Clinical immunity

Introduction:

Clinical immunity is the study of diseases caused by **disorders of the immune system** (Mistake or failure in the action), and malignant growth of the cellular elements of the system).

The diseases in clinical immunology classified into two types:

1. **Immunodeficiency;** Defect in **ability** of immune system to fight infectious disease and cancer cells (ex. HIV infection).
2. **Autoimmunity**; the immune system attacks its own host's body (examples include systemic lupus erythematosus, rheumatoid arthritis, Hashimoto's disease & others.

Rheumatologic Diseases:

Rheumatism is a conditions causing chronic pain affecting the joints ,connective tissue.

Arthralgia: Joint pain (there may not be any inflammation)

Arthritis: Inflammation of the Joint

What are the Factors that Predispose to Rheumatologic Diseases:-

I. Genetics or the Susceptibility Genes :-

A. MHC class I (i.e., HLA-B27 in Ankylosing spondylitis)
B. MHC class II (i.e. HLA-DR4 in **Rheumatoid Arthritis**)
C. **Complement deficiency** states (i.e., C2 or C4 deficiency in SLE)

II. Environmental Factors :-

A. Viral infections (hepatitis B, hepatitis C, others).
B. Bacterial infections (Shigella, Salmonella, group A strep)
C. Drugs (Procainamide, others).
D. Toxins and UV-light (in SLE)

III. Status of the Immune System :-

IV. Status of Target Organ/Tissue :-

What is the Chronic Arthritis? gradual onset (days to weeks) disease, the Symptoms are more moderate, Muscle stiffness , Mediated by the adaptive immune response, especially **T cells (Th1 in RA)** and macrophages.

Rheumatoid arthritis (RA):

Definition: It is a common chronic autoimmune, inflammatory arthritis m**ost** common in age between (25-55) years and in women **3:1** for men. RA affects **lining of joints** cause painful swelling result in bone erosion and join deformity.

The etiology of RA and factors increase risk factor of RA:

Family history , age , sex (hormonal factors), obesity.

environmenal factors (smoking and **exposure to silica asbestos)**

Genetic factor : (HLA class II-DR4) gene.

The allel**e HLA-DRB1- 0101 ,0401, 0404**

What are the Universal Criteria of RA?

1- Morning stiffness in or around joints,, > 1 hour.
2- Arthritis (swelling of 3 or more joint area)
3- Symmetric arthritis
4- Arthritis of Hands joints(wrist, MCP metacarpo -phalangeal)
5- Rheumatoid nodules
6- Rheumatoid factor in serum (70% positive)
7- Radiographic changes like erosions

What are the main immune characterization of RA?

- T and B lymphocytes are highly represented. It forms lymphoid aggregates
- **pro-inflammatory cytokines** produced by macrophage such as tumor necrosis factor (TNF) and interleukin-1, 6 ,17 (IL-1) (IL-6) IL17, and metalloproteinases (including collagenase ,elastase, gelatinase) produced **from fibroblast** causing tissue damage.
- The presence of immune complexes and autoantibodies .
- The autoantibody : rheumatoid factor (RF sensitive), and anti-cyclic citrullinated peptide antibodies (Anti CCP,**specific** autoantibody).

Difinition of RF (Rheumatoid factor) :an auto-antibody mostly (IgM) with specificity for the **Fc portion** of IgG, which have been used in diagnosis of RA (70%) and other disease as sensitive test.

What are the Signs and symptoms of RA in different organs?

Skin : Cutaneous *rheumatoid nodule* ("necrotizing granuloma"). Nodules are associated with a positive RF (rheumatoid factor) titer and severe erosive arthritis..

Lungs Fibrosis of the lungs (Kaplan's syndrome) **and** Pleural effusions

Kidneys RA may affect the kidney glomerulus directly through a vasculopathy or a mesangial infiltrate lead to immune complex-mediated hypersensitivities

Heart and blood vessels : RA are more prone to atherosclerosis, and myocardial infarction (heart attack) .

Other like Eyes episcleritis. scleromalacia. **And** keratoconjunctivitis sicca

Liver .Increased production of acute-phase proteins, such as **C-reactive protein. & Increased release of enzymes such as alkaline phosphatase**

Anemia: RA may also cause a warm autoimmune hemolytic anemia.

Neurologica Peripheral neuropathy and mononeuritis multiplex may occur.

Bones : Local osteoporosis occurs in RA around inflamed joints.

Morning stiffness: persists for **at least one hour** due to accumulation of edema fluid within joints during sleep. The joints most commonly involved first are **small joints** of the hands and feet, Larger joints generally infected **after** small joints.

What are the most common clinical signs of RA?

1- association of pain (chronic)
2- swelling in small joints
3- stiffness of the metacarpo -phalangeal and wrist joints,
4- pain in the sole of the foot, indicating metatarso-phalangeal involvement.

