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A REVIEW ON RHEUMATOID ARTHRITIS

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ABSTRACT
Rheumatoid arthritis (RA) is a chronic inflammatory and systemic auto immune disease affecting people predominantly between the ages of 20-50 years with unpredictable course. About 1% of the world's population is afflicted by rheumatoid arthritis and is two - three times more common in women than men. Rheumatoid Arthritis occurs in about 5% of 1000 people and can lead to severe joint damage and disability. There are different types of arthritis. The rheumatoid arthritis due to the presence of pro-inflammatory markers, cytokines and leukotrines. The primary inflammatory markers are IL-1, TNF-α, IL-6, IL-15, IL-16, IL-17, IL-18, IFN-γ, and granulocyte macrophage-colony stimulating factor, chemokines such as IL-8, macrophage inflammatory protein-1 and monocyte chemo attractant protein-1. TNF-α blockade, IL-1 blockade, B cells therapy, IL-6 blockade and Angiogenesis blockade, these are therapeutic target for its treatment. Besides early diagnosis, these advances include early institution of disease modifying therapy with a goal of "treat to target", frequent assessments of disease activity to control, consideration for and introduction of alternative or additive diseases modifying therapeutic agents in case of inadequate or persistent disease activity.

KEYPOINT: Auto immune disease, Anti-arthritic potential, cytokines, Rheumatoid arthritis.

INTRODUCTION
Rheumatoid arthritis (RA) is an autoimmune disease that results in a chronic systemic inflammatory disorder that may affect many tissues and organs.but principally attacks flexible (synovial joints) it can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility if not adequately treated. The hallmark feature of this condition is persistent symmatric polyarthritis (synovitis). Though any joint lined by a synovial membrane may be involved. Extra articular involvement of orgens such as the skin, heart, blood vessels, lungs and eyes are the significant. Although RA affects approximently 1% of world population it can occurs at any age, usually begins after age 40 (peak incident is between 4th and 6th decade). The disorder is much more common in women than in men genetic and autoimmune factors are mainly responsible for the initiation of disease process. It causes joints to swell and can result in pain, stiffness, and progressive loss of function. In addition to joint pain and stiffness, people with RA may also have symptoms such as weight loss, low-grade fever, and fatigue. RA often affects pairs of joints (both hands, both feet, etc) and can affect more than one joint, including the small joints in the wrists and hands. Over time, other joints can be affected such as shoulders, elbows, knees, feet, and ankles.

Over time, the inflammation of RA can cause damage to the joints. In some patients, this may lead to permanent joint damage. As this joint damage progresses, in severe cases, it can cause deformity of the joints and loss of function. It may begin to interfere with daily activities, making them more difficult and painful to do. A standardized mortality ratio derived from a meta-analysis of North American and European studies suggests that mortality from CV events is 1.5 fold higher among RA patients than among the general population. India can be characterized as a sub-continent, given that it has the second largest population (1.2 billion).

For these reasons, it's important to get an accurate diagnosis as early as possible. Talk to your doctor.

General Consideration of Arthritis
RA can be classified as

1) Palindromic rheumatoid arthritis - consists of sudden and rapidly developing attacks of arthritis. There is acute pain, redness, swelling, and disability of one or multiple joints. The interval between recurrent palindromic attacks and the length of an attack is extremely variable from few hours to days.
2) Juvenile rheumatoid arthritis - also known as juvenile rheumatoid arthritis, is the most common form of arthritis in children and adolescents.

3) Rheumatoid spondylitis - is a type of arthritis in which there is long term inflammation of the joints of the spine.

Other types of arthritis

Osteoarthritis - is a type of joint disease that results from breakdown of joint cartilage and underlying bone. The most common symptoms are joint pain and stiffness. Initially, symptoms may occur only following exercise, but over time may become constant. Other symptoms may include joint swelling, decreased range of motion, and, when the back is affected, weakness or numbness of the arms and legs.

