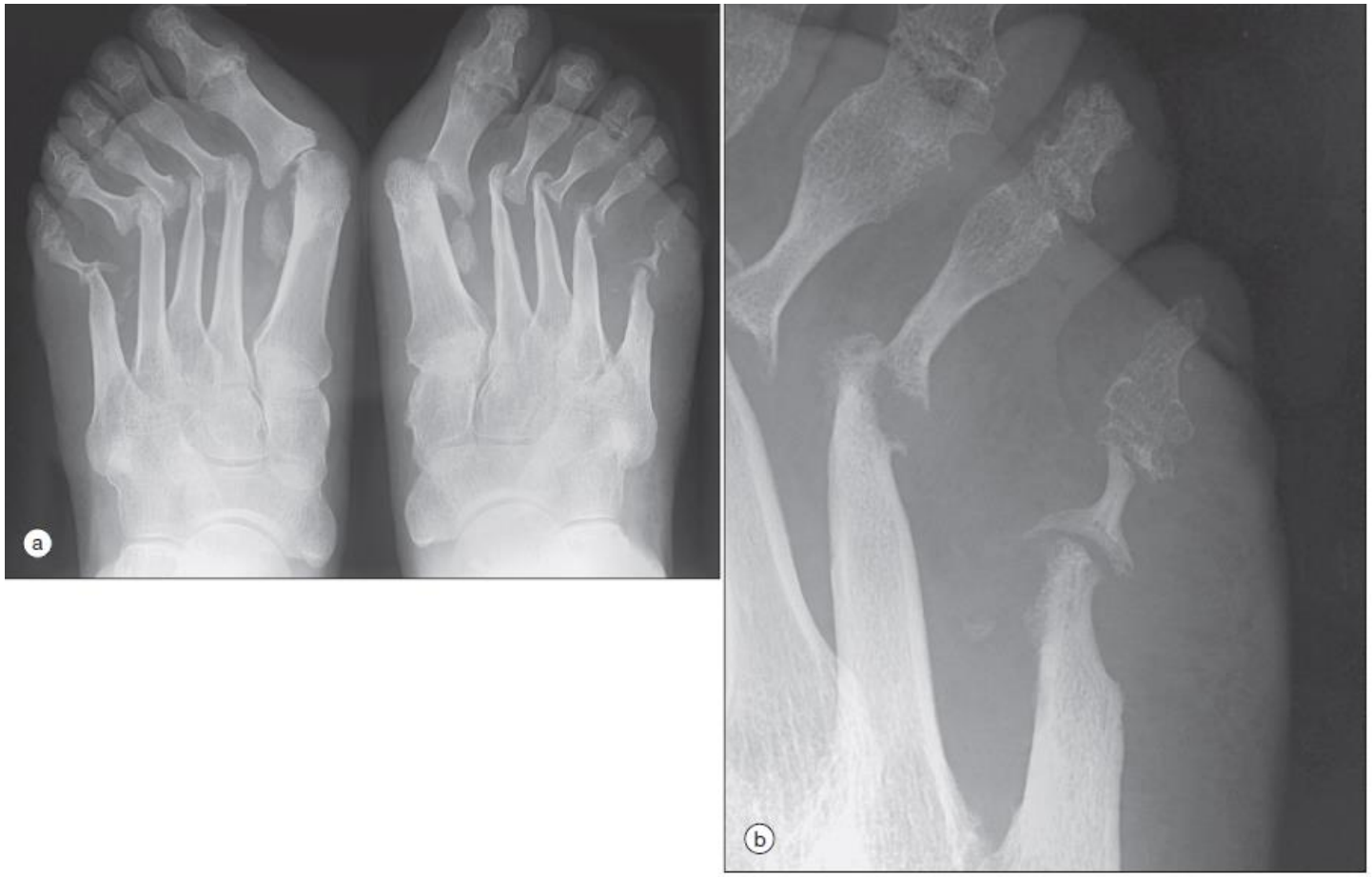
- Osteolysis may result in whittling or penciling of a phalanx.

- This can occur alone or in association with erosion at the base of the adjacent phalanx,which causes the classic “pencil-in-cup” deformity.

- Such destruction is typical of the arthritis mutilans pattern of disease



Radiograph of the hands showing erosive changes at the distal and proximal interphalangeal joints with sparing of the metacarpophalangeal joints and wrists

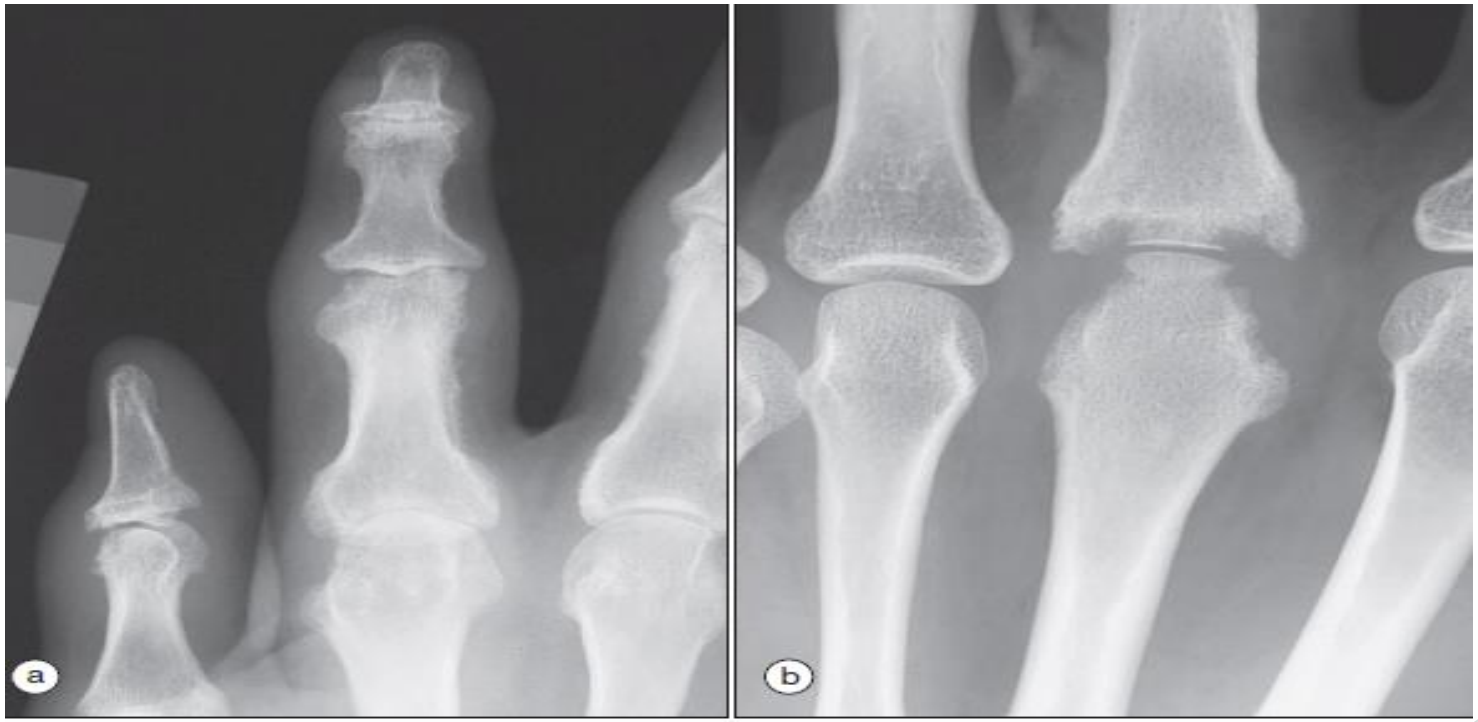


Arthritis mutilans. (a and b) Marked osteolysis and “penciling” have resulted in complete disorganization of the metatarsophalangeal (MTP) joints.
There is also a “pencil-in-cup” deformity of the right fifth MTP joint (b).

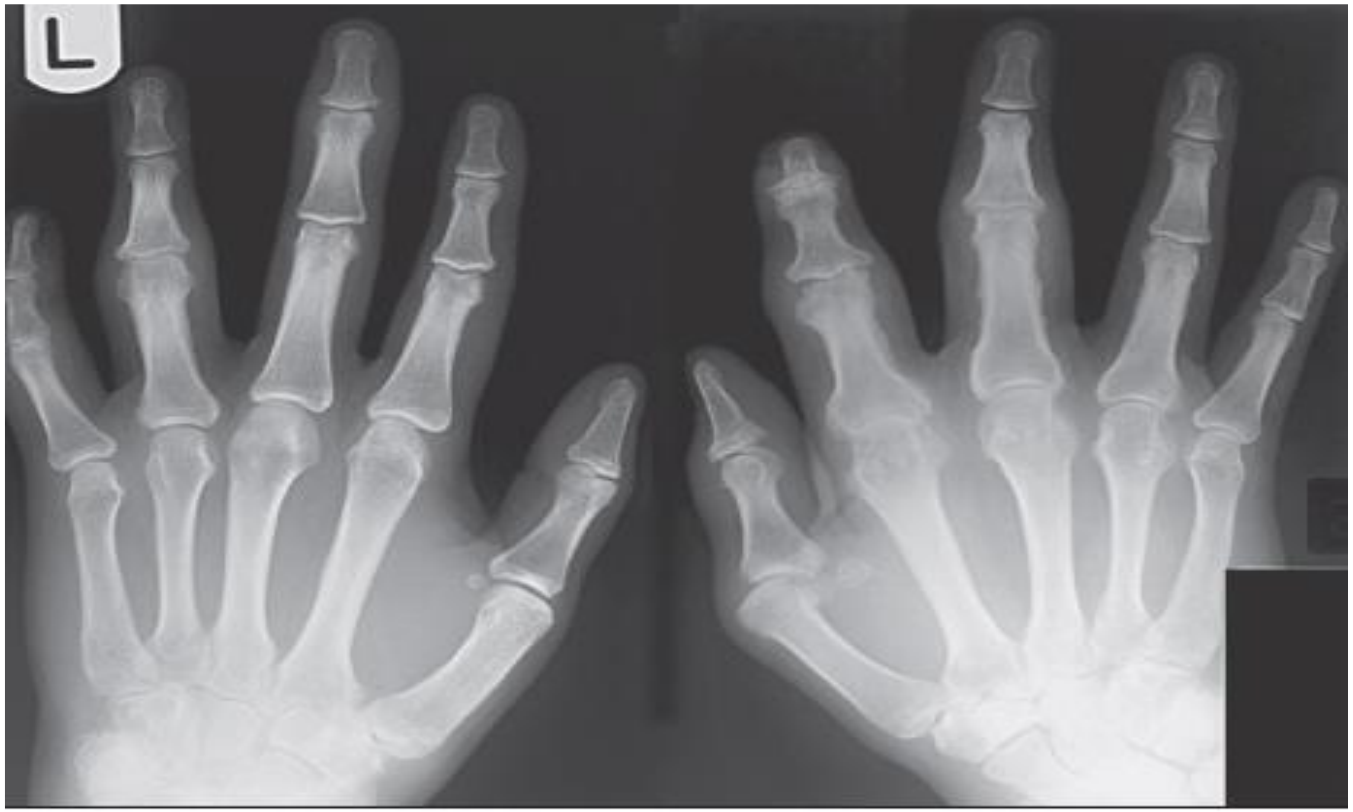
- Proliferative changes

In periostitis, proliferative new bone formation can occur along the shaft of the metacarpal and metatarsal bones When this change occurs adjacent to an erosion, the term whiskering is often used .

marked periostitis may eventually result in the radiologic phenomenon of the “ivory phalanx.
bony ankylosis and joint fusion .



periosteal reactions. (a) Along the shaft of the proximal phalanx.
(b) Adjacent to a large erosion and producing “whiskering.”



