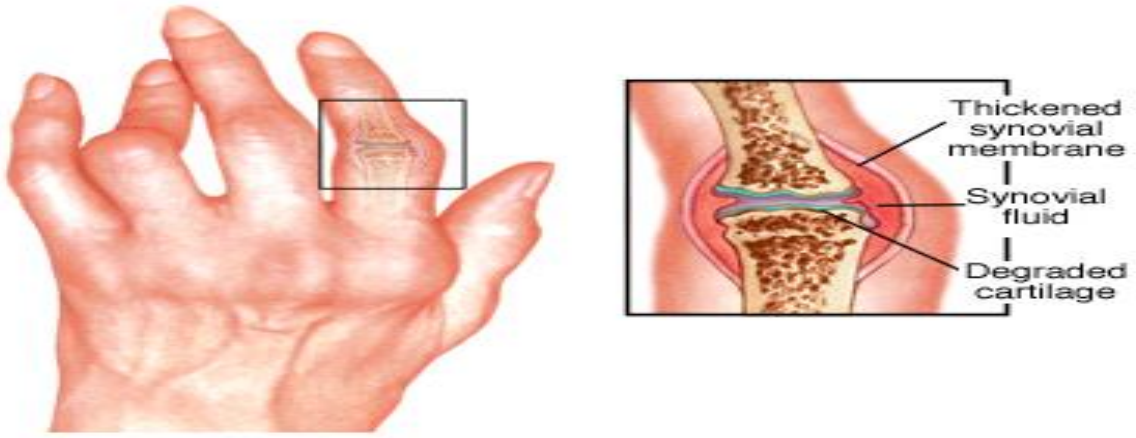
Lec 1

Rheumatoid arthritis

Rheumatoid arthritis (RF) is a chronic inflammatory disorder that can affect more than just your joints. In some people, the condition also can damage a wide variety of body systems, including the skin, eyes, lungs, heart and blood vessels.

An autoimmune disorder, rheumatoid arthritis occurs when your immune system mistakenly attacks your own body's tissues. Unlike the **wear-and-tear damage** of osteoarthritis, rheumatoid arthritis affects the lining of your joints, causing a painful swelling that can eventually result in bone erosion and joint deformity.

The inflammation associated with rheumatoid arthritis is what can damage other parts of the body as well. While **new** types of **medications** have improved treatment options dramatically, severe rheumatoid arthritis can still cause physical disabilities.



Epidemiology:

RA incidence worldwide is estimated to be between 0.5 and 1 percent of the general population. RA is one of many chronic inflammatory diseases that predominate in women. The ratio of female to male patients is estimated to be from 2:1 to 4:1.

Etiology

There are many factors that may increase the risk of rheumatoid arthritis which include:

1- **Gender**: Women are **more likely than** men to develop RA.
2- **Age**. Rheumatoid arthritis can occur at any age, but it most commonly begins between the ages of 40 and 60.
3- **Family history**: If a member of your family has rheumatoid arthritis, you may have an increased risk of the disease.
4- **Environmental exposures**: Although uncertain and poorly understood, but it is possible to explain with some shortness
   a- Silica may increase the risk for developing rheumatoid arthritis.
   b- Infections (may be viral infection like Epstian bar virus have association with RA).
   c- Trauma thought to trigger the development of RA.
   d- Vitamine D deficiency
   e- Smoking for a person who has a genetic predisposition for RA
   f- Alcohol consumption.
5- **Obesity**: People who are **overweight** higher risk of developing rheumatoid arthritis, **especially in women** diagnosed with the disease when they were 55 or younger.
6- **Genetic markers:** such as human leukocyte antigen DR4 (HLA-DR4) have been associated in triggering the inflammatory process in RA. However, HLA-DR4 are not considered diagnostic because 30% of people with HLA-DR4 never develop RA.