There are two types of osteoarthritis –

a) Primary osteoarthritis - It occurs in elderly.
b) Secondary osteoarthritis- It occurs at any stage.

- Ankylosing spondylarthritis
- Infectious arthritis
- It can be classified as fallows

a) Supportive arthritis
b) Tuberculous arthritis
c) Lyme arthritis
d) Viral arthritis

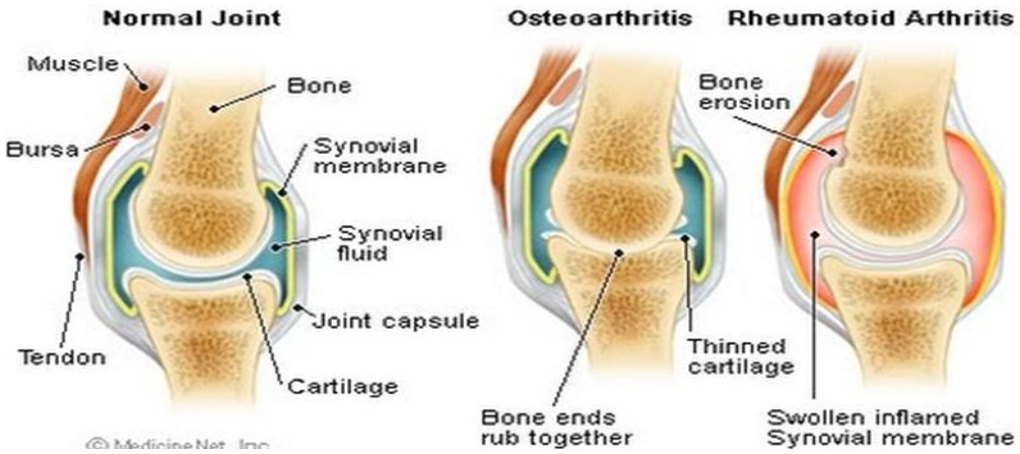

Fig: Difference in Rheumatoid Arthritis and Osteoarthritis.

Epidemiology of Rheumatoid arthritis

Worldwide, the annual incidence of RA is approximently 3cases per 10,000 populations, and prevalence rate is approximently 1% increasing with age and peaking between the ages of 35 and 50 years in 2010. It results in about 49,000 deaths globally.

About 1.5 million people in the united state have RA nearly three times in many women have the disease as men. In women, most commonly begins between ages 30 and 60. In men, it occurs later in life.

RA is a chronic disease though rarely, a spontaginious remission may occure, the natural course is almost in variably one of persistent symptoms, waxing and wanning in intensity, and progressive deterioration of joint structure leading to deformations and disability.

Etiology of Rheumatoid arthritis

The cause of RA is unknown genetic, environmental, hormonal immunologic and infectious factor may play significant roles socioeconomic, psychological and lifestyle factor (e.g. tobacco use, the main environmental risk may influence disease outcome.

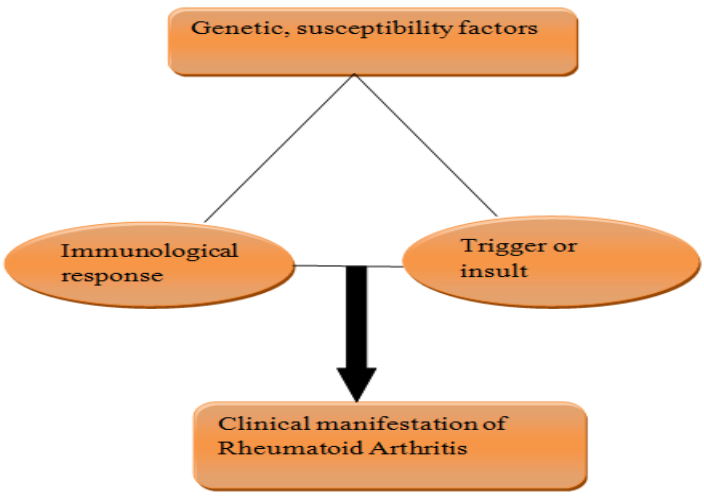

Fig. 1: Etiology of RA.