Asymmetric involvement of the hands, Soft tissue swelling and a periosteal reaction are evident in the right second and third fingers in the typical “ray” distribution.

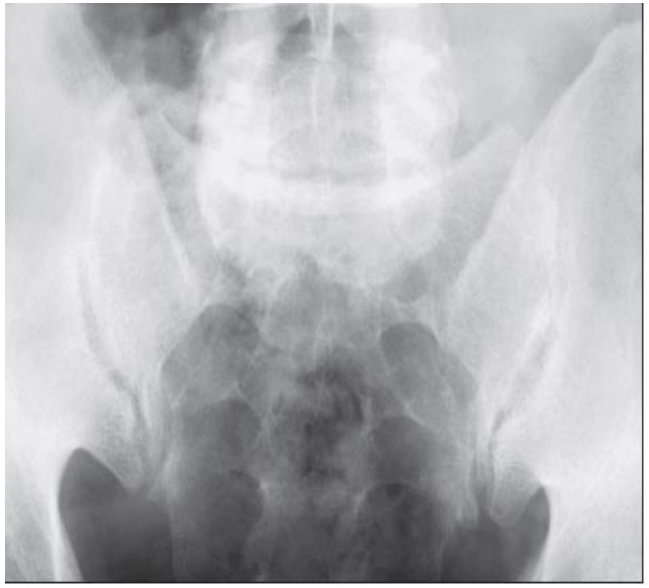
Spinal changes

Asymmetric sacroiliitis is more common in psoriatic arthritis than in ankylosing spondylitis.

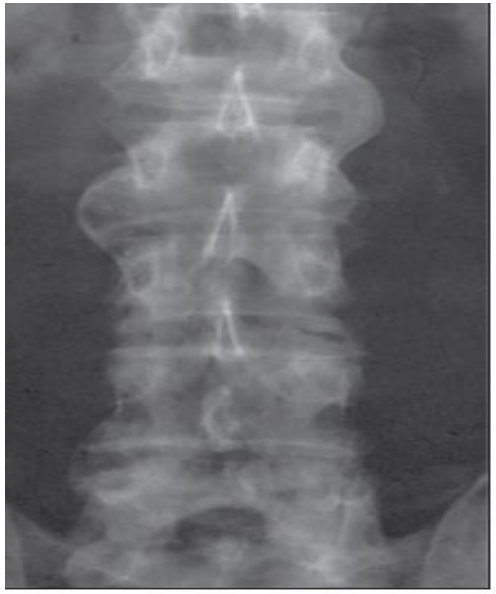
paravertebral ossification or “chunky” syndesmophytes.

These bony outgrowths appear to be distinct from the classic marginal” syndesmophytes observed in ankylosing spondylitis.

The chunky syndesmophytes again occur in a patchy and asymmetric fashion throughout the axial spine



Early asymmetric sacroiliitis with erosion and sclerosis of the left sacroiliac joint.



Non marginal “chunky” syndesmophytes

Other imaging modalities

- MRI
- Scintigraphy
- US

TREATMENT

- NSAIDs

provide relief of symptoms such as pain and stiffness
NSAIDs have been found to be efficacious in treating the spinal pain in ankylosing spondylitis
However, do not prevent disease progression and may worsen skin lesions

- Glucocorticoid in the form of intraarticular injections of corticosteroids (triamcinolone, methylprednisolone) is often used when only one or a few joints are affected.

- Oral corticosteroids are used occasionally for relief of symptoms in patients with polyarthritis or an inadequate response to NSAIDs Glucocorticoids need to be used with extreme caution and a slow taper because psoriasis worsens in many instances and could occasionally evolve into more severe forms such as pustular psoriasis.

TRADITIONAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

- Methotrexate
- Cyclosporine
- Sulfasalazine
- Leflunomide

Small molecules

- Apremilast is a potent, orally active phosphodiesterase 4 inhibitor that suppresses multiple proinflammatory mediators and cytokines.

Tumor necrosis factor antagonists

- Etanercept, infliximab,adalimumab, golimumab, certolizumab.
  proved to be efficacious and relatively safe for the treatment of peripheral arthritis and psoriasis and inhibit structural damage.

Infliximab and golimumab are efficacious for dactylitis and enthesitis.

- Secukinumab afully human immunoglobulinG1 kappa monoclonal antibody that directly inhibits interlukin17A.

- Ustekinumab, an antibody to the common p40 subunit of interleukin-12 and interleukin-23, is efficacious in the management of psoriasis, peripheral arthritis, enthesitis, and dactylitis

crystal arthropathy

Gout is an inflammatory disease caused by the deposition of monosodium urate (MSU) crystals in joints and other tissues.

- The formation of the crystals is the consequence of hyperuricaemia, a condition so called when serum uric acid (SUA) levels are >6.0 mg/dL (360 μmol/L)
- most patients with hyperuricaemia do not have clinical gout.

- Gout is the most common form of inflammatory arthritis in men and its incidence and prevalence are rising in postmenopausal women.

Gout affects about 1–2% of adults, with a prevalence increasing with age, being 7% in men over 65 years and 3% in women over 85 years.

- Deposits of MSU crystals known as tophi may form usually in and around joints but also elsewhere

- Emerging data suggest that gout is a deposition disease from the first attack or even earlier.
- Identification of MSU crystals in synovial fluid (SF) obtained during the attacks ,from previously inflamed asymptomatic joints of untreated subjects during intercritical periods or in an aspirate from a tophus is simple and allows immediate unequivocal diagnosis.

- Ultrasound studies have demonstrated deposition of MSU crystals in patients with asymptomatic hyperuricaemia who have not yet developed clinical manifestations of gout.

- Renal lithiasis and formation of tophi in internal organs and other structures may also occur.
- The crystals slowly dissolve and finally disappear when SUA levels are lowered below a certain threshold.
- In an important proportion of patients hyperuricaemia is part of the metabolic syndrome and the presence of gout should alert us to this problem and its associated morbidities, which may require modification of dietary and lifestyle habits and often drugs.
- Gout has also been found to be an independent risk factor for atherosclerotic cardiovascular disease

Pathogenesis and risk factors

The formation of the crystals requires

(1) Raised SUA levels (hyperuricemia)
(2) Some local conditions

- Uric acid is the final metabolite of purine metabolism .

- At a physiological pH of 7.4 in the extracellular compartment, 98% of uric acid is in the ionised form of urate, and Because of the high concentration of sodium in the extracellular compartment, urate is largely present as MSU, with a low solubility limit of about 380 µmol/L So, when urate concentrations exceed this limit, the risk of MSU crystal formation and precipitation increases.

- The levels of SUA depend on the balance between
- purine ingestion
- synthesis and degradation.

- The ingestion of purine and/or urate is very limited, contributing about 10% of the total pool of urate in the body.

- The main site of the synthesis is the liver.

Since purines are difficult to synthesise, during their degradation there are salvage pathways aimed at their reutilization,the salvage pathways are a major source of nucleotides for synthesis of DNA, RNA and enzyme cofactors.

- The enzymes most involved in these salvage pathways are

- adenosine phosphoribosyltransferase and
- hypoxanthine-guanine phosphoribosyltransferas

- In the distal end of the purine pathway there is the enzyme xanthine oxidase that catalyses the oxidation of hypoxanthine to xanthine, and xanthine to uric acid.

- The starting point of uric acid synthesis is the ribose-5-phosphate, a pentose derived from glycidic metabolism converted to phosphoribosyl pyrophosphate (PRPP) and then to phosphoribosilamine, that will be transformed into inosine monophosphate (IMP), From this intermediate compound are derived adenosine monophosphate (AMP) and guanosine monophosphate (GMP), the purinic nucleotides useful for DNA and RNA synthesis, and inosine that will be degraded into hypoxanthine and xanthine and finally, into uric acid by the enzyme xanthine oxidase.

Hypoxanthine and guanine may enter in a salvage pathway, using HGPRT, an enzyme that reconverts these purines bases into their respective nucleotides.
In a similar salvage pathway,
adenine phosphoribosyltransferase (APRT) converts adenosine to AMP.

- In humans and other primates, urate oxidase (uricase), a hepatic enzyme, is inactive as a result of a non-sense mutation.
- So, only animals which possess uricase can transform uric acid in a more soluble and more eliminable molecule: allantoin.

Defects of the enzymes involved in the salvage pathways may cause severe diseases, as in the case of partial or total deficiency of HGPRT, which causes Lesch–Nyhan disease in boys. Another cause of secondary hyperuricaemia is the raised activity of phosphoribosyl pyrophosphate synthetase, in which hyperuricaemia and gout are associated with renal over excretion of uric acid and lithiasis.

However, these genetic defects account for the minority of cases of gout associated with raised production and excretion of uric acid and frequently with urinary lithiasis .

- SUA levels depend on gender and age.

- Prepubertal children of either sex have low SUA levels.

At puberty SUA levels rise to the levels that will be maintained throughout life owing to a decrease in the renal clearance of urate.

- in men these levels rise slightly with age, Oestrogen and progesteron are uricosuric , both promote uric acid excretion ,so that uricaemia will be lower in women up to the menopause or end of hormonal substitution treatment .

- This explains why children do not have gout,with the exception of boys with very unusual enzymatic defects, and of children affected by familial hyperuricaemic nephropathy, an inherited kidney disease with low urinary urate excretion.
- It also explains why in men the risk of gout starts soon after puberty, while in women gout is exceptional before the menopause.

- Excess uric acid may result from an increase in the amount of purines being degraded, either endogenously from tumours, or haematological conditions like leukaemia or lymphomas, especially when treated, or in

psoriasis, or exogenously owing to raised ingestion of purines from food or drinks—in particular, beer or fructose-rich beverages For haematological diseases, only patients with chronic conditions develop gout, owing to the time necessary for MSU crystal deposition.

- Decreased urate clearance results in raised SUA levels and is the most common cause of gout.
- only 5–10% of the filtered urate is finally excreted by the kidneys, the largest part being reabsorbed in the tubules.

- intestinal excretion of uric acid in SUA levels has not been well evaluated, it seems responsible for about a third of the excretion of uric acid produced daily.

- Reduced intestinal excretion of urate has been recently shown to be a possible cause of hyperuricaemia

❑ Local conditions for MSU crystal formation

- The formation of MSU depends on several factors, including mainly the local concentration of urate,However its solubility may be influenced by the articular hydration state, temperature, pH, concentrations of cation and the presence of extracellular matrix proteins such as proteoglycans, collagen and chondroitin sulphate.

- Cartilage damage related to OA may help to expose collagen fibres which may act as templates for epitaxial formation, prompting MSU crystal nucleation and growth.

Other risk factors and secondary causes of hyperurecemia

- Medications

many diuretics promote hyperuricemia and subsequent gout

The increase in gout risk as a result of diuretic use is substantial and may range as high as 3- to 20-fold

The mechanisms through which diuretics raise serum urate are incompletely elucidated but include the induction of sodium wasting and volume depletion, with a resultant decrease in the fractional excretion of urate.

despite the volume-depleting effects of diuresis, not all diuretics promote hyperuricemia.
the potassium-sparing diuretics triamterene, amiloride, and spironolactone
do not increase urate levels.

- Low dose salicylates including the low doses of aspirin raise urate by impairing renal urate efflux.

At high doses, salicylates become uricosuric,apparently through the inhibition of URAT1.

- The anti tuberculous agent pyrazinamide is the most potent urate

Retaining agent known.

Another antituberculous agent,ethambutol, can also reduce renal tubular urate excretion

- Calcium channel blockers modestly promote serum urate excretion.

ß-blockers are associated with increased serum urate levels, possibly as a result of decreased renal perfusion

- Cyclosporine promote decreased renal urate excretion and hyperuricemia.

Cyclosporine causes tubulointerstitial injury and arteriolar hyalinosis,reciprocally, hyperuricemia may exacerbate the nephrotoxic effects of cyclosporine.

