Rheumatoid arthritis

Fatima Alnaimat, MBBs, CCD

A case..

A 20 year old female comes to see you because 4 months ago she began having pain and stiffness in the MCPs and wrists.

The symptoms are worse in the morning lasting for 1 hour and improve with movement.

There is fatigue but no other problems identified on review of systems.

On exam the wrists are slightly swollen and tender and MCPs are tender but not swollen.

Can this be rheumatoid arthritis?

Rheumatoid arthritis

Rheumatoid arthritis is a chronic, progressive inflammatory disease affecting primarily the small joints of the hands, feet, wrists and ankles in a symmetric fashion and characterized by the presence of erosions on radiographs.

Epidemiology of RA

The overall world prevalence of RA is approximately 0.5% to 1%

Females are 2.5 times more likely to be affected than males

Peak incidence 4^{th} and 5^{th} decades but can occur at any age

Unknown cause of RA. ?RA is the result of an environmental exposure or "trigger" in genetically susceptible individual

Lower incidence in women on oral contraceptives compared with women who never took oral contraceptives

Both female subfertility and the immediate postpartum period after a first pregnancy (especially when breastfeeding) appear to increase the risk of RA.

Epidemiology of RA

Viral infections, such as those of Epstein-Barr virus, parvovirus, and bacterial infections with organisms such as Proteus and Mycoplasma can trigger RA.

Cigarette smoking appears to be associated with an increased risk of RA, and the severity of the disease especially in those who are seropositive.

Epidemiology of RA

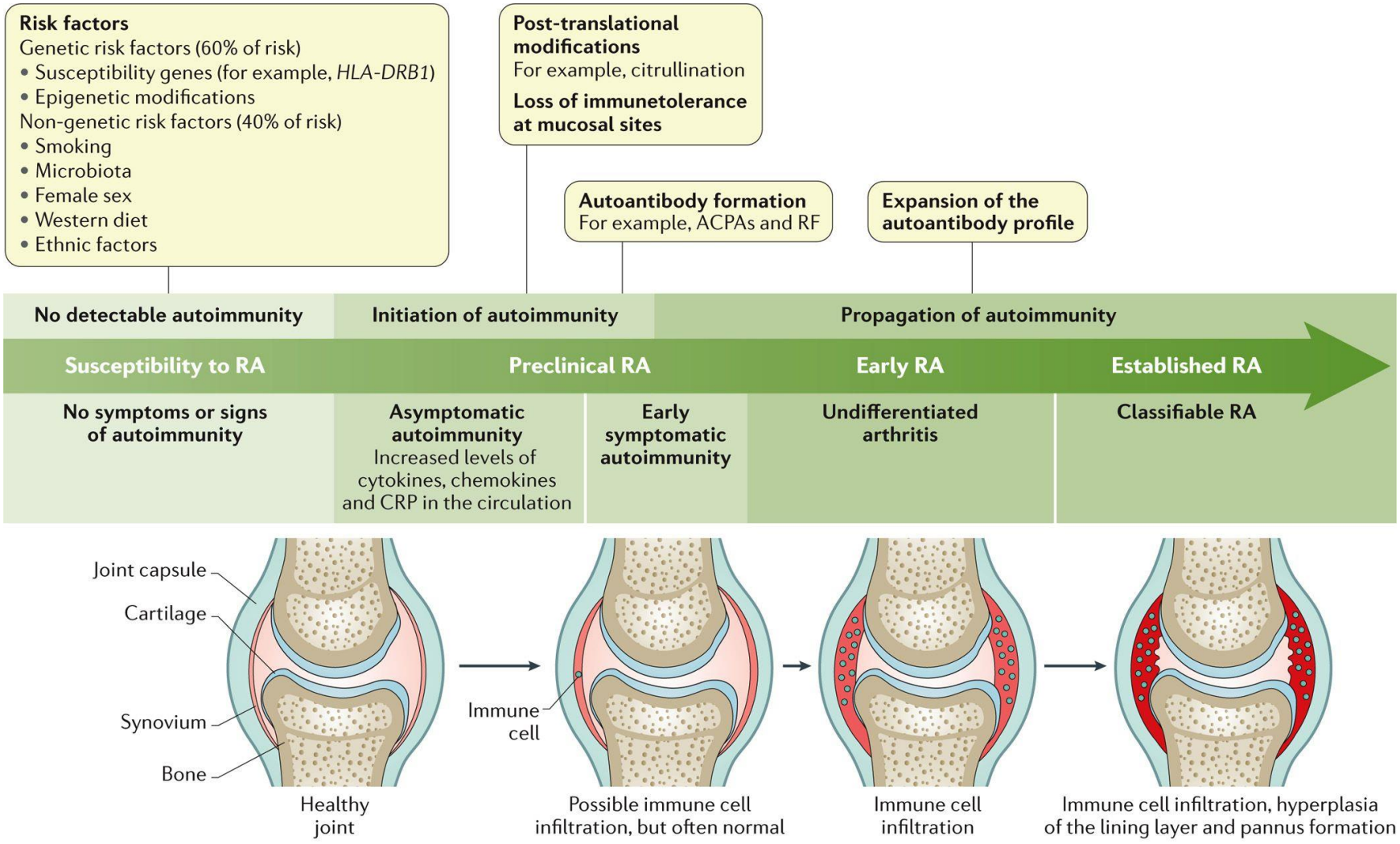
Twin studies show concordance rates of 15% to 30% between monozygotic twins and 5% among dizygotic
twins

Differences in human leukocyte antigen (HLA)-DRB1 alleles, especially in patients positive for RF and ACPA, affect both disease susceptibility and disease severity.

An increased incidence of RA in HLA-DRB1 individuals
who smoke cigarettes.

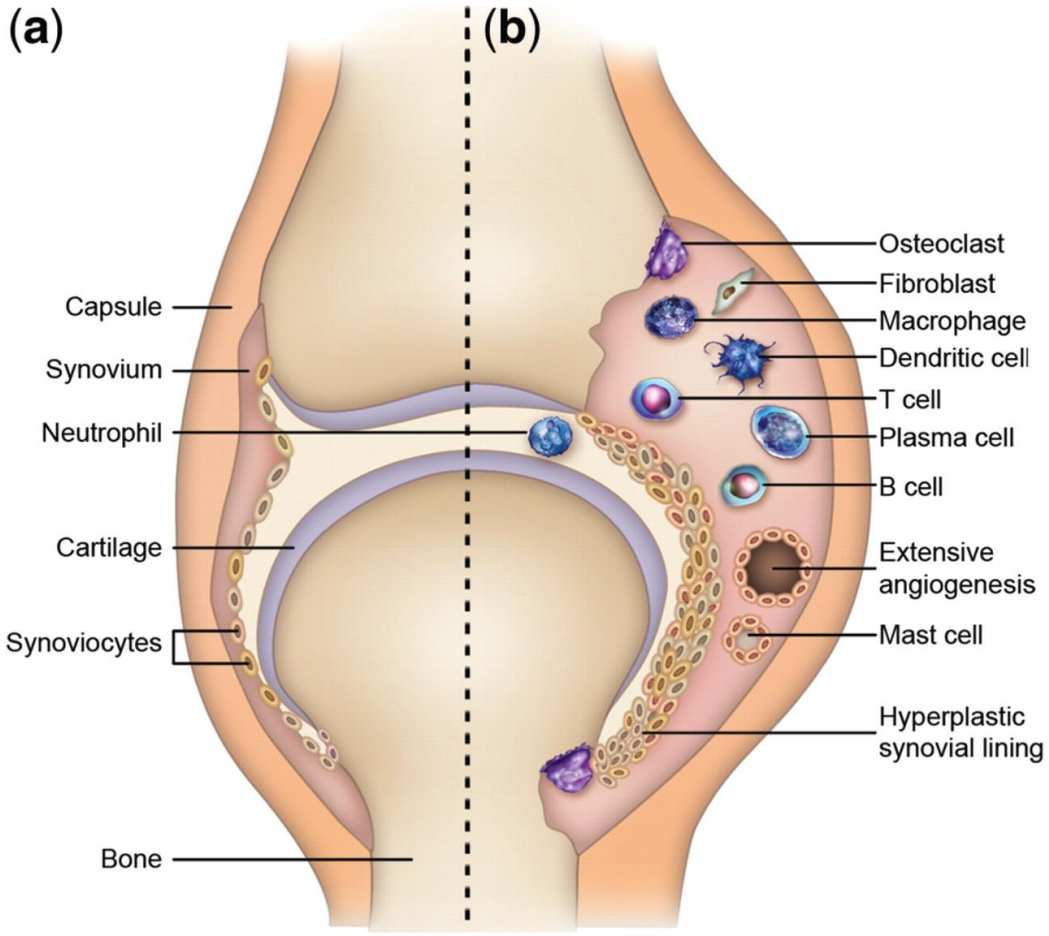
Chromosome 6, which contains the genes for HLA-DRB1, influences a number of immune processes, including production of tumor necrosis factor (TNF).