There are many possible causes, including:

1) **Genetics:** People with family members who have RA may be more likely to get it
2) **Hormones:** Female hormones may play a role in the disease
3) **Viruses or bacteria:** RA may be related to viruses or bacteria that you come in contact.

Signs and Symptoms of RA

RA affects different people in different ways. Symptoms may slowly develop over several years, or the disease may progress quickly. Symptoms may be mild or very severe. You may go through phases called "flares" or "flare-ups" when symptoms are severe. At other times, it may seem as if the disease and its symptoms have gone away. This is called "remission."

Joint pain and swelling may happen slowly and may occur over weeks or months. The small joints in the wrists and hands are often inflamed first. Over time, other joints may be painful and swollen due to RA.

1. Painful joints
2. Swollen joints
3. Stiffness in joints, particularly in the morning
4. Low fever
5. Fatigue
6. Loss of appetite
7. Feeling weak
8. Lumps under the skin, especially on the hands or elbows
9. Weight loss
10. Over time, decreased range of motion
11. Dry eyes and mouthwith during your life.
12. Redness and warmth
13. Muscle aches

Pathophysiology

The pathogenesis of RA is not completely understood. It is an external trigger (e.g.: ciggarate smoking infection or trauma) that trigger an autoimmune reaction leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestation, is theorized to occur in genetically susceptible individuals.

RA starts in synovium, the membrane produces sac surrounding the joint. This sac containing synovial fluid which lubricate and cushioning the joints along with that supplies nutrients and oxygen to cartilage which coats the end of bones. Cartilage is made of collagen and gives support and flexibility to joints. In rheumatoid arthritis, destructive molecules produced by an abnormal immune system response which is responsible for continuous inflammation of the synovium. Collagen is gradually destroyed, narrowing the joint space and finally damaging bone. In a progressive rheumatoid arthritis, destruction of the cartilage accelerates. Further pannus (thickened synovial tissue) formation occurs due to the accumulation of fluid and immune system cells in the synovium. The pannus produces more enzymes which destroy nearby cartilage, worsening the area and attracting more inflammatory white cells.