- Tacrolimus does not promote similar levels of hyperuricemia.

- Purine-Rich Foods

- not all purine-rich foods convey equivalent risk: seafood and red meat, particularly organ meats, convey an increased risk for hyperuricemia, whereas consumption of purine-rich, leafy green vegetables apparently does not convey such a risk.

- Fructose

- patients who consume excessive fructose in the form of fructose-sweetened soft drinks or fruit juices demonstrate both higher serum urate levels and an increased incidence of gout.

- Alcoholic Beverages

Ethanol ingestion is associated with the development of gout and hyperuricemia.

- Due to the requirement for ATP degradation during ethanol metabolism, resulting in increased purine turnover and urate generation.
- The ability of binge alcohol consumption to induce increases in lactate levels also contributes to hyperuricemia by decreasing renal urate excretion.

- Ethanol also promotes a diuresis, dehydration and volume depletion then promote renal urate retention.

- some alcoholic beverages, particularly beers and ales, are high in purines, mainly in the form of guanosine.

- in contrast to beer,moderate consumption of wine (which is relatively low in purines) does not increase serum urate levels.

Other Dietary Components

consumption of low-fat dairy products is independently associated with reduced serum urate levels and risk of gout.
consumption of milk or milk proteins has a direct uricosuric effect that results in lowering of serum urate
Interestingly, dairy products may also have anti inflammatory effects

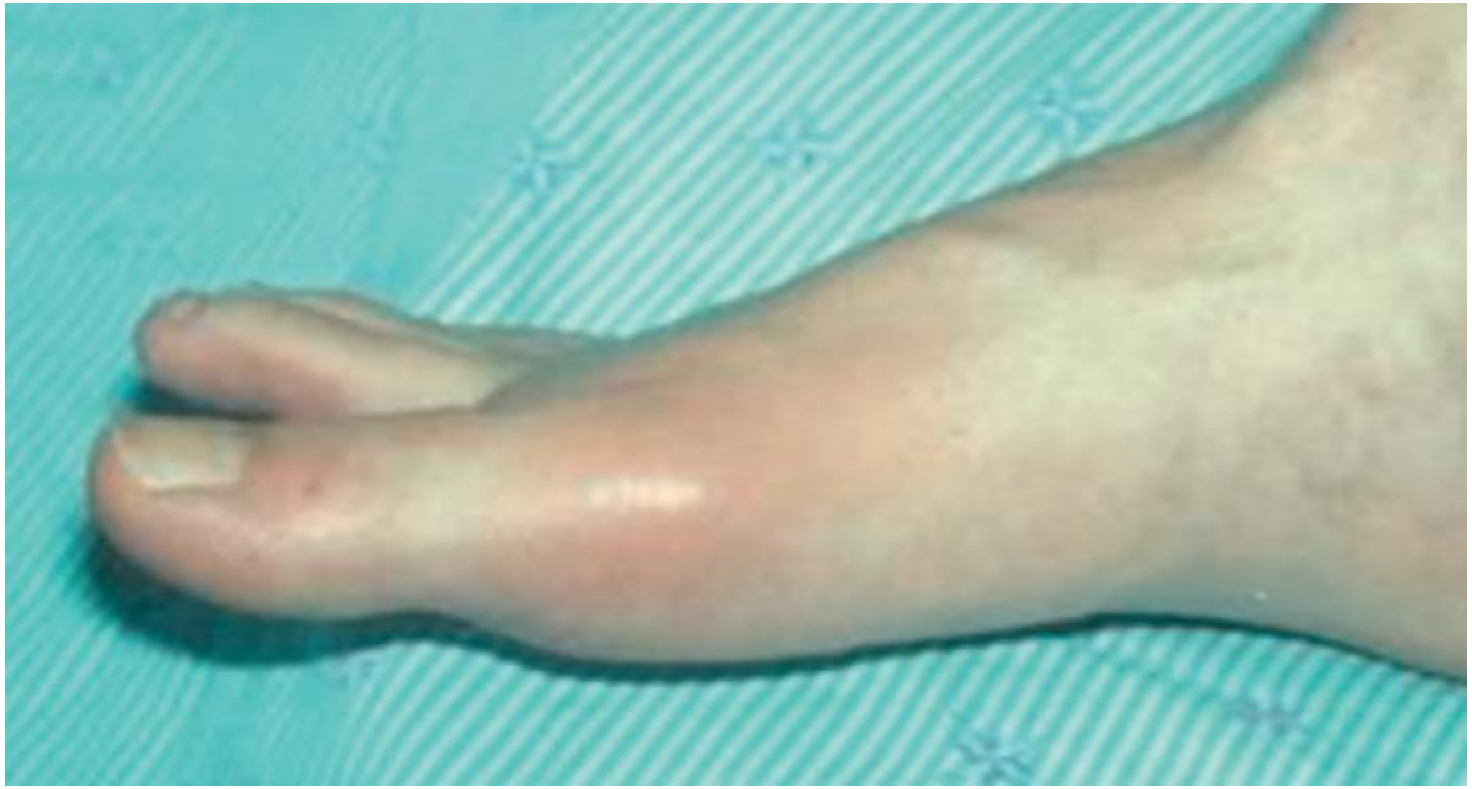
Regular heavy coffee consumption (4 to 6 cups daily) may have urate-lowering properties that are independent of caffeine ,these effects appear to be concordant with a reduced risk of incident gout.

In contrast, intermittent heavy coffee consumption may be transiently pro hyperuricemic, perhaps as a result of caffeine induced diuresis and volume depletion.

Clinical features

- The classic presentation of acute gout is characterised by a typical rapid development of severe pain, swelling, with overlying erythema and tenderness that reaches its maximum within 6–12 h, often starting at night or in the early morning.

- Most often gout presents as acute monoarthritis and usually it involves a single joint in the lower extremity—in particular, the first metatarsophalangeal joint (podagra), which has been considered as a hallmark of the disease Less often, the disease starts in other joints: tarsal and subtalar joints, ankle, knee, wrist, metacarpophalangeal or interphalangeal joints of the hand are frequently affected.



Podagra, or acute monoarticular inflammatory arthritis of the first metatarsophalangeal(MTP) joint.

- In about 10% of cases, gout may have an oligoarticular presentation.

- In some cases, the attack of acute gout may involve more joints, in a polyarticular manner, as seen in the elderly, especially women, and in patients who have had a transplant.

- The three stages of gout are

- Asymptomatic hyperuricemia.
- Acute and intercritical gout.
- And chronic gouty arthritis.

Asymptomatic Hyperuricemia

- Asymptomatic hyperuricemia is a condition in which the serum urate level is high, but gout manifested by arthritis or uric acid nephrolithiasis—has not yet occurred.

- Most people with hyperuricemia remain asymptomatic throughout their lifetimes, although the tendency toward acute gout increases with the serum urate concentration.

- The annual incidence rates of gout per 1000 person-years for

serum urate levels of 6.0,mg/dl were 0.8
6.0 to 6.9 mg/dl were 0.9
7.0 to 7.9mg/dl were 4.1
8.0 to 8.9mg/dl were 8.4
and greater than 9.0 mg/dL 49.0.

Acute Gouty Arthritis

- The first attack of acute gouty arthritis usually occurs between age 40 and 60 years in men and after age 60 years in women.
- Onset before age 25 years should raise the pos sibility of an unusual form of gout, perhaps one related to a specific enzymatic defect that causes marked purine over production,an inherited renal disorder, or the use of certain medications, especially cyclosporine.
- A single joint is involved in about 85% to 90% of first attacks, with the first metatarsophalangeal joint being the most commonly affected site.
- The initial attack is oligoarticular or polyarticular in 10% to 14.5% of cases.

- Acute gout is predominantly a disease of the lower extremities,but any joint of any extremity may be involved.

- Ninety percent of patients experience acute attacks in the great toe at some time during the course of their disease .

- Next in order of frequency are the insteps, ankles, heels, knees, wrists, fingers, and elbows.

Acute attacks rarely affect the shoulders, hips, spine, sacroiliac joints, sternoclavicular joints, acromioclavicular joints,or temporomandibular joints.

Urate deposition and subsequent gout appear to have a predilection for previously damaged joints such as in Heberden's nodes of older women.

The differential diagnosis is usually septic arthritis
or other crystal-induced arthritis, but a broader differential should be considered in confusing cases as cellulitis ,trauma reactive arthritis.

- In most patients the initial attack occurs with explosive suddenness and commonly begins at night , and Within a few hours of onset, the affected part becomes hot, dusky red, swollen, and extremely tender and occasionally, lymphangitis may develop.

- Systemic signs of inflammation may include leukocytosis, fever, and elevation of the erythrocyte sedimentation rate.

- Radiographs usually show only soft tissue swelling during early episodes.

- Mild attacks may subside in several hours or persist for only a day or two and never reach the intensity described for the classic attack.

- Severe attacks may last days to weeks.

The skin over the joint often desquamates as the erythema subsides.

- With resolution, the patient becomes asymptomatic and enters the intercritical period.
- Certain drugs may precipitate acute gout by either increasing or decreasing serum urate levels acutely.

The occurrence of gout after the initiation of urate-lowering therapy is well established, And the more potent the urate-lowering effect, the more likely there is to be an acute attack .

- Drug-induced gout as a result of increased serum urate levels occurs on occasion with diuretic therapy, administration of intrave Nous heparin, and use of cyclosporine.

- Diuretic therapy in elderly people is important precipitating factor for gouty arthritis.

- Other triggering factors include trauma, alcohol ingestion, surgery, dietary excess, hemorrhage, foreign protein therapy, infections, and exposure to radiographic contrast material.

- Patients with gout have a 20% risk of experiencing an attack during Hospitalization.

Intercritical Gout

- Is the periods between gouty attacks.

- Although a few people never have a second attack, most experience a second attack within 6 months to 2 years.

- 62% had recurrences within the first year, 16% in 1 to 2 years, 7% had experienced no recurrence in 10 or more years.

The frequency of gout attacks usually increases over time in untreated patients. Later attacks have a less explosive onset, may be polyarticular, become more severe, and abate more slowly.

- Radiographic changes may develop during the intercritical period despite no signs of tophi on physical examination.

These changes are more likely in patients with more severe hyperuricemia and more frequent acute attacks

- The diagnosis of gout in a hyperuricemic patient with a history of acute attacks of monoarthritis may be difficult or inconclusive during the intercritical phase.

- Aspiration of an asymptomatic joint can be a useful adjunct in the diagnosis of gout if urate crystals are demonstrated.

- Joint fluid obtained from patients with gout during the intercritical phase revealed monosodium urate crystals in 12.5% to 90%of joints.

- Such crystals in asymptomatic joints are often associated with mild synovial fluid leukocytosis, which suggests a potential to contribute to joint damage even in the intervals between attacks.

Chronic Gouty Arthritis

Eventually, the patient may enter a phase of chronic poly articular gout with no pain-free intercritical periods,At this stage, gout is easily confused with other types of arthritis or other conditions.

The time from the initial attack to the beginning of chronic symptoms or visible tophaceous involvement is highly variable ranging from 3 to 42 years, with an average of 11.6 years between the first attack and the development of chronic arthritis.

Ten years afterthe first attack, about half the individuals were still free of obvious tophi, and most of the remainder had only minimal deposits.

The rate of formation of tophaceous deposits correlates with both the degree and the duration of hyperuricemia, the severity of renal disease and the use of diuretics

- Tophaceous gout is the consequence of the chronic inability to eliminate urate as rapidly as it is produced.

- As the urate pool expands, deposits of urate crystals appear in cartilage, synovial membranes, tendons, soft tissues, and elsewhere.