Pathogenesis of RA



Nature Reviews | Disease Primers

Fig. 1 Schematic view of a normal joint (a) and a joint affected by RA (b) [12].
The joint affected by RA (b) shows ...



Rheumatology, Volume 51, Issue suppl_5, July 2012, Pages v3–v11, https://doi.org/10.1093/rheumatology/kes113

Initial clinical presentation

Most common: gradual onset of polyarticular symmetric joint pain and swelling.

Initially, the small joints in the hands, wrists, and feet are involved

Arthritis symptoms can affect the patient's capacity to perform the activities of daily living (eg, walking, stairs, dressing, use of a toilet, getting up from a chair, opening jars, doors, typing) and their ability to do their job.

Other initial clinical manifestation

Palindromic rheumatism :

Episodic joints involvement with one to several joint areas being affected sequentially for hours to days, alternating with symptom-free periods that may last from days to months

Up to 50 % of patients progress to full blown RA

The presence of anti-citrullinated peptide/protein antibodies (ACPA) might predict progression of palindromic rheumatism to RA

The use of hydroxychloroquine in such patients may reduce the risk of progression to RA.

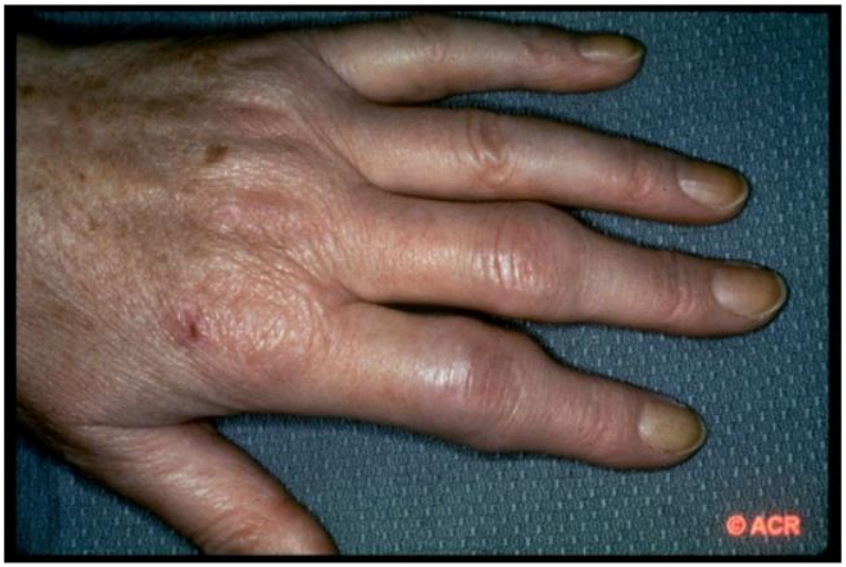
Other initial clinical manifestation

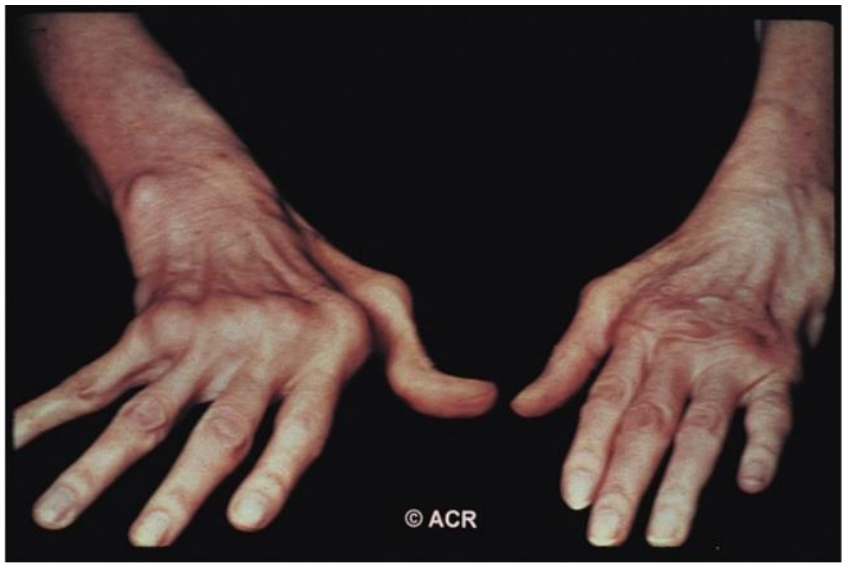
Monoarthritis: may be the sole manifestation of RA or may precede the onset of polyarticular disease.

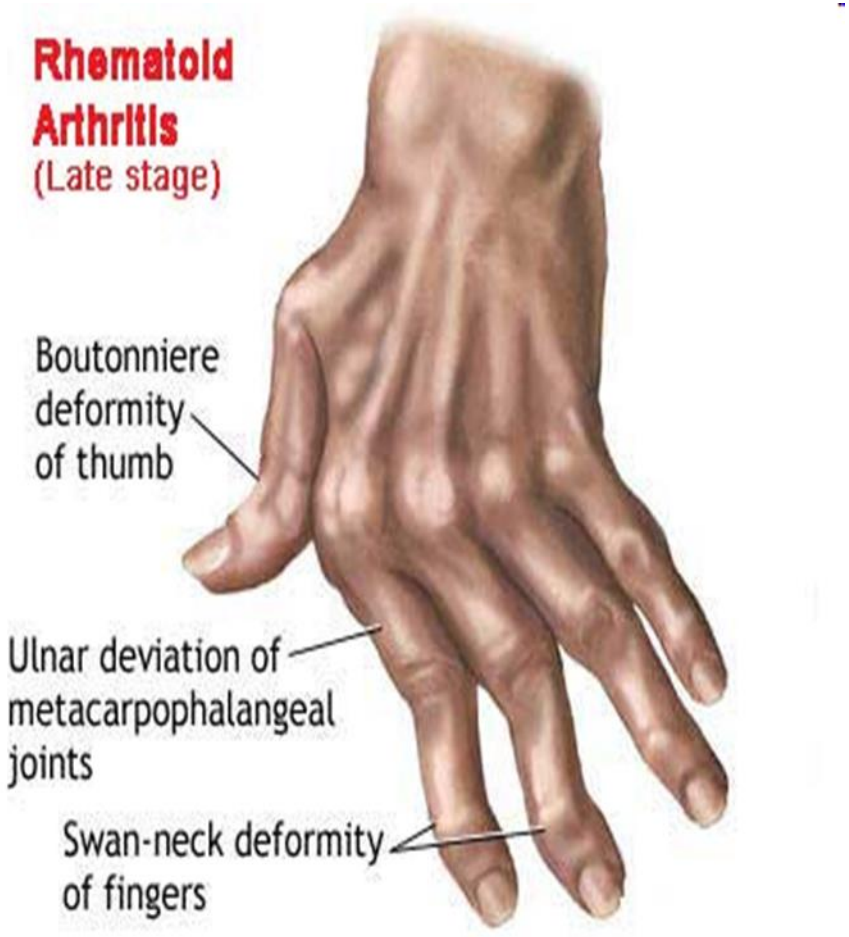
Systemic symptoms : 1/3 of patients: myalgia, fatigue, low-grade fever, weight loss, symptoms of bilateral carpal tunnel syndrome and depression.