The earliest pathologic changes :

1- increase the permeability of the endothelium of the microvasculature
2- development of edema and edematous subsynovial space.
3- presence of polymorphonuclear leukocytes.

In the chronic stage:

1- Hyperplasia of the synovial lining cells the synovial lining cells increases .
2- The synovial membrane takes a villous appearance.

3- Formation of **pannus**, it is a Massive infiltration by lymphocytes, plasmablasts, and granulation tissue.This thick pannus after months and years continues to grow, protruding into the joint. The synovial space filled by exudative fluid, and causes pain and limits motion.

Diagnosis of Rheumatoid Arthritis:

RA can be difficult to diagnose in its early stages because the **early signs and symptoms mimic those of many other diseases.**
By ImagingX-rays of the hands and feet are generally performed .

What are the laboratory test for Diagnosis of RA?

1- **ESR.** Elevated erythrocyte sedimentation rate **.**

2- **C-reactive protein (CRP)** levels are an even better indication than ESR of the amount of inflammation present.

3- **Rheumatoid factors (RF)** are a variety of antibodies that are present in about 70% of people with (RA). RF can be found in people without RA or with other autoimmune disorders.

4- (anti-CCP)) is more specific new test for RA that measures levels of antibodies that bind citrulline modified proteins (anti-CCP). Also Anti mutated citrullinated vimentin Anti-MCV**.**

5- For HLA typing in RA have involved amplification by the polymerase chain reaction (PCR) of the HLA-DR4, HLA-DRB1 gene.

6- ANA anti-Nuclear antibody.

Treatments

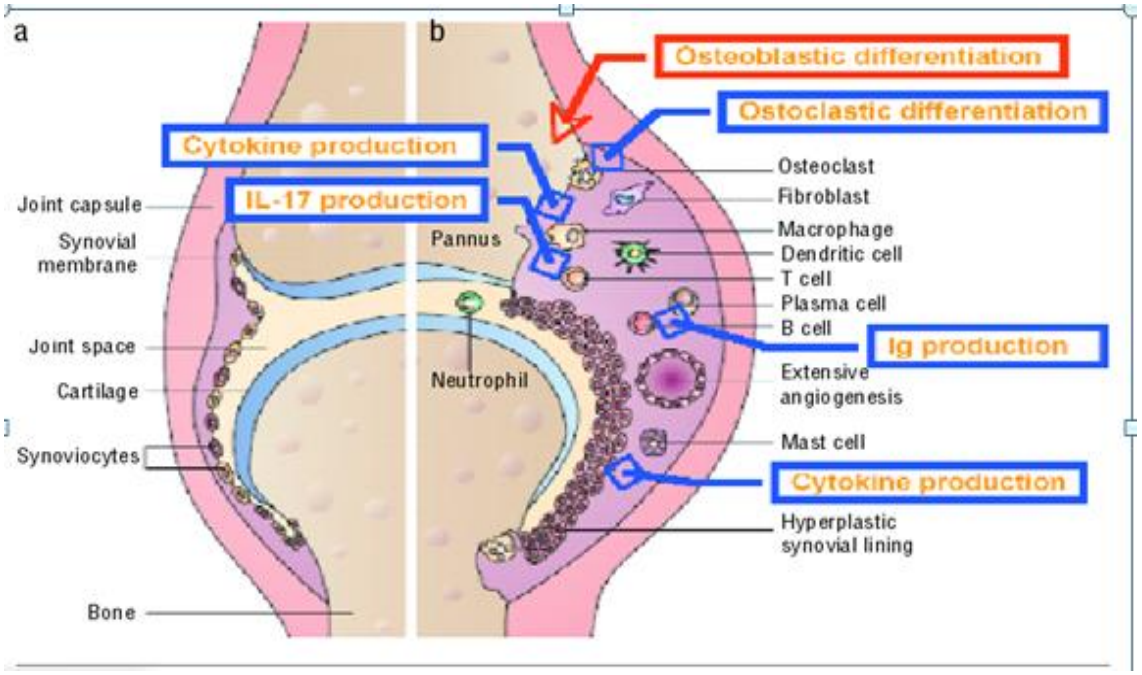
1-NSAIDs : Nonsteroidal anti-inflammatory drugs (NSAIDs) can relieve pain and reduce inflammation. Include aspirin ,diclofenac (voltaren) ,ibuprofen.