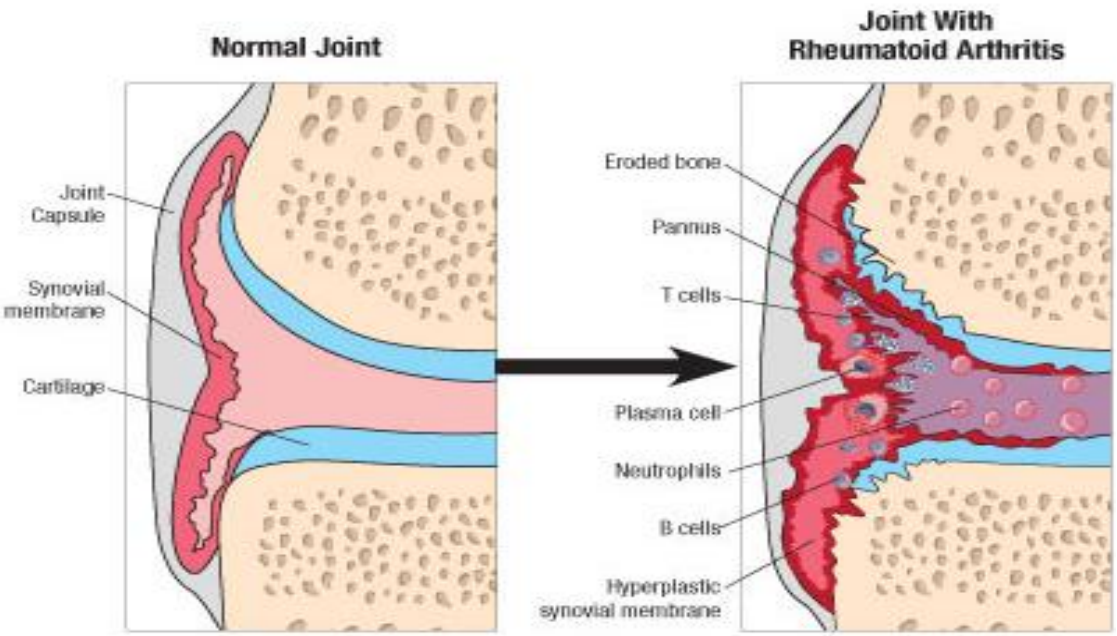

Fig. 2: Pathophysiology of RA.

Important environmental and biological factors associated with RA

1) Cigarette smoking.
2) Tumor necrosis factor (TNF)-an activity.
3) Abnormal and inappropriate B-lymphocyte activity, i.e. abnormal antibody production.
4) Detection of circulating auto antibodies against Ig Fc; these auto antibodies have been termed 'rheumatoid factor', and they may be involved in the

inappropriate presentation of antigens to T cells by B cells.

5) Abnormal activity of certain signaling pathways in synovial tissue, e.g. the signaling pathway, which is involved in embryonic development and cell renewal. In patients with RA, it has been reported that the synovial cells have abnormally high activity of the gene, as well as a number of other genes for several of the cytokines, cell adhesion molecules and chemokine's. At present, it is not known whether these abnormalities are causative or a result of the more fundamental abnormalities.

Rheumatoid Arthritis cause due to the Inflammation of Synovium

There are two most important components of immune system i.e. B cells and T cells lymphocytes that play important role in inflammation associated with rheumatoid arthritis. If the T cell recognizes an antigen as "non-self," it will produce chemicals (cytokines) which cause B cells to multiply and release antibodies circulate largely in the bloodstream, recognizing the foreign particles and triggering inflammation in order to rid the body of the invasion7. There are various steps involved in inflammatory responses in RA disease.

The rheumatoid joint contains a various proinflammatory cytokinesIL-1, IL-6, IL-8, IL-15, IL-16, IL17, IL-18, IL-23, IFN-γ, TNF-α, granulocyte macrophage-colony stimulating factor, macrophage inflammatory protein-1 and monocyte chemo attractant protein-1, Anti-inflammatory cytokines, such as IL-4, IL10, IL-11, andIL-13, and natural cytokine antagonists, including IL-1Receptor antagonist (IL-1ra), soluble type 2 IL-1 receptor, soluble TNF receptor (TNF-RI), and IL18 binding protein are responsible for maintenance of balanced action of these pro-inflammatory cytokines, in normal physiological condition. In the rheumatoid joint, the balance swings towards the pro-inflammatory cytokines. The recruitment of inflammatory cells to the inflammatory site can be up regulated by the expression of cell adhesion molecules on endothelial cells with the help of IL-1 and TNF-α. Both IL-1 and TNF-α activate a variety of inflammatory cell types found in the synovial, including macrophages, fibroblast, mast cell, neutrophils, chondrocytes, dendritic cells and osteoclasts, resulting in the release of other proinfalmmatory mediators and derivative enzymes. Both stimulate proliferation of synovial cells leading to pannus formation. Both cytokines influence immunological activity by causing T cell and B cell activation.