Extraarticular involvement : most common is secondary Sjogren's syndrome (35% of pts), rheumatoid nodules (25% of pts), or episcleritis may also be present at time of initial diagnosis.

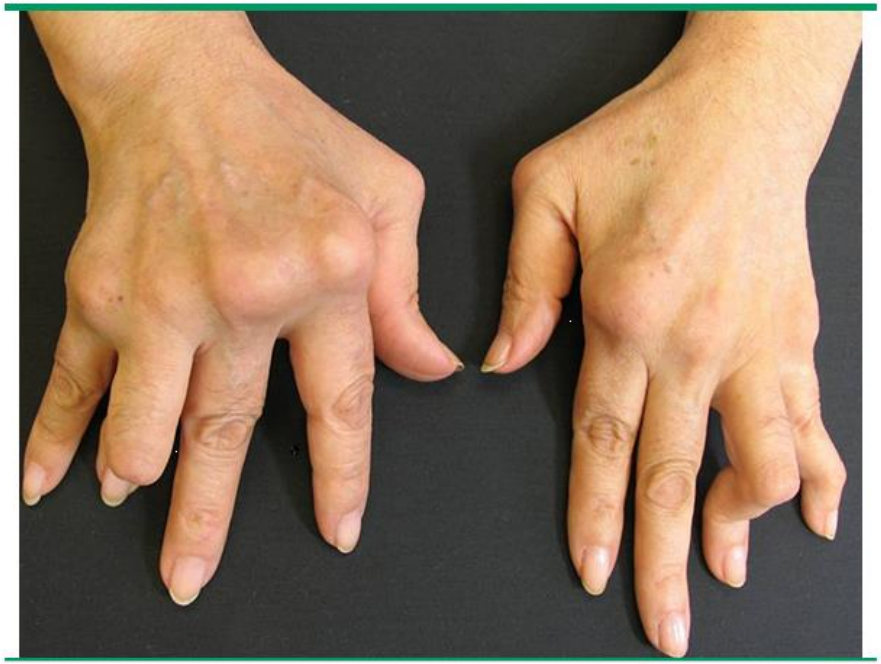
Physical exam





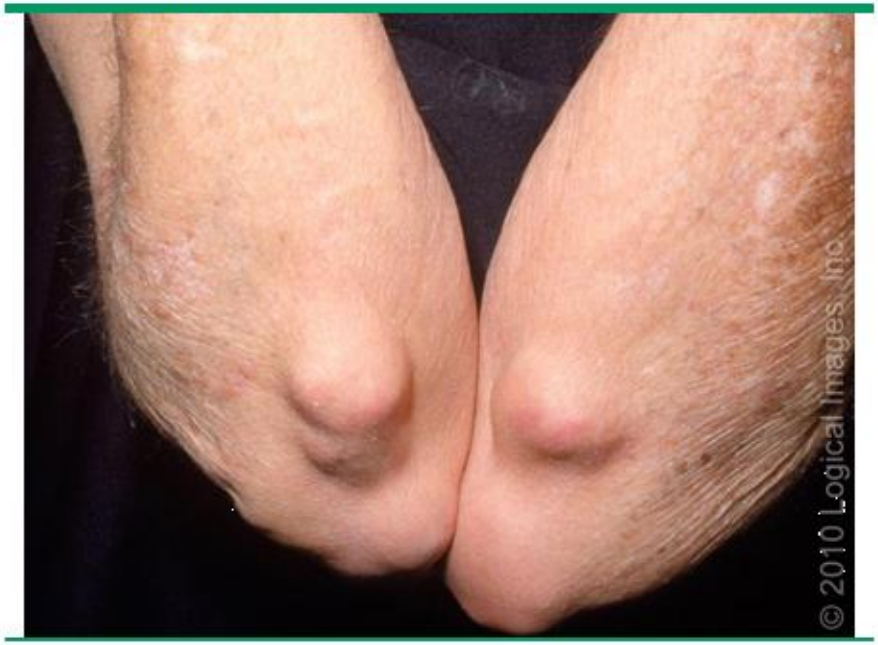

Rhematoid
Arthritis
(Late stage)
Boutonniere
deformity
of thumb
Ulnar deviation of
metacarpophalangeal
joints
Swan-neck deformity
of fingers

Rheumatoid arthritis hand deformities: Boutonniere deformity and Z-deformity of the thumb



A woman with longstanding rheumatoid arthritis has soft tissue swelling and subluxation of the metacarpophalangeal joints. The right thumb shows hyperextension of the interphalangeal joint (a Z deformity). Both ring fingers have boutonniere deformities with flexion of the proximal and hyperextension of the distal interphalangeal joints.

Rheumatoid nodules



Rheumatoid nodules are firm, nontender lesions that typically occur in areas of trauma in individuals with rheumatoid arthritis. Nodules are present near the elbows in this patient.

Laboratory findings

CBC:

Anemia: Most RA patients are anemic (anemia of chronic disease, NSIADs induced anemia of blood loss ..etc)

Leucopenia: Felty's syndrome (splenomegaly and neutorpenia in long standing RA) or medications- induced

Thrombocytosis (inflammation) or **thrombocytopenia**(Felty's or medications)

KFT/LFT : usually normal (but needed as baseline prior to initiation of medications)

ESR: elevated

CRP: elevated

RA markers

Rheumatoid factor

Antibodies(Mostly IgM) against the Fc portion of IgG.

Found in 75% of RA pts: some pts are negative in the first 6 months of the illness but later seroconvert to positive.

66% sensitive and 82 % specific to RA

High titer is indicative of more aggressive and erosive disease and extraarticular manifestations.

Differential of positive RF beside RA (usually low titer) : bacterial endocarditis, HCV with cryoglobulinemia, aging and primary billiary cirrhosis.

RA markers

ACPA or CCP antibody:

Antibodies against the citrullinated residues of proteins.

Citrullination is a non naturally occurring process resulting in the generation of amino acid citrullin via the enzyme peptidylarginine deiminase (PAD).

70% sensitive but 95% specific to RA.

Indicative of more severe erosive disease especially in smokers and carrier of the shared epitope (HLA-DRB1)

Both RF and ACPA can be found in patients 10 years prior to the onset of RA.

*****Small percentage of patients remain seronegative for both RF and ACPA throughout their illness**

ANA

can be found in 20-30 % of RA specially those with high titer RF and extra articular manifestations.

Other laboratory investigations

Synovial fluid: WBC elevated , mostly neutrophils

Pleural fluid: exudative: low to mildly elevated WBC, low glucose, high LDH, and high protein.