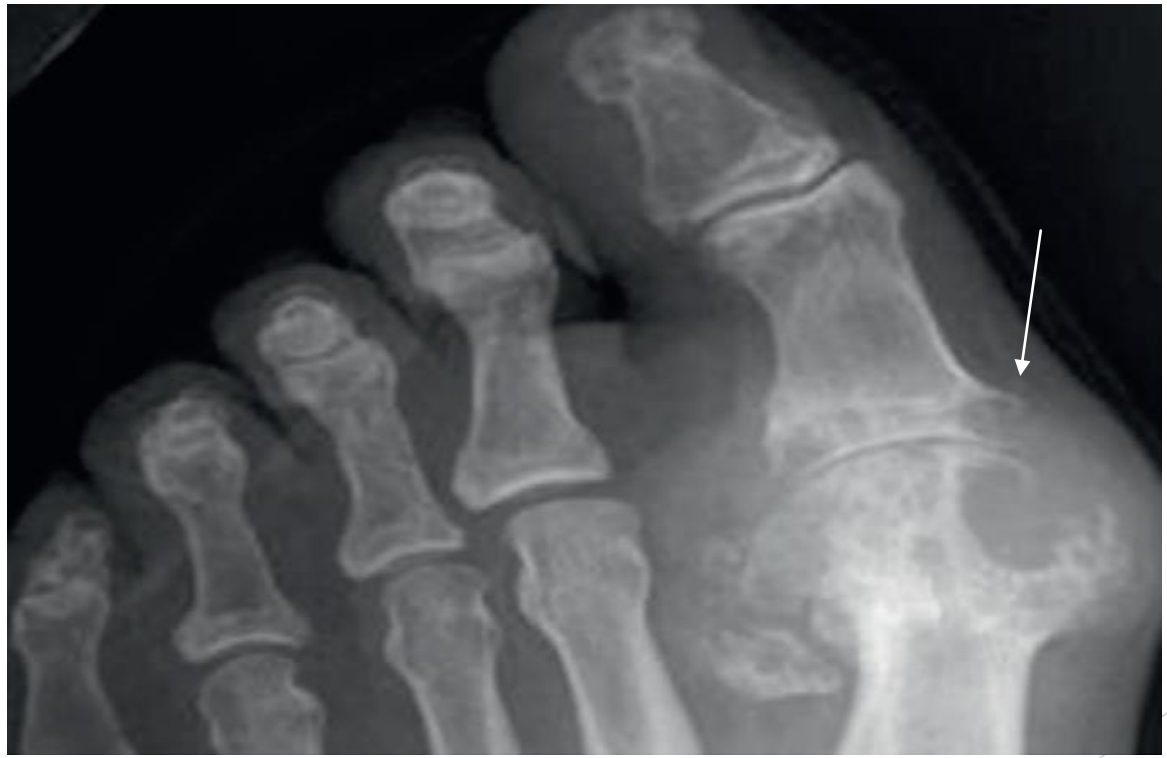
- Tophi are rarely present at the time of an initial attack of primary gout.

- They are more likely to be present in people with gout as a result of myeloproliferative diseases, in people with juvenile gout-complicating glycolgen storage diseases, in people with Lesch-Nyhan syndrome,or after allograft transplantation in patients treated with cyclosporine

- The tense, shiny, thin skin overlying the tophus may ulcerate and extrude white, chalky, or pasty material composed of urate crystals.

Secondary infections of tophi are rare.

- Typical radiographic changes, particularly erosions with sclerotic margins and overhanging edges of bone, occur with the development of tophi .



- Factors that might trigger acute attacks include

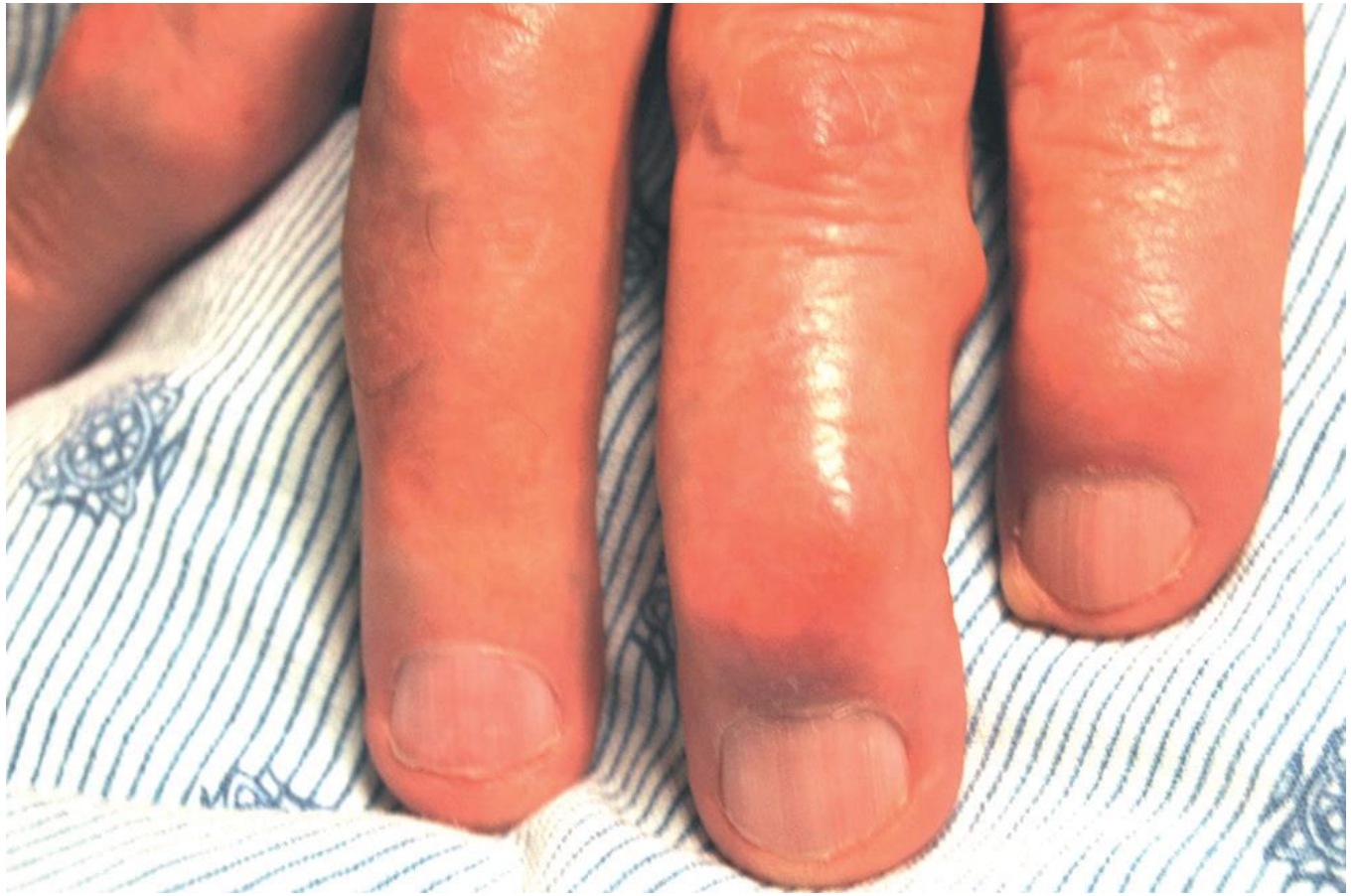
- alcohol intake, heavy meals rich in animal purines, fasting, trauma,infection and surgery .
- Different drugs can also precipitate acute gout by raising or lowering SUA concentrations, such as diuretics and urate-lowering therapy (ULT) shortly after initiation.
- Gouty inflammation tends to be very intense and painful, It is characteristic of the disease that the maximal inflammation is reached within a few hours.
- Erythematous skin can desquamate after some days.

- As the disease progresses without treatment, gouty attacks tend to be more frequent, affect additional joints and become more polyarticular and persistent, leading to chronic gout.

- Then, palpable tophi can appear and gouty inflammation can be less acute and low-grade chronic arthritis also occurs.

- In older subjects receiving diuretics, gout may result in modest inflammation and simulate or occur at Heberden and Bouchard's nodes .

- Tophi are nodules of a palpable size generally placed near joints and may be the initial clinical feature of gout, but are usually seen in longstanding undiagnosed or improperly treated gout.



Dorsal digits of the hand of a patient with tophaceous gout

- Tophaceous gout is not a different type of gout, large crystal accumulation just indicates delayed diagnosis or poor treatment.

- Tophi are often easily seen and can be palpated usually close to joints, and their white content is often seen through the skin ,When abundant, tophi can result in joint deformation ,They can also form in the subcutaneous tissue, skin, and their formation along the outer border of the helix is quite characteristic.

- Aspiration with a needle of a tophus yields a snow white chalky material which is very suggestive of the nature of the nodule, the material should be examined by a polarised microscope for definitive identification of the crystals.

- Chronic urate arthropathy is a late feature of neglected gout and is generally associated with palpable tophi.
- This destructive arthropathy, due to urate infiltration of joints, is responsible for mechanical pain and permanent disability, interspaced with acute or subacute inflammatory episodes.

Diagnosis

- When hyperuricaemia accompanies consistent clinical features makes the diagnosis more likely, but to use hyperuricaemia as an aid to the diagnosis of gout has important limitations.

Hyperuricaemia most frequently is asymptomatic and must not be confused with clinical gout, even if US studies have shown that a large proportion of asymptomatic hyperuricaemic subjects have asymptomatic deposits, Only 0.9 people per1000/year among those whose SUA is between 7 and 7.9 mg/dL (0.42–0.47 mmol/L) will present with gout.

- Identification of MSU crystals in SF samples drawn from joints undergoing gouty attacks or from tophi allows an unequivocal definitive diagnosis of gout .

- MSU crystal deposits can be detected by sonography, which shows crystals deposited along the surface of the joint cartilage, and also in synovial tissue and tendons.

Treatment

acute treatment is directed towards reducing inflammation rather than eliminating crystals.
Standard treatment includes

- non-pharmacological treatment, such as rest and application of ice to the affected joints and mainly, pharmacological modalities
- The most appropriate drugs for this are anti-inflammatory substances, which include traditional drugs such as colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, and innovative drugs, such as the biological drugs acting as IL-1 inhibitors, in patients with inadequate response or contraindication/intolerance to standard drugs.

Overall, all anti-inflammatory drugs work much better when given early after the onset of gouty flares.
gouty attacks subside spontaneously after a short period; drugs with anti-inflammatory properties hasten the process and most often result in a rapid relief of the symptoms.
It is accepted that treatment early after the start of an attack results in faster resolution.

All drugs indicated for an acute attack may be used alone or in combination with each other.
The treatment can be maintained after subsidence to avoid rebounds, generally at lower, prophylaxis doses of a single drugs:

Colchicine
NSAIDs
Glucocorticoids
Interleukin-1 blocker

Urate-lowering therapy

For all SUA-lowering drugs it is an often accepted rule that they should not be started until the gouty attack has fully resolved; furthermore, it must be kept in mind that the initiation or increase in dosage of SUA-lowering therapy in patients with gout frequently results in a gouty attack if prophylactic colchicine is not co-administered

- The ULT could be started during an acute attack, provided that the anti-inflammatory therapy has been instituted and is effective.

- Three classes of drugs are approved for ULT:
- xanthine oxidase inhibitors,
- uricosuric agents and
- uricase agents

Allopurinol

Allopurinol is a purine analogue that competitively inhibits xanthine oxidase, the enzyme responsible for the degradation of hypoxanthine and xanthine to uric acid, reducing the total amount of uric acid formed.

Non-purine inhibitor of xanthine oxidase:
Febuxostat is a non-purine selective inhibitor of xanthine oxidase, The doses of 80 mg/day and 120 mg/day.

Uricosuric drugs
work by raising the renal clearance of urate,the most used are probenecid, sulfinpyrazone and benzbromarone.
They are valid options as second-line therapy especially if use of allopurinol is problematic.