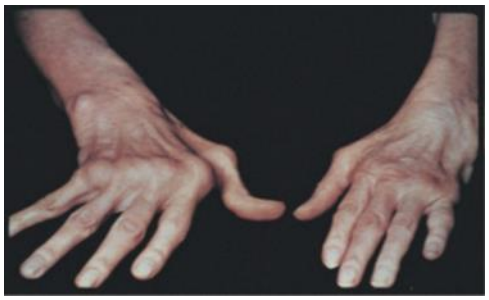
2- Corticosteroid medications, such as prednisone, reduce inflammation,pain and slow joint damage .used in acute stage

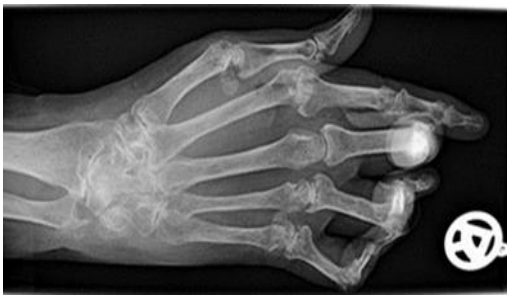
3-DMARDs : Disease-modifying antirheumatic drugs These drugs can slow the progression of RA and save the joints and other tissues from permanent damage. Common DMARDs include methotrexate hydroxychloroquine and sulfasalazine.

4- Biologic agents : modified newer class of DMARDs includes AntiTNF infliximab,

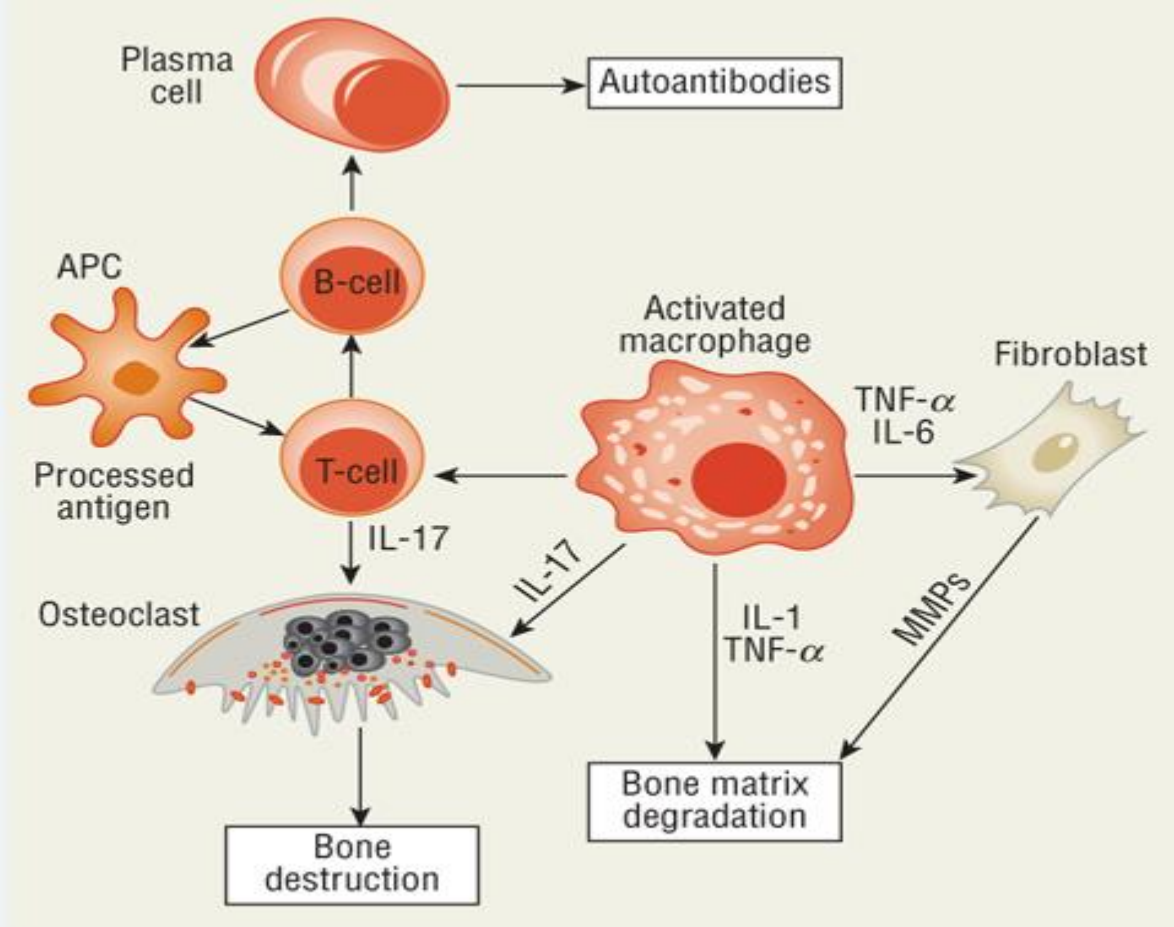
5-Surgery :-, Hip and knee replacements are most common .







Multiple Cell Types and Cytokine Involved in Chronic Inflammatory Arthritis



Source: J.T. DiPiro, R.L. Talbert, G.C. Yee, G.R. Matzke, B.G. Wells, L.M. Posey: Pharmacotherapy: A Pathophysiologic