- **Pannus** is an abnormal layer of fibrovascular tissue or granulation tissue (الانسجة الليفية الوعائية او المحببة). Common sites for pannus formation include

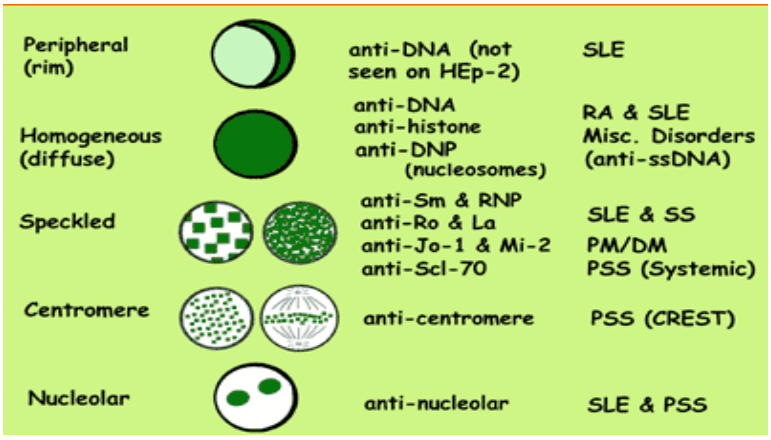
(a)Over the cornea (القرنية), (b)over a joint surface (as seen in rheumatoid arthritis), (c) Prosthetic heart valve (صمام القلب الاصطناعي), (d)Tumor-like fashion (نمط مشابه للورم) as in joints where it may erode(تآكل) articular cartilage and bone.

Anticitrullinated protein antibodies (ACPAs) are autoantibodies (antibodies to an individual's own proteins) that are directed against peptides and proteins that are citrullinated. **They are present in the majority of patients with rheumatoid arthritis.** Clinically, **cyclic citrullinated peptides (CCP)** are frequently used to detect these antibodies in patient serum or plasma (then referred to as **A**nti–**C**itrullinated **P**eptide **A**ntibodies) **(ACPAs)**.

Citrullination or deimination is enzymatically process that led to convert of the amino acid **Arginine** in a protein into the amino acid called **citrulline**. This altered protein may be seen as **antigens** by the immune system and cause immune response so, 2% of ACPAs carrier are powerful biomarkers that allow the diagnosis of rheumatoid arthritis (RA) to be made at a very early stage.

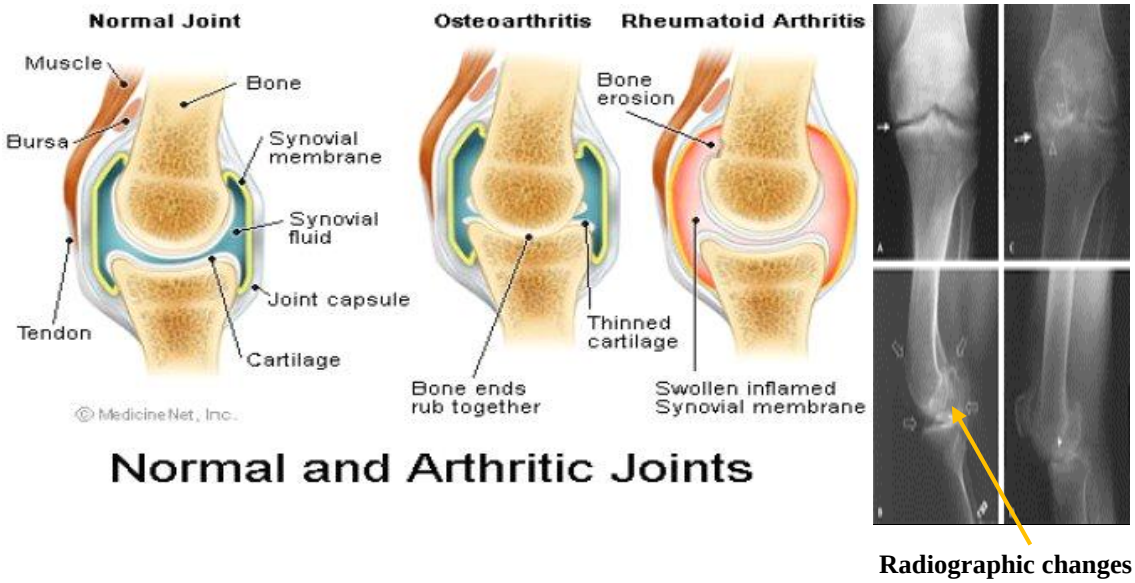
Anti-CCP is now the lead marker for detection of RA, **because it is much more specific than RF**. In addition, low titers of **antinuclear antibodies (ANA)** are present in about 40 percent of patients. The pattern most identified is the **speckled pattern** directed against ribonucleoprotein. The significance of this group of autoantibodies remains unclear, because they do not appear to be directly related to pathogenesis.