- Uricase

uricase degrades uric acid to allantoin which is soluble and can be easily disposed.
In humans uricase is a very effective means of preventing and treating tumour lysis syndrome and SUA levels as low as 0.78 ± 0.4 mg/dL (0.05 mmol/L) after 4 h of administration can be achieved .

- Rasburicase, a recombinant uricase, has been now successfully used in unusually severe cases of gout .

- Other drugs

Losartan, calcium pump inhibitors, statins and clofibrate are uricosuric and have a SUA level reducing effect.
They can be useful adjuvants in the management of patients with gout, who can also benefit from their effect in reducing blood pressure and lowering lipids.

Prophylaxis of ULT-induced gouty attacks

Urate lowering frequently induces mobilisation of persisting urate crystals, resulting in the occurrence of acute flares when ULT are started.

This should be explained to the patient and prevented as such flares can make the patient stop taking the ULT.
The daily administration of 0.5–1.5 mg colchicine avoids in most cases such ULT-induced attacks of inflammation

Prophylaxis is recommended during the first 6 months.

Reduce intake of food rich in purine (such as anchovies, herring and animal organs) and alcohol, sugar-sweetened soft drink consumption should also be kept to a minimum, as the latter also is associated with hyperuricaemia, in contrast to diet soft drinks.

Axial Spondyloarthritis

Spondylarthritis (SpA) is a heterogeneous group of chronic inter-related inflammatory arthropathies affecting mainly the spine,sacroiliac joint, but also showing peripheral symptoms in the joints, entheses and certain extra-articular sites.

Forms of Axial Spondyloarthritis include:
Radiographic ankylosing spondylitis (AS) and nonradiograhic AS/axial spondyloarthritis (axial spondyloarthritis).

Reactive arthritis

Arthropathy of inflammatory bowel disease (Crohn’s disease, ulcerative colitis)

Psoriatic arthritis

Juvenile-onset ankylosing spondylitis

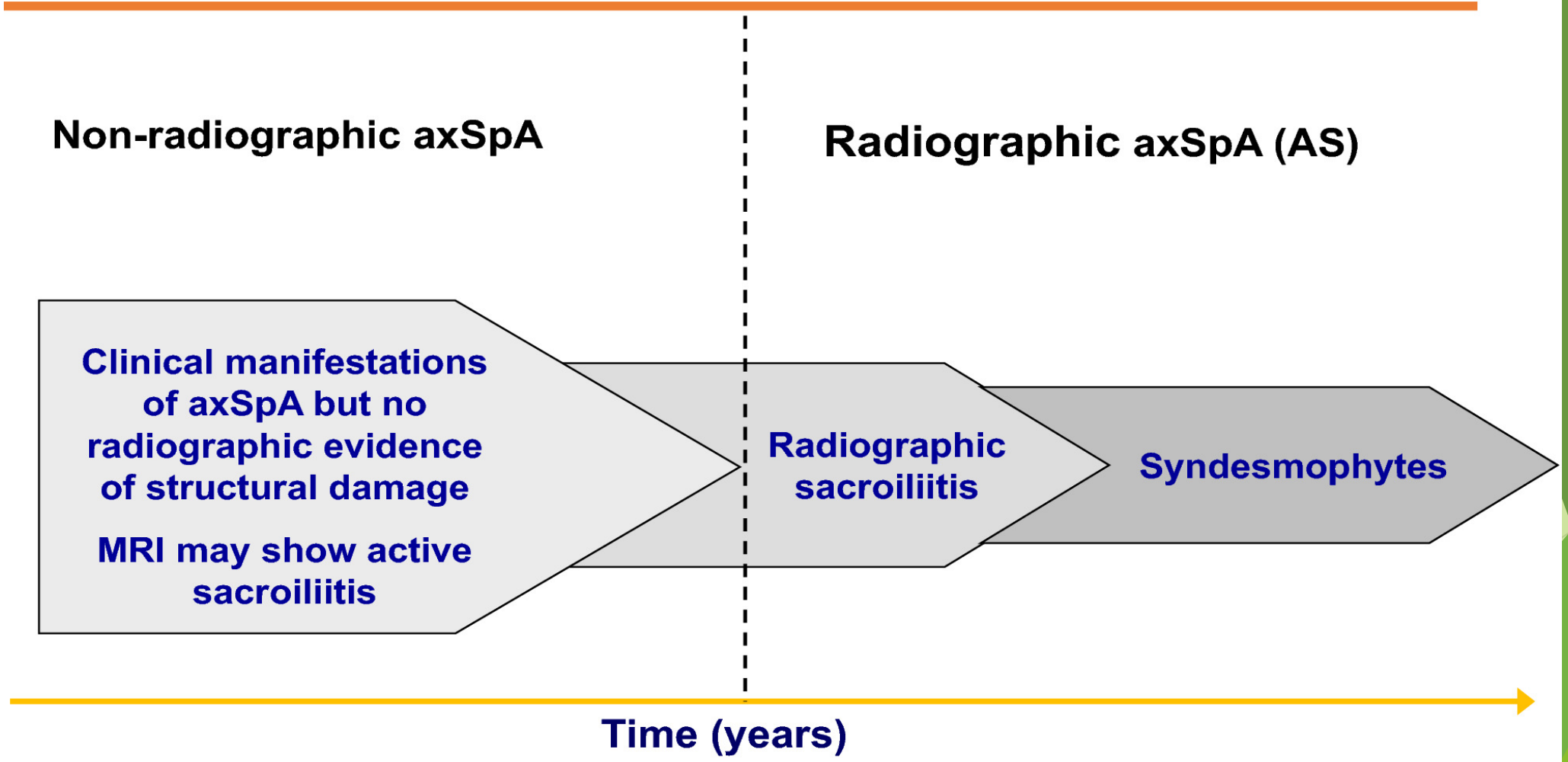
The inflammation of the sacroiliac (SI) joints and the spine eventually may lead to bony ankylosis.
Spinal ankyloses tends to appear in late stages of the disease and does not occur in many patients with mild disease.

Many patients with AS have onset of back pain during the third decade of life.
It takes, on average, 6 to 8 years from the onset of back pain until a clinician establishes a definite diagnosis of AS.

This delay in the majority of patients results from the relatively late appearance of definite radiographic sacroiliitis on conventional plain radiographs.

Active sacroiliitis on MRI predicts the later appearance of sacroiliitis on radiographs,so many patients at an early stage of AS typically are seen with characteristic clinical symptoms of AS, but without definite sacroiliitis on radiographs, and so they may not be classified with AS according to the modified New York criteria.

The Concept of axSpA



Radiographic sacroiliitis such as structural damage of SI joints may develop in a substantial proportion of such patients with time (approximately 20% to 25% over 15 years) and will progress to AS.

This means that a significant proportion of patients will remain at the stage of nonradiographic disease.

The term axial spondyloarthritis (axial SpA) includes both non radiographic AS and classic radiographic AS .

The total prevalence of axial SpA estimated to be two to four times that of AS according to the modified New York criteria.

There is no male preponderance for AS among patients with nr-axial SpA.

prevalence of human leukocyte antigen (HLA)-B27 prevalence varies widely (from 20% to 97%) depending on how patients were included.
At the group level, nr-axial SpA patients tend to respond less favorably to treatment with TNF inhibitors than AS patients by modified New York criteria.

About 5% to 10% of patients with nr-axial SpA develop radiographic sacroiliitis after 5 years follow-up, especially in those with MRI inflammation.

The prevalence of axial SpA among chronic back pain patients is about 5%.

Epidemiology

The prevalence of AS roughly matches the frequency of HLA-B27.

Among whites, the estimated prevalence rate of AS, ranges from 68 per 100,000 in a population older than 20 years in the Netherlands,to 197 per 100,000 in the United States.

In the general population, radiographic AS is likely to develop in approximately 1% to 5% of HLA-B27+ adults who have a disease-associated B27 subtype, although there may be regional or geographic differences.

in northern Norway, radiographic AS may develop in 6.7% of HLA-B27+ people.

The disease is much more common among HLA-B27+ first degree relatives of HLA-B27+ AS patients, roughly 10% to 30% of them have signs or symptoms of AS, and approximately 30% of apparently healthy first-degree relatives fulfill classification criteria for axial SpA.

Positive family history of AS is a strong risk factor for the disease.

The prevalence of axial SpA could be two to four times the prevalence of radiographic AS.

Around 90% of white patients with radiographic AS possess HLA-B27, whereas AS and HLA-B27 are nearly absent (prevalence of B27 <1%) in African blacks and Japanese.

While 50% of black patients with AS possess HLA B27, and therfore african Americans are affected far less frequently than American.

AS is more common in males , with the male: female ratio being 2:1 to 3:1. However this ratio has been found to be more equally distributed between genders in AxSpa.

The mean age of diagnosis is 26 years, but it can present from late adolescence to 45 years of age.

Genetics

The risk for AS runs strongly in families and is largely genetically determined, and that genetic factors also play major roles in determining disease activity and severity.

❑ Major Histocompatibility Complex Associations with Ankylosing Spondylitis

There are more than 100 subtypes of HLAB27 now known, the majority of these subtypes are too rare for us to know whether they are disease associated.

AS occurs with the following HLA-B27 subtypes: B*2702, B*2703, B*2704, B*2705, B*2706, B*2707, B*2708, B*2710, B*2714, B*2715, and B*2719.

2 subtypes appear to show reduced or possibly absent association with AS, HLA-B*2706, which is found in Southeast Asia, and HLA-B*2709, which is found in Sardinia.

HLA-B27 is found in 85% to 95% of cases of primary AS compared with a prevalence in most populations of European descent of approximately 8%.
A lower prevalence of HLA-B27 (~60%) is found in AS associated with psoriasis or IBD.
HLA-B27 homozygotes have roughly double the risk of AS, compared with B27 heterozygotes.

screening of population for HLA-B27 is not recommended as only approximately 5% of HLA-B27 cases develop AS.

Disease develops in HLA-B27 negative individuals on average a decade later than HLA-B27+ individuals, but their disease activity and severity of ankylosis is not different.

It should be noted that HLA-B27 is protective for HIV infection

HLA-B27 is not the only HLA-B allele associated with AS,but also there is a role for HLA-B60 which further increases AS risk by approximately 1.5 fold, and many other HLA-B, HLA-A, and HLA Class II alleles

- Non–major Histocompatibility Complex Associations of Ankylosing Spondylitis

Over 110 non-MHC loci have been convincingly demonstrated to be associated with the disease,in addition to Aminopeptidase Genes and Interleukin-23 Pathway Genes

Classifications of axial spondyloarthritis

Modified New York criteria for ankylosing spondylitis (AS) Diagnosis

- Clinical criteria:

- Low back pain and stiffness for more than 3 months which improves with exercise but is not relieved by rest
- Limitation of motion of the lumbar spine in both the sagittal and the frontal planes
- Limitation of chest expansion relative to normal value, corrected for age and sex.

Radiological criterion (x-ray)

- Sacroiliitis grade ≥ 2 bilaterally or sacroiliitis grade 3–4 unilaterally

Definite Ankylosing Spondylitis
Unilateral grade 3 or 4
or bilateral grade 2 to 4 sacroiliitis and
any clinical criterion

- Grading:

GRADE 0 normal.
Grade 1 suspicious.
Grade 2 evidence of erosion and sclerosis(minimal sacroiliitis).
Grade 3 erosions, sclerosis and early ankylosis(moderate sacroiliitis).
Grade 4 total ankyloses.

ASAS classification criteria for axSpA

Patients with back pain ≥ 3 months and age at onset <45 years.