Imaging findings

X-rays:

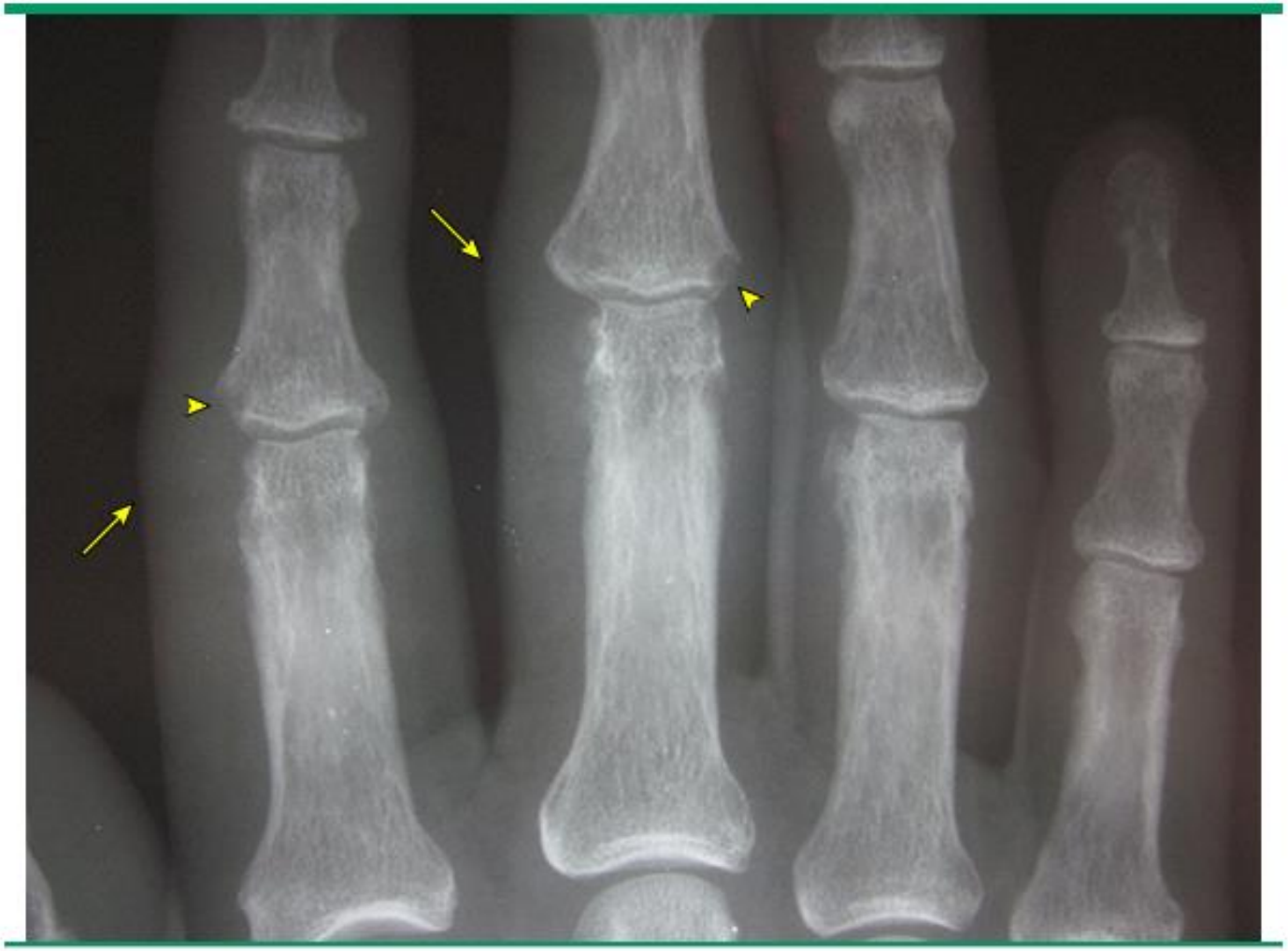
Periarticular osteopenia (Earliest finding), Uniform joint space loss, bone erosions (at the margins of the joints) , and soft-tissue swelling

Late findings : joint subluxation and loss of joint alignment and secondary osteoarthritis changes(osteophytes and cysts).

Target sites of rheumatoid In the ***hands arthritis include the MCP's, PIP's, radiocarpal, and distal radioulnar joints, with predilection for the ulnar styloid process***

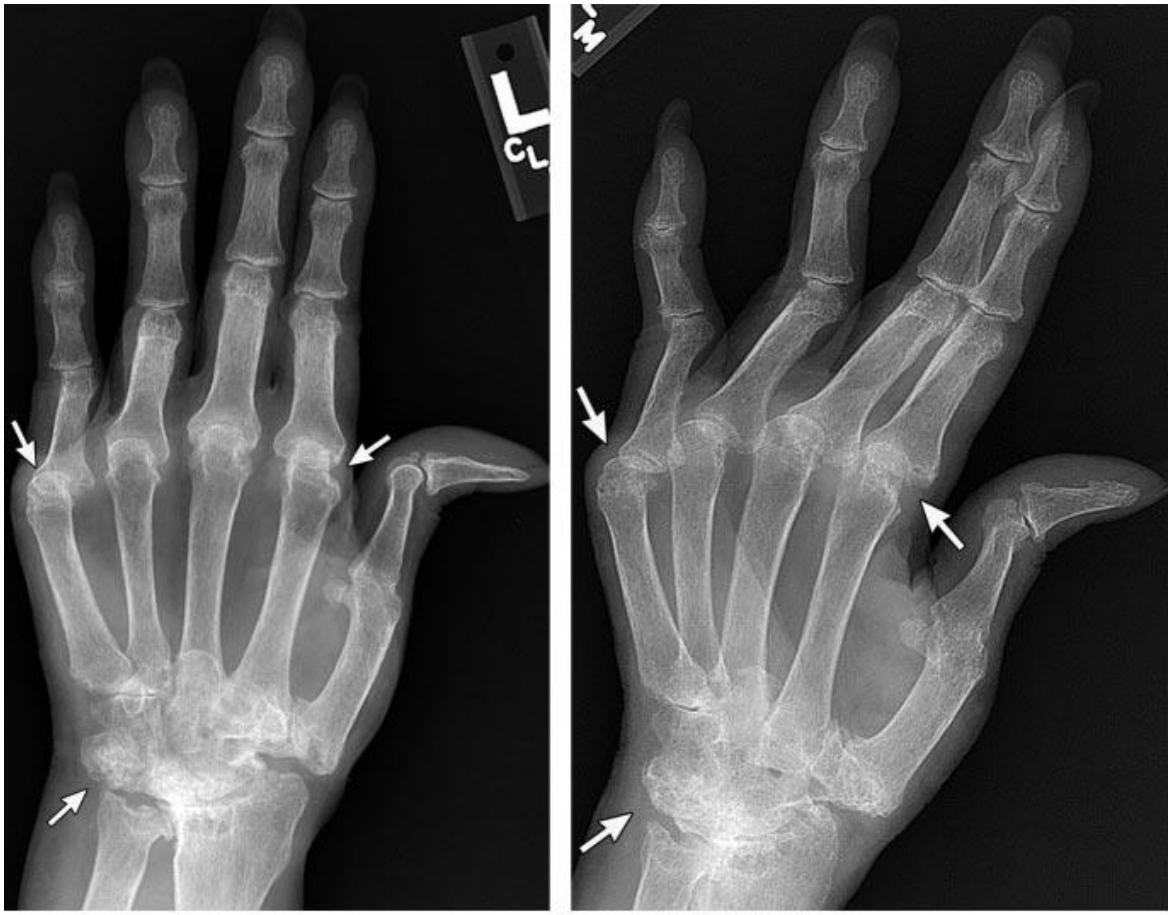
****We always obtain base line hands and feet x-rays in RA patients and repeat them to follow disease progression and response to treatment.