ANA patterns ⟶



Rheumatoid arthritis criteria to diagnosis (Symptoms)

1- **Morning stiffness** around joints.
2- **Soft tissue swelling** (arthritis) of 3 or more joint areas observed by physician.
3- **Symmetric swelling** (arthritis). (Important feature for diagnosis disease).
4- Arthritis of hand (proximal interphalangeal, metacarpo-phalangeal, or wrist joint).
5- **Rheumatoid nodules**
6- The presence of **rheumatoid factor in serum** (RF).
7- Radiographic changes (erosions and periarticular osteopenia)in hand and wrist joints(تاكل و هشاشة العظام حول المفصل).
8- Fever , Fatigue , Wight loss



Radiographic changes

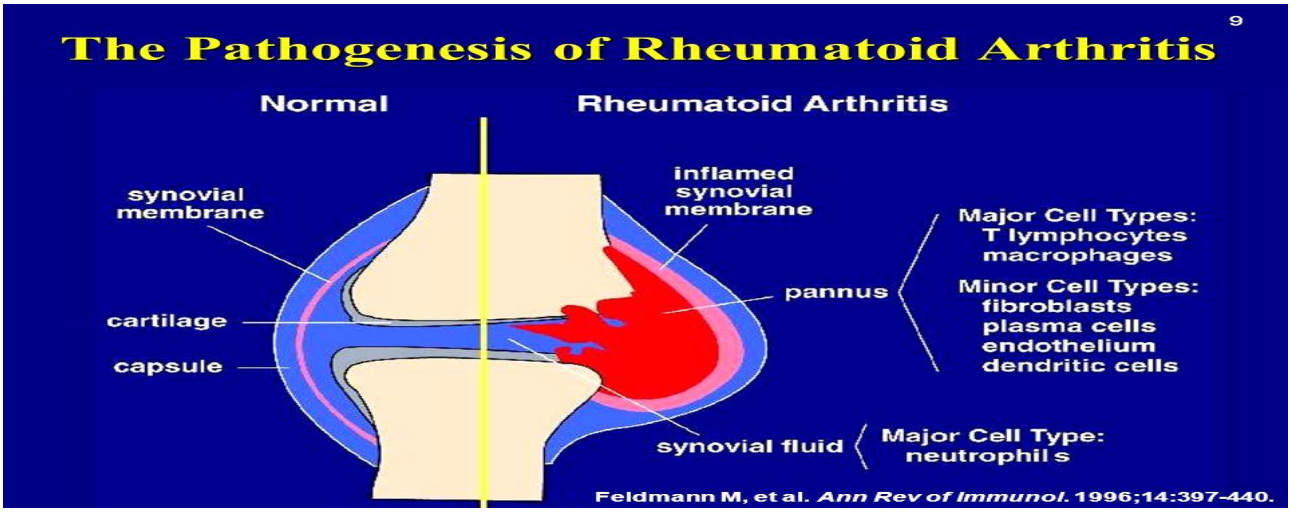
Pathophysiology (immune mechanism)

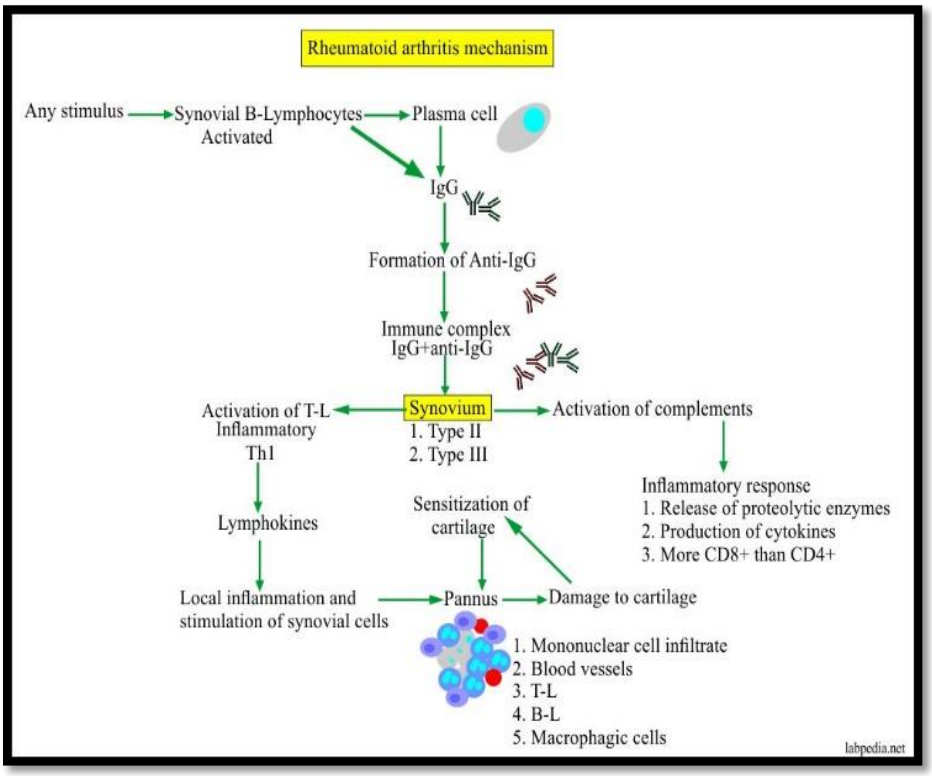
The pathogenesis of RA is not completely understood.