- Sacroiliitis on imaging*

plus ≥1 SpA feature** or

- HLA-B27

plus ≥2 other SpA features**

*Sacroiliitis on imaging = definite radiographic sacroiliitis according to the modified New York criteria or positive sacroiliac MRI **

SpA features:

- Inflammatory spinal pain
- Arthritis • Enthesitis (heel)
- Uveitis • Dactylitis
- Psoriasis • Crohn's/colitis
- Good response to NSAIDs
- Family history of SpA
- HLA-B27 • Elevated CRP

ASAS, Assessment of SpondyloArthritis international Society; CRP, C-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis

ASAS classification criteria for peripheral SpA

Arthritis or enthesitis or dactylitis (without current back pain) Plus ≥1 of

- Uveitis
- Psoriasis
- Crohn´s/colitis
- Preceding infection
- HLA-B27
- Sacroiliitis on imaging

OR ≥2 of:

- Arthritis
- Enthesitis
- Dactylitis
- IBP (ever)
- Family history of SpA

Clinical Manifestations

- Skeletal Manifestations:

Low Back Pain and Stiffness.

Back pain is common symptom, occurring in as much as 80% of the general population.
so it is important to note that back pain in AS/axial SpA has inflammatory features that differentiate it from mechanical back pain.
Back pain is the most common feature of AS ,
Estimates of the proportion of adults with chronic back pain having IBP vary between 2.3% and almost 25%

The most important predictors for progression of IBP to spondyloarthritis were uveitis, family history of spondyloarthritis,and male gender.

The pain is initially felt primarily deep in the gluteal region, dull in character, idifficult to localize, and is insidious in onset.

It localizes in the SI joints but is occasionally referred toward the iliac crest
or greater trochanteric region or down the dorsal thigh.

Radiation of buttock pain may suggest root compression of the sciatic nerve.
area becomes stiff

The buttock pain typically alternates from side to side. coughing, sneezing, or other maneuvers that cause a sudden twist of the back may accentuate pain.

Although the pain is often unilateral or intermittent at first, within a few months, it usually becomes persistent and bilateral, and the lower lumbar area become painful and stiff.

The pain is associated with a feeling of low back stiffness that is worse in the morning and may awaken the patient from sleep, particularly during the second half of the night.

The morning stiffness may last as long as 3 hours. Both the stiffness and the pain tend to be relieved by a hot shower, an exercise program, or physical activity but they do not improve with rest.
Fatigue is a result of chronic back pain and stiffness may be an important problem and can be accentuated by sleep disturbances due to these symptoms.

Berlin inflammatory back pain criteria

These require a patient to be aged <50 years with chronic back pain (>3 months duration) and at least two of the following:

- Morning stiffness ≥30 min
- Improvement with exercise but not with rest
- Awakening because of back pain during the second part of the night
- Alternating buttock pain

If two of these four criteria are fulfilled, sensitivity is 70% and specificity is 81%. If three out of four criteria are fulfilled, sensitivity is 33% and specificity is 98%.

Chest pain:

The Patients may experience chest pain accentuated by coughing or sneezing, which is sometimes characterized as pleuritic due to the involvement of the thoracic spine (including costovertebral and costotransverse joints) and the occurrence of enthesitis at the costosternal and manubriosternal joints.

chest pain at the sternal region may also be an early manifestation of the disease.

The pain is often associated with tenderness over the costosternal junctions. Also reduction of chest expansion may be detectable in an early stage of AS

Tenderness due to enthesitis:

At certain sites is a prominent complaint in some patients,these lesions are caused by enthesitis.

Common tender sites are the costosternal junctions, spinous processes, iliac crests, greater trochanters, ischial tuberosities, tibial tubercles, and
heels (Achilles tendonitis or plantar fasciitis).

Dactylitis (sausage digit):
Dactylitis is characteristic of SpA, although not entirely specific and also seen in other conditions.
It is not as common in AS but is more typical of ReA, PsA or undifferentiated SpA.
Unlike synovitis, the swelling is not confined to a joint but involves the whole digit (sausage digit).
It is a combination of synovitis, enthesitis, tenosynovitis and soft tissue swelling .

Joints:

The hips and shoulders are the most frequently involved extra-axial joints in AS, and pain in these areas is
the presenting symptom in as many as 15% of patients.

involvement of these joints , may cause considerable physical disability.

Knee and temporomandibular joints can be affected as well.

Ankylosis

Results from ossification of the ligaments and of the costovertebral and sternocostal joints.
The first sign of an abnormal posture is loss of lumbar lordosis, followed by thoracic hyperkyphosis and, in severe cases, forward stooping of the neck.
Spinal movement is restricted in all planes.

However, ankylosis in the thoracic and lumbar spine is not necessarily linked to severe physical limitations unless the hips are affected, in which case bending forward is a major problem.

Ankylosis at the cervical level often has major physical consequences—for example, in driving, as patients cannot turn their head to view cars alongside them.

❑Extramusculoskeletal Manifestations:

Constitutional symptoms such as fatigue, weight loss, and low-grade fever.

Eye Disease:
Acute anterior uveitis (AAU) or iridocyclitis is the most common extra-articular manifestation of AS, occurring in 25% to 30% of patients during the course of the disease.

There is no clear relationship between activity of the articular disease and this extra-articular manifestation.
Eye inflammation is usually acute and typically unilateral, but the attacks may alternate.

Symptoms include: red and painful eye, with visual impairment.
Photophobia and increased lacrimation .

If the eye remains untreated or if treatment is delayed, posterior synechiae and glaucoma may develop.

AAU is more common in B27+ than B27− patients with AS.

Cardiovascular involvement:

May be clinically silent
Manifestations of cardiac involvement include
Ascending aortitis
Aortic valve incompetence due to inflammation and dilation of the aorta
Conduction abnormalities, increasing with time and disease progression.
Cardiomegaly, and pericarditis.
Aortic incompetence in late stages of the disease.

In AS the prevalence of myocardial infarction is increased (4.4%) compared with 1.2% in the general population.

Pulmonary Disease

Rare and late manifestation of AS
slowly progressive fibrosis of the upper lobes of the lungs, appearing, on average, 2 decades after the onset of AS.

Vital capacity and total lung capacity may be moderately reduced as a consequence of the restricted chest wall movement, whereas residual volume and functional residual capacity are usually increased.

Neurologic Involvement:

Can be caused by vertebral fracture, instability, compression, or inflammation.

Minor trauma can cause fractures of a vulnerable osteoporotic spine.

The C5-C6 or C6-C7 level is the most commonly involved site.

Atlantoaxial joint subluxation, atlanto-occipital subluxation, and upward subluxation of the axis may occur in AS as a consequence of instability resulting from the inflammatory process.

Spontaneous anterior atlantoaxial subluxation is a well-recognized complication in approximately 2% of patients and manifests with or without signs of spinal cord

Nontraumatic neurologic complications caused by compression include ossification of the posterior longitudinal ligament (which may lead to compressive myelopathy).

The cauda equina syndrome is a rare but serious complication of long-term AS, the syndrome affects lumbosacral nerve roots, this gives rise to pain and sensory loss, but frequently there are also urinary and bowel symptoms.

Renal involvement

IgA nephropathy

Amyloidosis is a very rare complication in severe longstanding disease.

Renal deficit is more commonly a result of NSAID related toxicity.

Gastrointestinal involvement

IBD may or may not have already been diagnosed in these patients.
The prevalence of IBD in AS has been reported to range between 6-15%.

About 28–35% of patients with enteropathic arthritis have axial disease:
10–20% have sacroiliitis alone,
7–12% have spondylitis and 10% have the classic features of SpA.

The axial radiology is similar to that of AS, characterised by symmetrical bilateral sacroiliitis.
The onset of axial involvement often precedes that of bowel disease.

Dermatological manifestations are common but are usually related to a specific disorder such as psoriasis or ReA. Psoriasis is seen in 20–40% of patients with SpA.

Osteoporosis

Decreased bone mineral density (BMD) can be seen in early stages of AS.

Osteoporotic deformities of the thoracic spine contribute significantly to abnormal posture, particularly fixed hyperkyphosis.

An increased occiput-to-wall distance is associated with vertebral fractures.

Symptomatic osteoporotic spinal fractures are increased in AS.

Proper assessment of bone density in the spine is difficult in the presence of syndesmophytes because they may give rise to falsely high BMD readings.

Psoriasis

- Psoriasis is a common skin disease ,It affects men and women equally.

About 10–20% of patients have associated PsA.

Psoriasis usually predates the appearance of arthritis, but the onset is simultaneous in 20% of patients, and in up to 15% the arthritis may precede the onset or diagnostic recognition of psoriasis. The arthritis usually starts between 30 and 50 years of age.

In most patients, exacerbations and remissions of skin and joint involvement occur with little or no apparent relationship.

axial skeleton involvement in 20-40% of cases.

dominant axial disease (~5%).

Inflammatory Bowel Disease

Enteropathic arthritis describes the occurrence of inflammatory arthritis in patients with ulcerative colitis or Crohn's disease.

The prevalence of arthritis in IBD ranges from 10% to 20%, with a higher prevalence in Crohn's disease.

The most common manifestation of enteropathic arthritis is inflammation of the knee and ankle joints as part of a peripheral oligoarthritis.

Axial involvement estimated to occur in 4 to 10% of patient with IBD.

- Intestinal symptoms usually antedate or coincide with joint manifestations, but arthritis may precede the intestinal symptoms by years.

Reactive arthritis

- ReA describes an episode of aseptic peripheral arthritis that occurs within 1 month of a primary infection elsewhere in the body, usually a genitourinary infection with Chlamydia trachomatis or enteritis due to Gram-negative enterobacteria such as Shigella, Salmonella, Yersinia or Campylobacter species.

- Genitourinary tract infection with Chlamydia trachomatis is the most commonly recognised initiator of ReA in developed countries, whereas infections with enterobacteria are the most common triggers in developing parts of the world .

In about 25% of cases, however, the triggering organism is unknown

ReA is typically an acute, asymmetrical oligoarthritis and is often associated with one or more characteristic extra-articular features, such as ocular inflammation (conjunctivitis or acute iritis), enthesitis, mucocutaneous lesions, urethritis and, on rare occasions, carditis.

Conjunctivitis occurs in one-third of patients, usually at the same time as arthritis flares, and acute anterior uveitis may occur at some time in about 5% of patients.

The triad of arthritis, conjunctivitis and urethritis is called classic ReA. However, most patients with ReA do not present with this triad.

The average duration of arthritis is 4–5 months, but two-thirds of patients have mild musculoskeletal symptoms that persist for more than 1 year.

Recurrent attacks are more common in patients with chlamydia-induced ReA.

About 15–30% of patients develop chronic or recurrent peripheral arthritis, sacroiliitis or spondylitis.
Most patients with chronic ReA have a positive family history of SpA or are HLA-B27 positive.

Laboratory features

ESR and CRP are raised in 40% of patients.
Increased CRP is one of the features of SpA used in the ASAS classification for axSpA, but must be present with other features.

A mild normochromic normocytic anaemia of chronic disease
Alkaline phosphatase may also be raised(derived from bone) but this does not correlate with disease activity.

Some elevation of serum IgA is frequent in AS, its level correlates with acute phase reactants.

The diagnosis of SpA is unlikely when imaging and HLA-B27 are both negative.

Active disease is associated with decreased lipid levels, particularly high-density lipoprotein cholesterol, resulting in a more atherogenic lipid profile.

imaging

The earliest, most consistent, and most characteristic findings are seen in the SI joints.

The radiographic findings of sacroiliitis consist of:

blurring of the subchondral bone plate, followed by erosions and sclerosis of the adjacent bone.