Plain radiograph of rheumatoid arthritis proximal interphalangeal joint erosions

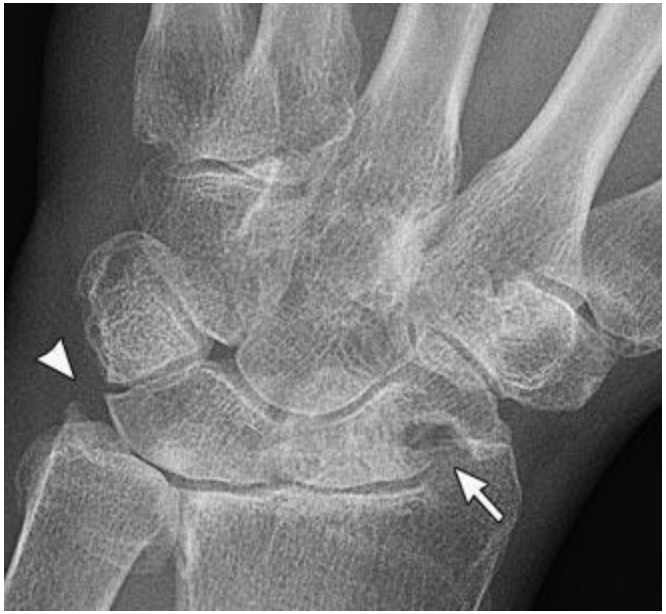


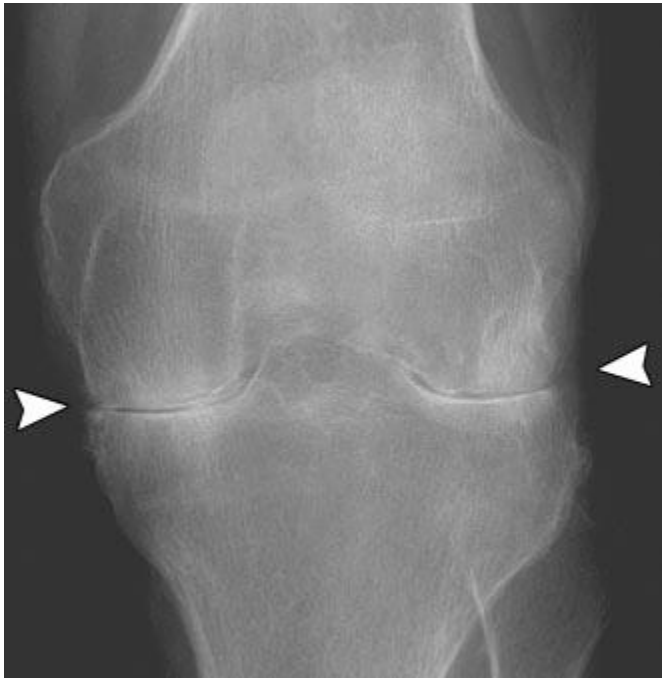
The plain x-ray of the right hand magnified at the proximal interphalangeal joints shows soft tissue swelling (arrows) and mild erosive changes (arrowheads).

Courtesy of Richard Waite, MD.



a. b.





Other Imaging

MRI:

For early RA with subtle synovitis and evaluation for tenosynovitis

MSK ultrasound:

For subtle synovitis, erosions and monitoring disease activity.

Bone scan:

? Polyarticular joints involvement with questionable synovitis

ARTHRITIS & RHEUMATISM
Vol. 62, No. 9, September 2010, pp 2569–2581
DOI 10.1002/art.27584

Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and www.interscience.wiley.com

2010 Rheumatoid Arthritis Classification Criteria

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

2010 ACR/EULAR RA Classification Criteria

Swollen/Tender Joints (0-5)	
0	1 large joint
1	2-10 large joints
2	1-3 small joints
3	4-10 small joints
5	> 10 joints (≥ small joint)

Symptom Duration (0-1)	
0	< 6 wk
1	≥ 6 wk

Acute-Phase Reactants (0-1)	
0	Normal CRP and normal ESR
1	Abnormal CRP or abnormal ESR

Serology (0-3)	
0	Negative RF and ACPA
2	Low-positive RF or ACPA
3	High-positive RF or ACPA

Patients with a score of ≥ 6 have "definite" RA

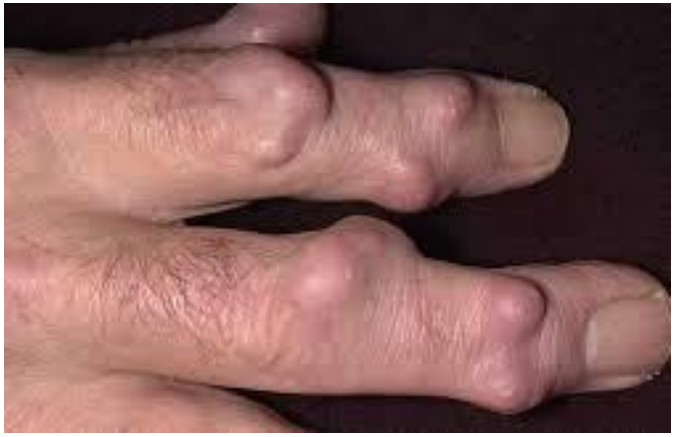
ACPA = anti-citrullinated protein antibody; ACR/EULAR = American College of Rheumatology/European League Against Rheumatism; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis; RF = rheumatoid factor.
Aletaha D, et al. *Arthritis Rheum*. 2010;62:2569-2581.

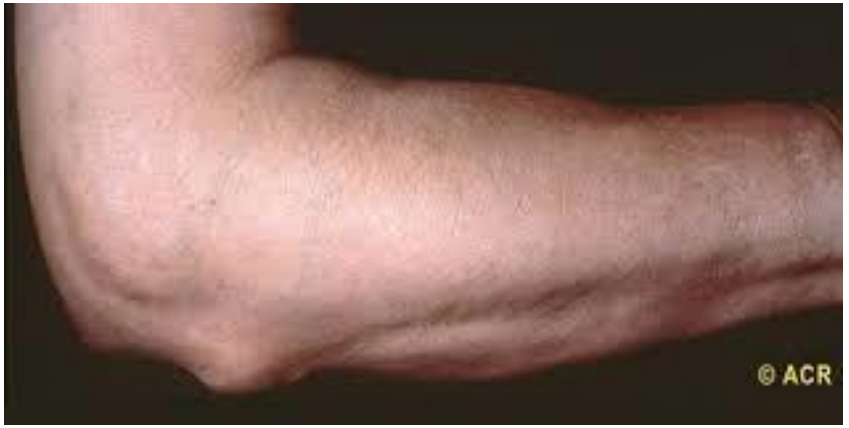
Extra-articular Manifestations in Rheumatoid Arthritis

- Extra-articular manifestations are more common in males
- Occur at any age after onset
- More frequently seen in patients with severe, active disease
- Associated with increased mortality
- Prevalence of these manifestations is about 40% of patients at any time during the course of the disease

Rheumatoid nodules

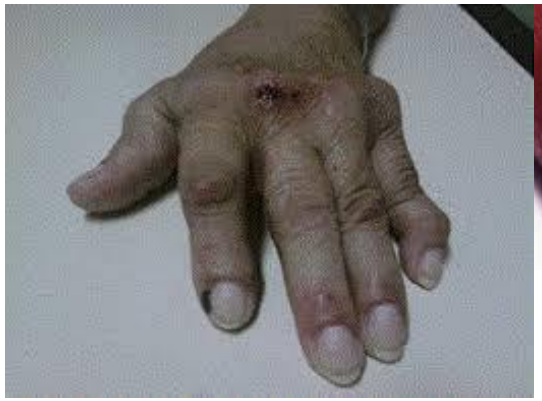
- Rheumatoid nodules are the most common (30%)
- They occur mainly in rheumatoid factor positive RA patients
- Histologically focal central fibrinoid necrosis with surrounding fibroblasts is observed: it is believed to occur as a result of small vessel vasculitis.