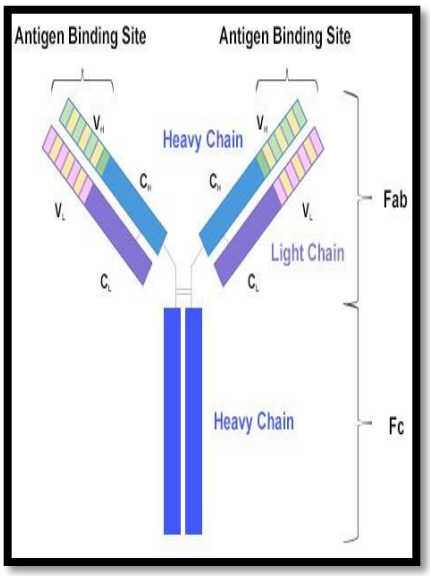
- Autoimmune reaction are triggered via some internal and external trigger (eg, cigarette smoking, infection, or trauma).
- CD4 T-lymphocytes cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils play major cellular roles in the pathophysiology of RA, whereas B cells produce autoantibodies (ie, rheumatoid factors).

- **Macrophages** and neutrophils are attracted to the area, and this result in the formation of an organized **mass of cells called a pannus**, which grows into the joint space and invades the cartilage.
- The balance between pro-inflammatory cytokines and regulatory cytokine lead to continuous of inflammation. Pro-inflammatory cytokines are Interlukine-1 (IL-1), 1L-6, IL-8 and tumor necrosis factor-alpha (TNF-α).
- TNF-α plays a key role in the inflammatory process by **inducing continual** secretion of IL-1, IL-6, and Il-8. In addition, TNF-α **facilitates** the **transport of** white blood cells (WBCs) to the affected areas.
- **Collagenase** and other tissue-degrading enzymes are also released from synoviocytes (الخلايا الزلالية) and chondrocytes(الخلايا الغضروفية) that line the joint cavity.
- The end result is destruction of connective tissue, cartilage, and bone.
- In RA, IgM antibodies combine with IgG, and these immune complexes become deposited in the joints, resulting in a **type III (or immune complex) hypersensitivity reaction.** The complement protein C1 binds to the immune complexes, activating the classical complement cascade. During this process, C3a and C5a are generated, which act as chemotactic factors for neutrophils and macrophages.
- The continual presence of macrophages leads to the chronic inflammation usually observed which damages the synovium itself.

The role of autoantibodies (IgM) or (RF) are unknown in the initiation of the inflammatory response. About 75% of patient have IgM autoantibodies that called Rheumatoid factor and its directed aginst FC portion of IgG antibody







IgG antibody structure

Laboratory diagnosis

1- Serological test (agglutination test)

There are two types of agglutination tests for RF has been developed:
A. One using sheep red blood cells coated with IgG.
B. Other testing by using latex particles coated with the same antigen (IgG coated with latex particles). The reaction occur between **IgM** isotype that found in approximately 75% of patients and IgG coated particles.

2- CBC (Complete Blood Count)

3- ESR high

4- Serum RF factor positive 70 % (IgM autoantibodies)

5- ANTI CCP Specific 100%.

6- ANA 40 %(Anti-Nuclear Antibody)

7-X ray .

8-CRP high (C reactive protein).