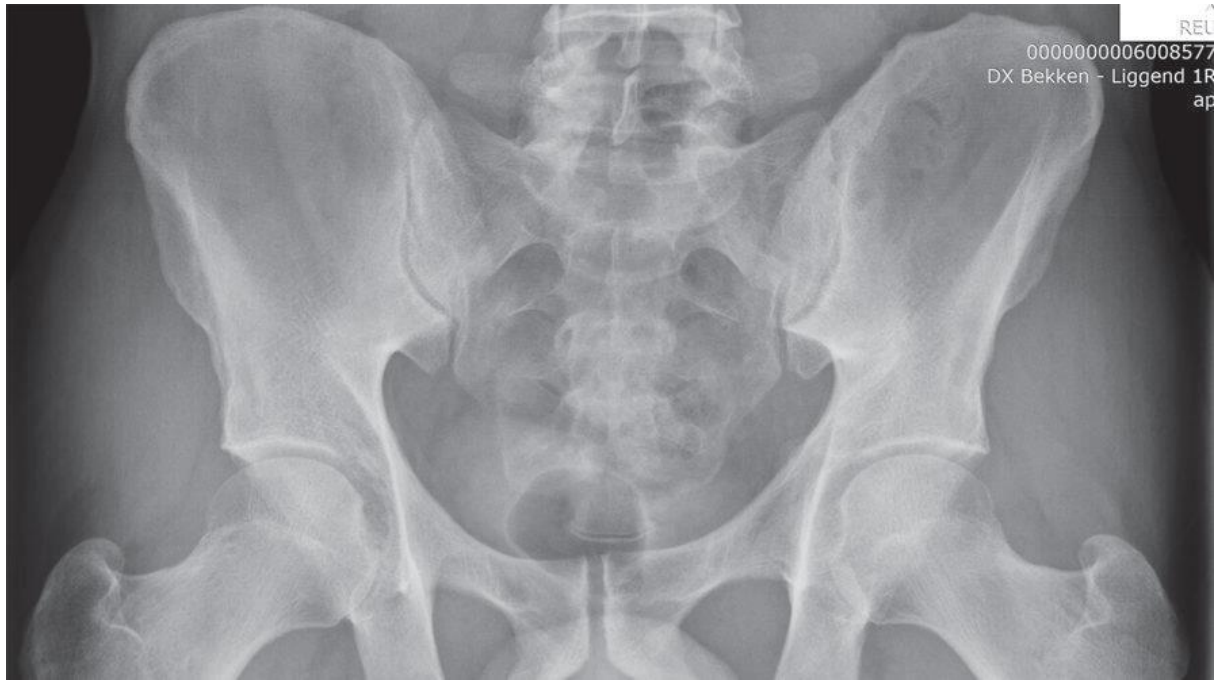
The changes in the synovial portion of the joint (the lower one-third of the joint)

Progression of the subchondral bone erosions can lead to pseudowidening of the SI joint space.

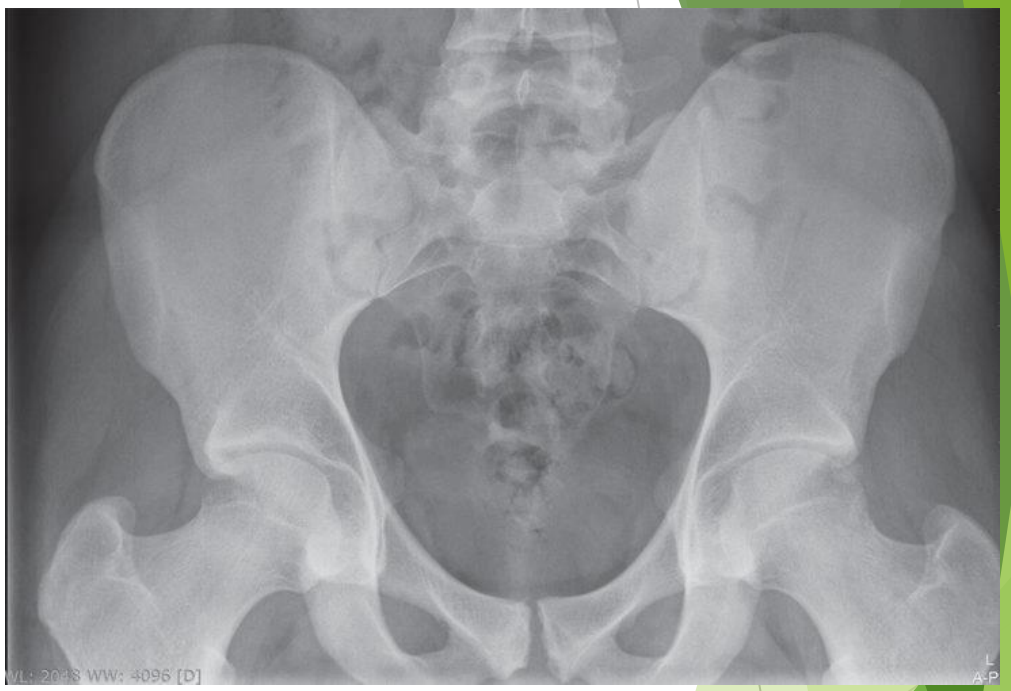
With time, gradual fibrosis, calcification, interosseous bridging, and bony ankylosis occur.

Joint changes usually become symmetrical during the course of the disease.

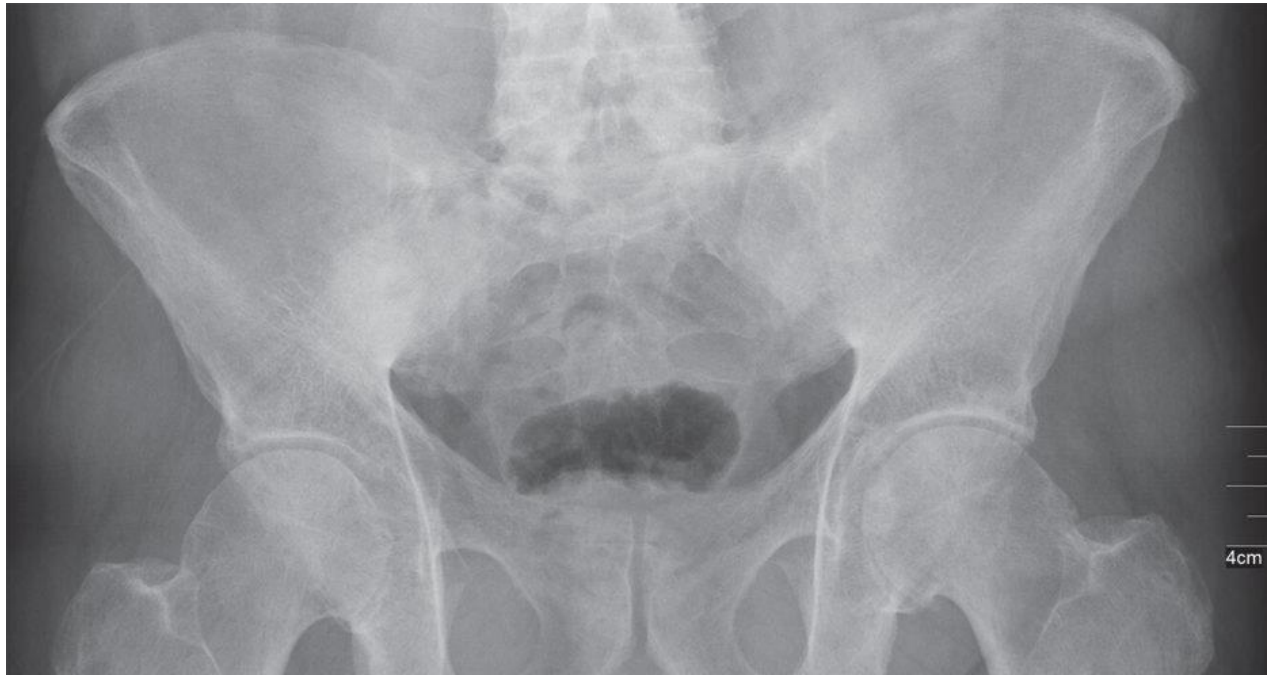
Radiographic sacroiliitis can be graded according to the New York grading system as follows
grade I suspicious,
grade II evidence of erosion and sclerosis,
grade III, erosions, sclerosis and early ankyloses,
grade IV, total ankylosis.



No abnormalities on the SI joints.



Bilateral grade 2 sacroiliitis (irregularity of the articular surface of the SI joint bilaterally due to erosions with sclerotic changes on the iliac side of the SI joint.

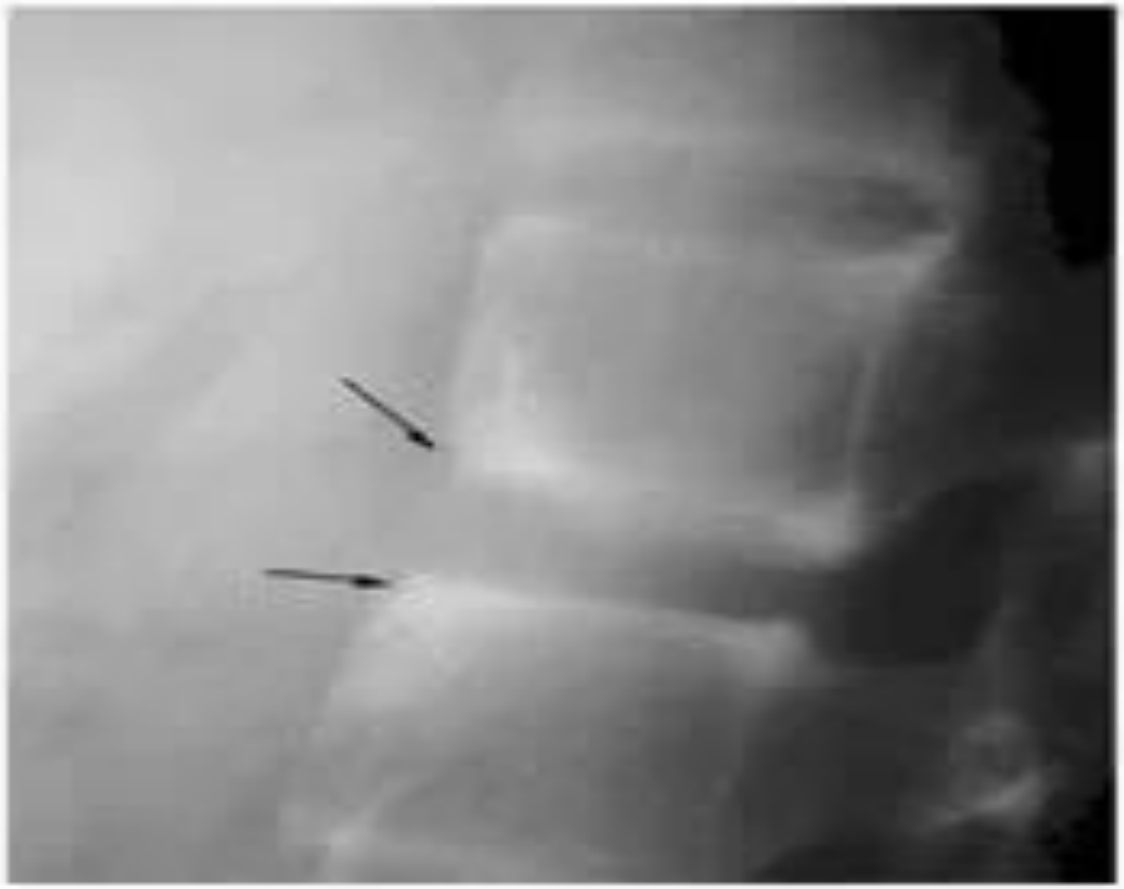


Bilateral grade 4 sacroiliitis with fusion of the SI joints.

Bony erosions and osteitis (“whiskering”) at sites of osseous attachment of tendons and ligaments are seen, particularly at the calcaneus, ischial tuberosities, iliac crest, and spinous processe of the vertebrae.

Inflammation of the superficial layers of the annulus fibrosus, leads to erosion of the adjacent corners of the vertebral bodies visible on radiography.

Tissue repair leads to “squaring” of the vertebral bodies and reactive bone sclerosis, which constitute the Romanus lesion seen on radiography.