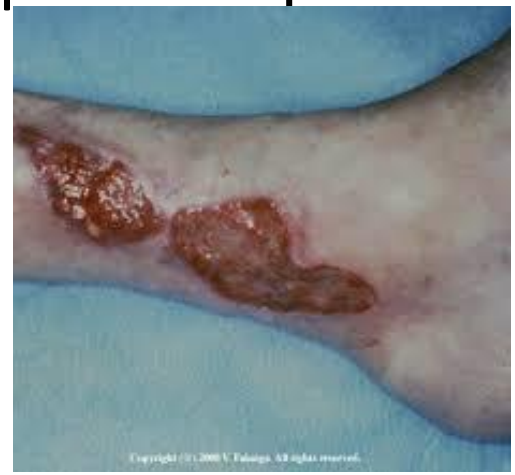


Cutaneous manifestations (Rheumatoid small vessel vasculitis)

- Splinter haemorrhages
- Periungual infarcts
- Leg ulcers
- Digital gangrene



- Mostly at the lower extremities or where skin is exposed to pressure.



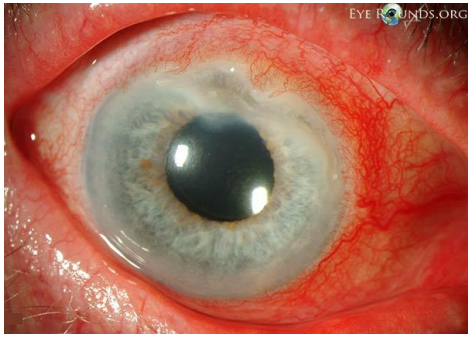
OCULAR MANIFESTATIONS

- The most frequent is keratoconjunctivitis sicca (10%) :Sjögren's syndrome

- Episcleritis, inflammation of the layer superficial to the sclera(less than 1%,a self-limiting)

- Scleritis : more aggressive process, intensely painful inflammation of the sclera itself.

Peripheral ulcerative keratitis :involvement of the peripheral cornea ; can lead to corneal melt

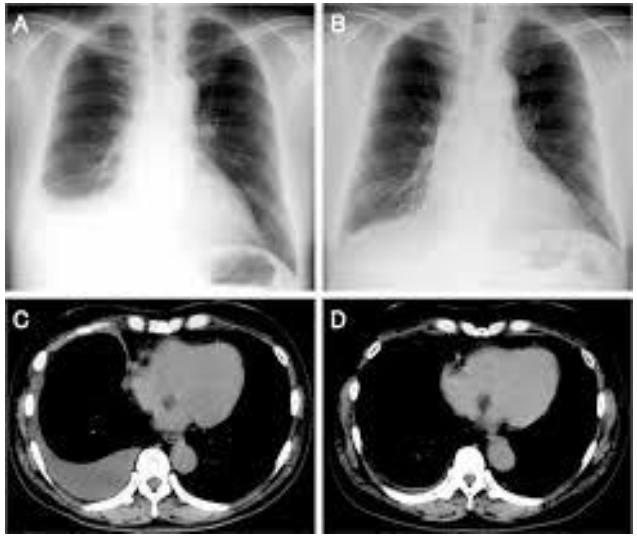


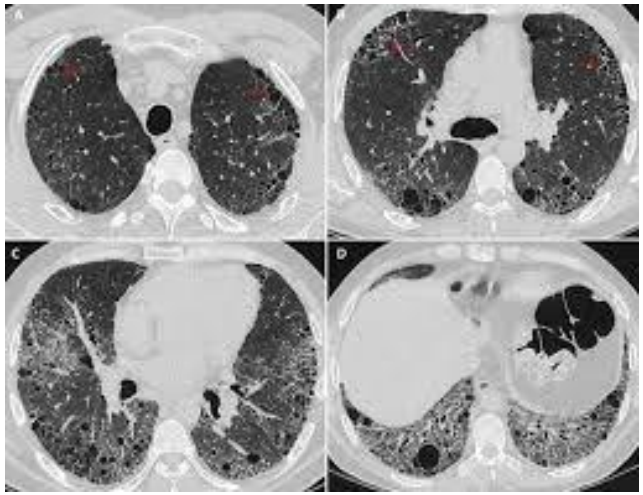
PULMONARY MANIFESTATIONS

- Pleural effusions ,exudative

- Parenchymal pulmonary nodules generally are asymptomatic and found in RF-positive patients with nodules elsewhere

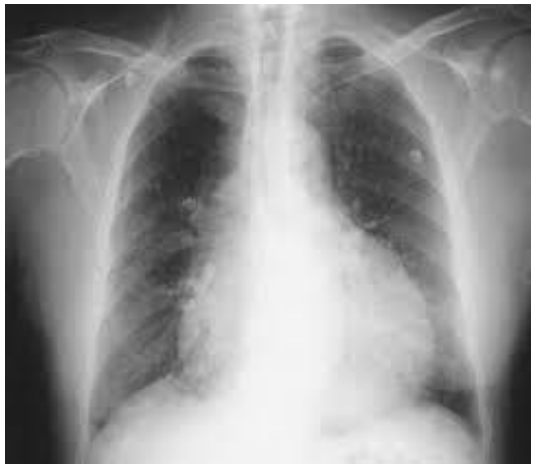
- Diffuse interstitial pulmonary fibrosis more often in RF-positive male patients longstanding nodular disease





CARDIAC DISEASE

- Accelerated atherosclerosis
- Pericardial effusion: can be silent
- Heart failure

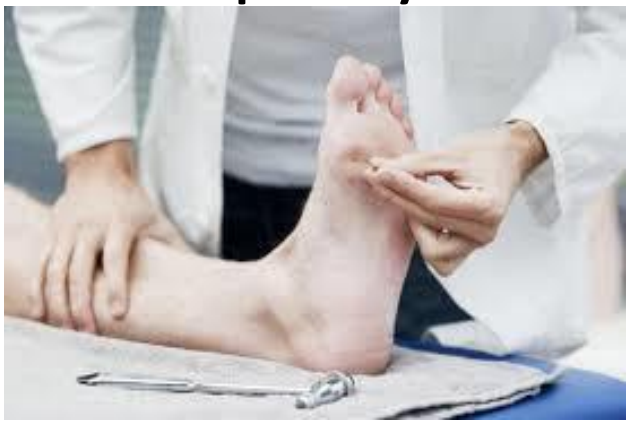


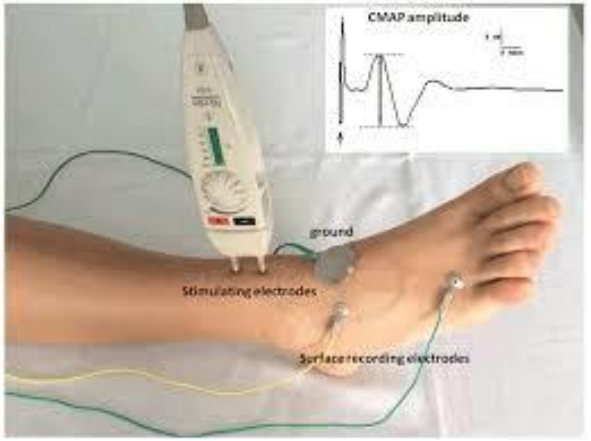
RENAL DISEASE

- Uncommon, mostly renal dysfunction is related to medications
- Mesangial glomerulonephritis can occur
- Amyloidosis was the most common finding among patients with nephritic syndrome.

NEUROLOGICAL MANIFESTATIONS

- Peripheral neuropathy; diffuse sensorimotor neuropathy or mononeuritis multiplex occur but not common
- Etiology is small vessel vasculitis of the vasa vasorum of the nerves with ischemic neuropathy and demyelinisation)





HAEMATOLOGIC MANIFESTATIONS

- Anemia is common: anemia of chronic disease and correlate with disease activity
- Felty syndrome: a triad of RA, splenomegaly and neutropenia

✓ chronic arthritis with severe joint destruction but with moderate or absent joint inflammation and severe extra-articular disease.

Risk factors for RA severity

- ✓ **RF, ACPA :Serological predictors of RA severity**
- ✓ **Environmental & epidemiological risk factors for RA** next slide…**:severity**
- ✓ **Genetic risk factors for RA severity:**

The *HLA-DRB1 alleles, in particular those* encoding the **shared epitope (SE**), are the best established genetic risk factors for seropositive RA, explaining approximately 36% of the heritability of RA. They also associate with a more severe phenotype

Table 2. Studies evaluating environmental and epidemiological prognostic factors for rheumatoid arthritis severity.

Risk factor	Study (year)	Size	Type	Severity outcome(s)	Main findings
Smoking	Masdottir *et al.* (2000)	63 Ca	Cross-sectional	Nodules, modified Sharp score, SJC, HAQ, grip strength	Significant associations between ≥20 pack years and nodules, higher Larsen scores, higher HAQ scores and worse grip strength
	Manfredsdottir *et al.* (2006)	100 Ca	Longitudinal	Joint counts, pain VAS, CRP, van der Heijde score	Over 24 months current smokers had the highest and those who had never smoked the lowest SJC ($p < 0.001$) and TJC ($p = 0.02$) scores, respectively
Alcohol	Maxwell *et al.* (2010)	873 Ca	Cross-sectional	Larsen score, DAS28-CRP, modified HAQ, pain VAS	Significant trends for reducing Larsen scores, DAS28-CRP, CRP, modified HAQ and pain VAS with increasing alcohol intake
	Nissen *et al.* (2010)	2908 Ca	Longitudinal	Ratingen score (radiographic damage), HAQ	Non-significant reduced radiographic progression in drinkers: 1-year mean progression 0.99% (95% CI: 0.89–1.09) in drinkers vs 1.13% (95% CI: 1.01–1.26) in non-drinkers
OCP	Spector and Hochberg (1990)	1407 Ca 181,081 Co	Meta-analysis	ORs for RA using hospital- or population-derived cases	Pooled OR for studies using hospital cases showed significant protective effect of OCP use on RA development; not observed in studies using population cases
Periodontitis	Abou-Raya *et al.* (2008)	100 Ca	Cross-sectional	DAS28, HAQ, Larsen score	Periodontitis severity significantly correlated with DAS28 score, ESR and CRP
	Mercado *et al.* (2001)	65 Ca	Cross-sectional	Joint counts, VAS for physician global/early morning stiffness/pain, ESR/CRP, HAQ	Periodontitis severity significantly associated with higher SJCs, higher HAQ scores and higher CRP/ESR levels
Gender	Jawaheer *et al.* (2010)	292 Ca	Longitudinal	DAS28, HAQ, pain/fatigue VAS, global health scores, CRP, Sharp scores	Females had worse disease progression reflected by DAS28, physician global and TJC scores
	Ahlmén *et al.* (2010)	549 Ca	Longitudinal	DAS28, HAQ, SOFI instrument, SHS	Females had significantly higher DAS28 and HAQ scores at all time points
Social deprivation	McEntegart *et al.* (1997)	814 Ca	Longitudinal	Pain score, articular index, ESR, CRP, HAQ	Cases from deprived areas had significantly higher HAQ scores
	ERAS Study Group (2000)	869 Ca	Longitudinal	Joint counts, HAQ, pain VAS, grip strength, ESR, erosive radiological changes	Significantly worse HAQ and joint scores, and grip strength in individuals with higher deprivation scores

Treatment of RA
oral DMARDs

- Hydroxychloroquine : Mild disease, pregnancy
- Sulfasalazine: mild-moderate disease
- **Methotrexate:** gold standard for moderate to severe RA; Improves overall and cardiovascular survival

- Azathiorpine
- Leflunomide
- Cyclosporine
- Minocycline

Combination therapy

Mono, double or triple therapy

MTX+ SSZ+ HCQ:OK

Avoid combining AZA plus MTX

SSZ+ AZA+ HCQ :OK

Triple plus biologic: anti TNF or non TNF inhibitors.

Other treatments

Glucocorticoids:

- Have both anti-inflammatory and immunoregulatory activity.

✓ can be given orally, intravenously, intramuscularly or can be injected directly into the joint.

✓ useful in early disease as temporary adjunctive therapy while waiting for DMARDs to exert their anti-inflammatory effects.

✓ Corticosteroids are also useful as chronic adjunctive therapy in patients with severe disease that is not well controlled on NSAIDs and DMARDs.

✓ The usual dose of prednisone is 5 to 10mg daily.

Adverse Effects of DMARDs

Table 1 – Nonbiologic DMARDs frequently used for RA

Drug	Onset of action	Major toxicities	Dosing	Monitoring	Comments
Methotrexate	1 - 2 months	Hepatotoxicity, myelosuppression, teratogenicity, stomatitis, interstitial lung disease	PO or SC, IM dosing (opt for SC, IM administration if mucositis/GI adverse effects with PO or if lack of response to PO); start at 10 - 15 mg/wk, increase 5 mg/mo to 20 - 25 mg/wk	Check baseline CBC count, CMP, hepatitis B and C serologies; monitor CBC count, CMP every 2 months	Give daily folic acid; contraindicated in hepatitis B and in hepatic failure; adjust dose for renal insufficiency; counsel patients to avoid alcohol use and about contraception
Hydroxychlor-oquine	2 - 3 months	Retinopathy	200 - 600 mg/d PO, < 6.5 mg/kg; can be divided into bid dosing	Annual eye examination	Exercise caution in hepatic failure; adjust dose for renal insufficiency
Sulfasalazine	4 - 6 weeks	GI upset, allergic reaction to sulfa moiety, rash, anemia, hemolysis, agranulocytosis and, rarely, drug-induced lupus	500 mg/d PO for 1 week, then 500 mg PO bid for 1 week, then 500 mg PO tid for 1 week, then 1 g PO bid	Check for G6PD deficiency before starting; check baseline CBC count, CMP; monitor CBC count at least monthly for the first 3 months, then every 3 months	Contraindicated in hepatic failure; adjust dose for renal insufficiency
Leflunomide	4 weeks	Hepatotoxicity, myelosuppression, teratogenicity, rash	100 mg/d for first 3 days, then 20 mg/d PO	Check baseline CBC count, CMP, hepatitis B and C serologies; monitor CBC count, CMP every 2 months	Contraindicated in hepatitis B and in hepatic failure; adjust dose for renal insufficiency; counsel patients to avoid alcohol use and about contraception

DMARDs, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; CBC, complete blood cell; CMP, comprehensive metabolic panel; G6PD, glucose-6-phosphate dehydrogenase.