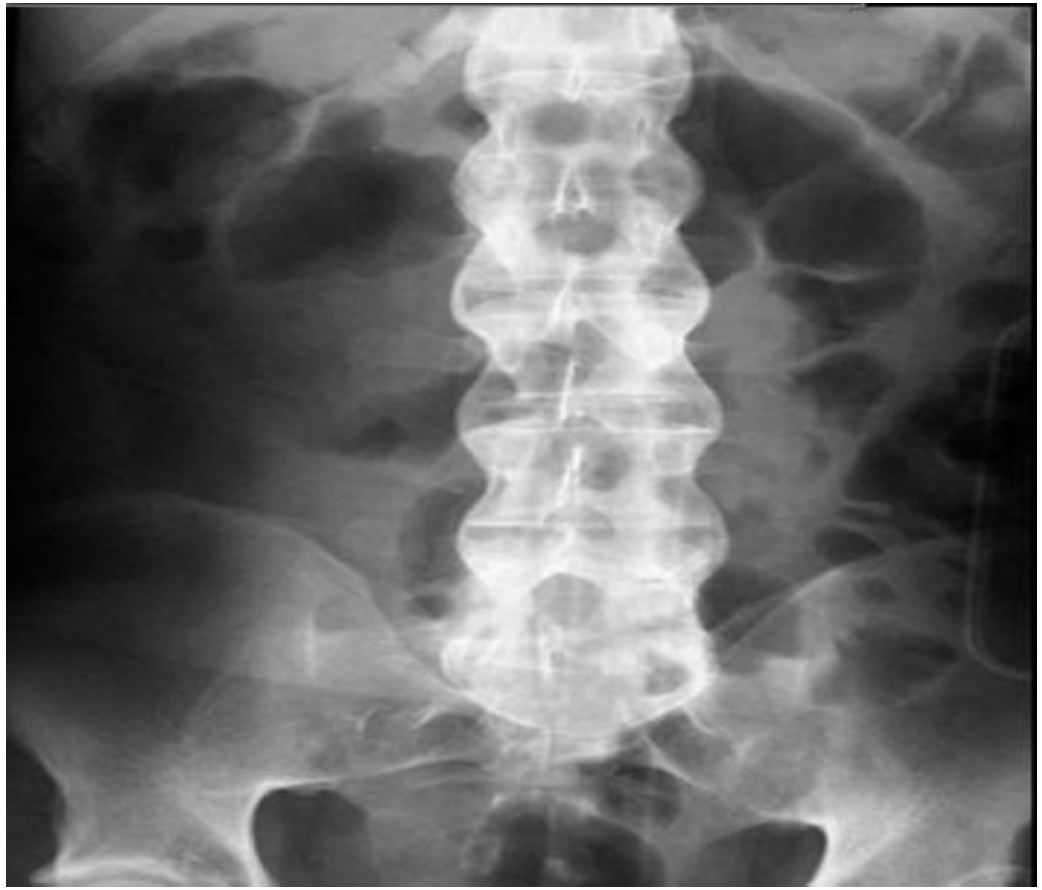
Anterior corner erosions at the T12 and L1 vertebral bodies , the typical shiny corner sign (or Romanus lesion) is present (arrows)

Gradual ossification of the annulus fibrosus may lead to complete bony “bridging” between vertebrae.

Concomitant ankylosis often occurs in the apophyseal joints, with ossification of the adjacent ligament, this may result in complete fusion of the vertebral column (“bamboo spine”).

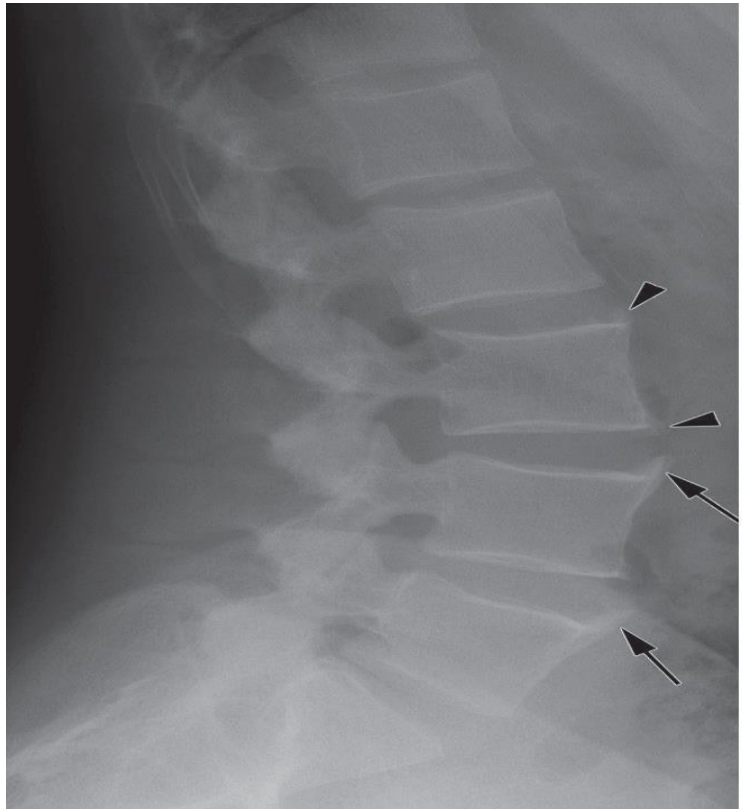
AS and enteropathic axial spondyloarthrits typically exhibit bilateral symmetrical sacroiliitis and continuous syndesmophytes, while in ReA and PsA characteristically exhibit asymmetrical sacroiliitis and discontinuous spondylitis.

Radiographs of other areas such as the heel or hip might show evidence of enthesitis

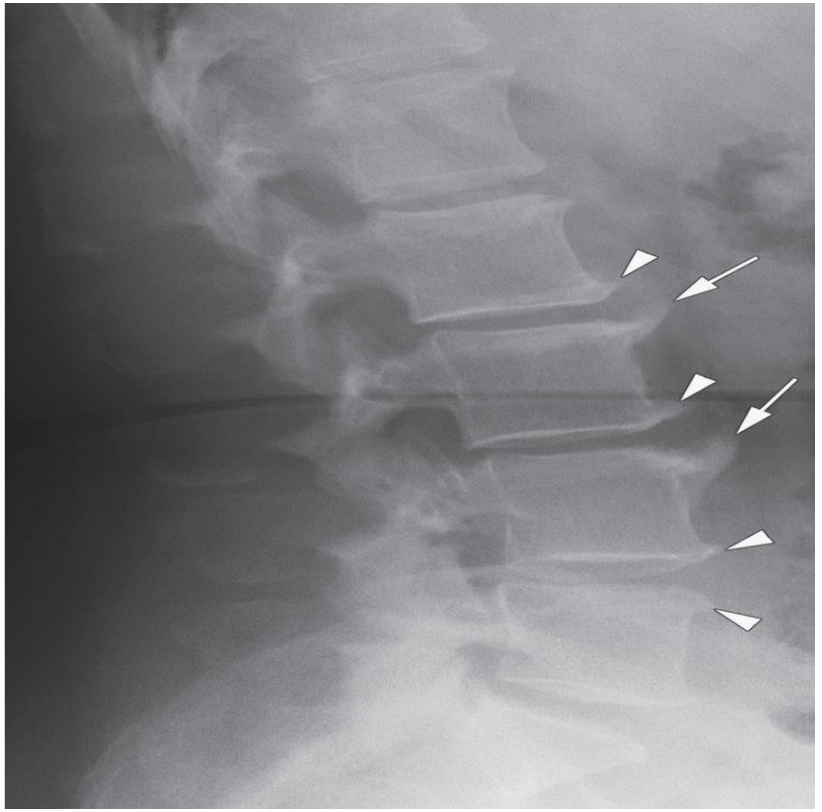


(“bamboo spine”).

syndesmophytes are usually thinner than spondylophytes, their identifying feature is the vertical growth direction alongside the annulus fibrosus fibres.
spondylophytes are rather bulgy and growth starts primarily horizontal in direction



Evidence of large syndesmophytes (black arrows) at the anterior edges of the upper endplates of L4 and L5 ,also early syndesmophytes growing at L3 (black arrowheads



spondylophytes (osteophytes)

MRI can detect inflammatory lesions long before definite lesions are visible on plain radiographs.

MRI evidence of sacroiliitis (positive MRI findings)

following findings are required:

- Active inflammatory lesions of the SI joints, BMO (on STIR) must be clearly located in typical anatomical areas (subchondral or periarticular bone marrow).
- When a solitary BMO lesion is seen, this should be present on at least two consecutive slices.
- When more than one BMO lesion is seen on one slice, documentation of inflammation by using one single slice only is sufficient.
- The presence of synovitis, enthesitis or capsulitis without concomitant BMO/osteitis is not sufficient for diagnosis.

definition of a ‘positive’ MRI of the spine.
According to this definition, evidence of spondylitis in three or more vertebral sites is highly suggestive of inflammatory lesions related to axSpA, while evidence of fatty deposition in several vertebral sites (at least 5) is highly suggestive of post inflammatory lesion-related axSpA.

Other imaging modalities
Bone scintigraphy is not recommended for identification of sacroiliitis or spondylitis in the context of axSpA owing to the associated radiation exposure and its low sensitivity (50–55%) and specificity (<80%).

Ultrasound of SI joints is also not frequently used
owing to lack of standardisation of both its use and interpretation of findings.

Computed tomography (CT) seems to have only an additional value in detection of structural changes but is also associated with higher radiation exposures, which is an important limiting factor for its use in daily routine.

management

Non-pharmacological treatment:
The cornerstone of non-pharmacological treatment is regular exercise and patient education.

It has been shown that regular exercises are effective in reducing pain and preserving functioning.
Overall, supervised exercises are more effective than home exercises

Exercises
Preferably, they should be started after a hot shower or a hot bath.
Swimming and extension-promoting exercises are appropriate.

These activities counteract the kyphotic effects of pain and fatigue on posture and reduce stiffness.
Patients should avoid vigorous or contact sports if the spine has become fused or osteoporotic because such a spine is susceptible to fracture.

Pharmacological treatment:

NSAIDs is recommended as first-line therapies in patients with SpA.

Anti-TNF therapy
Five TNF inhibitors are of proven benefit in AS
infliximab, etanercept, adalimumab, certolizumab, and golimumab .

In nr-axSpA, adalimumab, certolizumab, etanercept, and golimumab have been studied.

Infliximab is an IgG1 chimeric monoclonal antibody, with the Fab portion derived from the mouse.
Etanercept is a recombinant TNF receptor IgG1 fusion protein that is self-administered by subcutaneous injection .

Adalimumab and golimumab are human monoclonal antibodies that are self-administered by subcutaneous injection.

Certolizumab is a pegylated Fab fragment of a humanized TNFi monoclonal antibody that is given as a subcutaneous injection .

Anti-IL-17A drugs

Secukinumab, a fully human monoclonal antibody against IL-17A.

Janus Kinase (JAK) Inhibitors
Tofacitinib, a JAK 1,3 inhibitor.
Filgotinib, a JAK 1 inhibitor.

Consideration of Extramusculoskeletal Manifestations

If a patient also has IBD, then prescribing a TNFi that is a monoclonal antibody is recommended. Adalimumab, golimumab, and infliximab are approved for ulcerative colitis, while adalimumab, certolizumab pegol, and infliximab are approved for Crohn's disease.

In patients with frequently recurrent anterior uveitis,consideration for the use of a monoclonal antibody is also recommended.
In this case, the best evidence exists for adalimumab and infliximab.

The use of DMARDs in patients with AS did not show an effect on axial symptoms, so their use for axial disease is not recommended where biologic agents are available.

Surgery might be required in patients with AS with hip involvement, severe spinal deformity or vertebral fracture.

THANK YOU FOR YOUR ATTENTION