Biologic DMARDS

TABLE 1: BIOLOGIC DMARDS USED IN RHEUMATOID ARTHRITIS

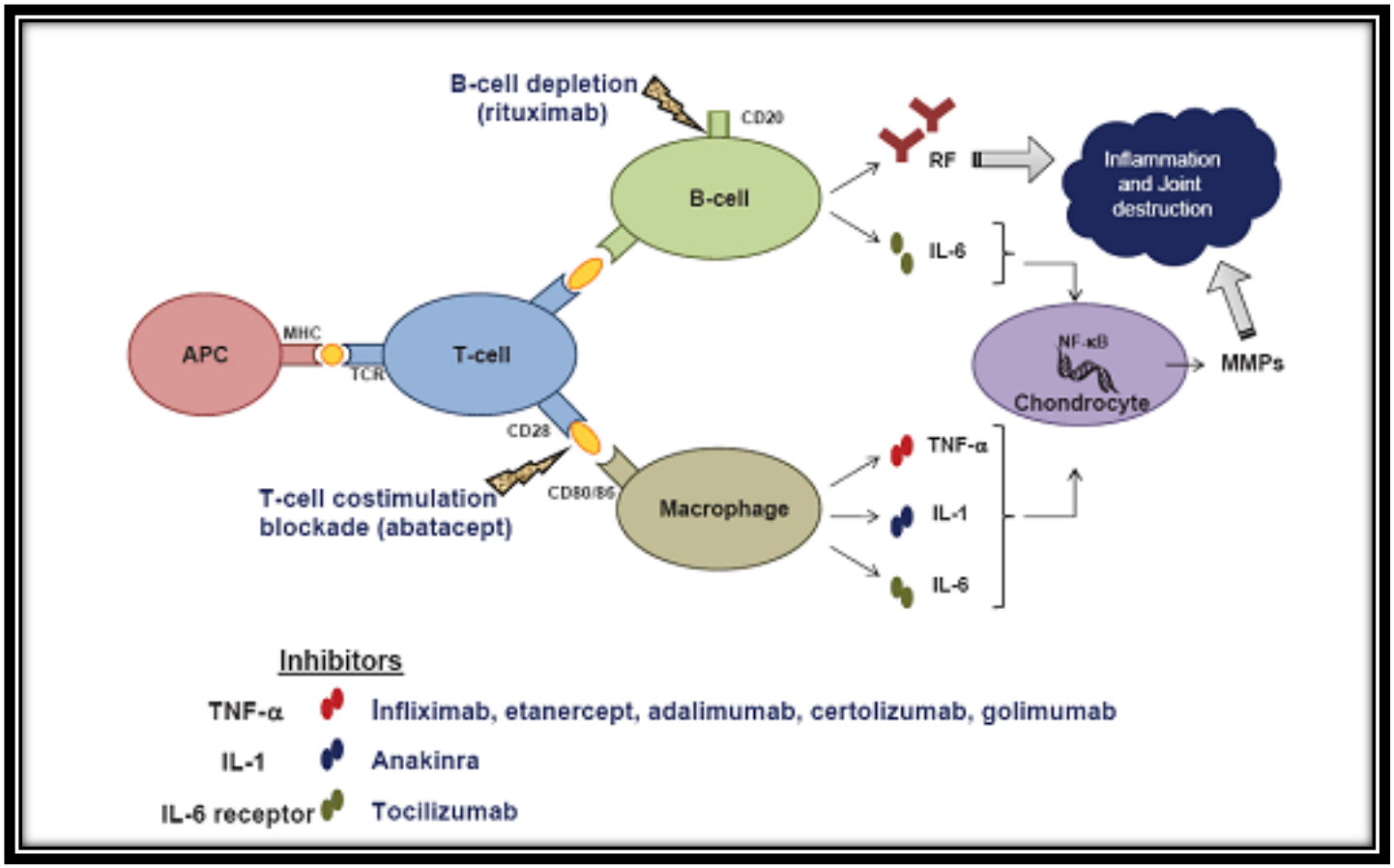
Drug Name	Target	Route of Administration	Dose in Rheumatoid Arthritis
Adalimumab (Humira)	TNF inhibitor	Subcutaneous	40 mg every other week
Etanercept (Enbrel)	TNF inhibitor	Subcutaneous	50 mg once weekly
Infliximab (Remicade)	TNF inhibitor	IV	3 mg/kg at 0, 2, 6 weeks, then every 8 weeks (max 10 mg/kg every 4 weeks)
Certolizumab pegol (Cimzia)	TNF inhibitor	Subcutaneous	400 mg at 0, 2, 4 weeks then 200 mg every 2 weeks (optional maintenance dose of 400 mg every 4 weeks)
Golimumab (Simponi ARIA/ Simponi)	TNF inhibitor	IV	2 mg/kg at 0, 4, 8 weeks, then every 8 weeks
		Subcutaneous	50 mg every month
Abatacept (Orencia)	CD80/CD86 to CD28 selective co-stimulation modulator to inhibit T-cell activation	IV	<60 kg – 500 mg 60 to 100 kg – 750 mg >100 kg – 1000 mg At 0, 2, 4 weeks, then every 4 weeks
		Subcutaneous	125 mg once weekly following single IV loading dose
Rituximab (Rituxan)	Binds to CD20 antigen inducing B-cell lysis	IV	1000 mg on day 1 and day 15; may repeat after 24 weeks
Tocilizumab (Actemra)	IL-6 receptor antagonist	IV	4 mg/kg every 4 weeks, may increase to 8 mg/kg every 4 weeks (max 800 mg total)
Anakinra (Kineret)	IL-1 receptor antagonist	Subcutaneous	100 mg daily (at approximately the same time each day)

DMARDS = disease-modifying anti-rheumatic drugs; IV = intravenous; TNF = tumor necrosis factor.

Biologics drawbacks

!Cost $$$

! Infections



Biologics adverse effects

Infections

Allergic reactions especially with biologics infusions

Re activation of TB or HBV

Lymphoma and solid tumor

Hepatotoxicity

GI perforation

Demyelinating disease

vasculitis

Management of patients with RA: Key points

The sicker they are and the faster they get that way, the worse the future will be.

Early intervention can make a difference

Damage occurs early in most patients

50% show joint space narrowing or erosions in the first 2 years

By 10 years, 50% of young working patients are disabled

Death comes early: Multiple causes

Increase risk of CVD and lymphoma

Compared to general population: Women with RA lose 10 years, men with RA lose 4 years

Management of patients with RA: Key points

The sicker they are and the faster they get that way, the worse the future will be.

Early intervention can make a difference

Damage occurs early in most patients

50% show joint space narrowing or erosions in the first 2 years

By 10 years, 50% of young working patients are disabled

Death comes early: Multiple causes

Increase risk of CVD and lymphoma

Compared to general population: Women with RA lose 10 years, men with RA lose 4 years

Management

Confirm the diagnosis

Determine where the patient stands in the spectrum of disease

When damage begins early, start aggressive treatment early

Use the safest treatment plan that matches the aggressiveness of the disease

Monitor treatment for adverse effects

Management

Education

Build a cooperative long-term relationship ✓

Use materials from the Arthritis Foundation and the ACR ✓

Consider assistive devices ✓

Exercise: ROM and strengthening exercises

Medications

Analgesic and/or anti-inflammatory

Immunosuppressive, cytotoxic, and biologic

Balance efficacy and safety with activity

Treat to target regardless of severity of disease.

Management of established joint damage

Reconstructive surgery :indicated when conservative measure to control pain fail

Synovectomy :excision of the synovial membrane

Tenorrhaphy :suturing a tendon

Arthrodesis :surgical fusion of the joint:

Arthroplasty :surgical repair and replacement of the joint.

Chronic pain programs: opioids ?

Other aspects of disease management

Depression and sleep deprivation may require the short-term use of low-dose antidepressant medications

THANK YOU