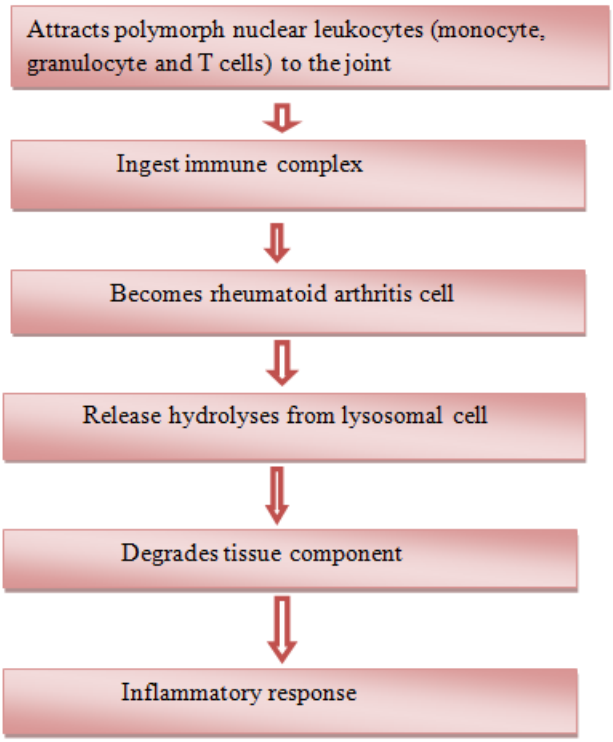

Fig: Inflammation of Synovium (Rheumatoid Arthritis).

Clinical Features

1) RA presents as a symmetrical polyarthritis affecting the small joints of the hands and feet.
2) The onset is most often insidious but can be episodic or acute.
3) Inflamed joints become swollen, painful, and stiff. Synovial fluid may accumulate, causing an effusion.

Joint pain is usually more prominent and more persistent than in osteoarthritis, occurring at rest, at night, and on activity. Prolonged early morning stiffness is also a key diagnostic feature suggestive of inflammatory disease.

4) In addition to causing peripheral symptoms, RA may also involve the cervical spine, causing pain in the neck and occipital headache.
5) Pain may also occur as a result of temporomandibular joint disease.
6) Uncontrolled disease eventually results in inflammation spreading beyond the synovium of the joint to other nearby structures, including the tenosynovium of tendons, ligaments, other soft-tissue structures, and bone. Subcutaneous nodules can occur in more severe disease and are associated with a worse prognosis.
7) Extra-articular features are common and may involve multiple organs, including the skin, eyes, lungs, and blood vessels.

Diagnosing and Managing RA

There is no one test that can show that you have RA. But your doctor can use a combination of tools to help diagnose RA:

1) Detection of serum RF (rheumatoid factor).
2) Morning stiffness for 1 hour or longer for 6 weeks or more.
3) Arthritis in three or more joints persisting for 6 weeks or more.
4) Persistence for 6 weeks or more of symmetrical arthritis.
5) Persistence for 6 weeks or more of arthritis of the hand joints.
6) Rheumatoid nodules.
7) Observation, using hand radiographs, of changes, erosion or unequivocal bony decalcification.

Physical examination of patient

• Reflexes, muscle strength, and general health.
• Ability to walk, bends, and carry out activities of daily living.
• Evidence of inflammation in the lungs.

Symptoms

• Pain, stiffness, and trouble with range of motion.

Lab tests

• Rheumatoid factor (RF).
• Anti-cyclic citrullinated peptide (anti-CCP) antibody test.
• Other tests include white blood-cell count, anemia test, erythrocyte sedimentation rate (ESR), and C-reactive protein

X-rays

• To determine the degree of joint damage. It is important to get an accurate diagnosis and appropriate treatment as early as possible. Even though symptoms may not appear like RA (for example, fatigue, weakness, low-grade fever, and weight loss), you should discuss all symptoms

Treatment for Rheumatoid Arthritis

1. Lifestyle changes.
2. Medicine.
3. Surgery.
4. Regular doctor visits.
5. Alternative therapies.

Lifestyle Changes Here are some ways to take care of you

1. Keep a good balance between rest and exercise.
2. Take care of your joints.
3. Lower your stress.
4. Eat a healthy diet.

Medicine

Most people with rheumatoid arthritis take medicine. Drugs can be used for pain relief, to reduce swelling, and to stop the disease from getting worse. What a doctor prescribes depends on:

1. The person's general health.
2. How serious the rheumatoid arthritis is.
3. How serious the rheumatoid arthritis may become.
4. How long the person will take the drug.
5. How well the drug works.
6. Possible side effects.

Surgery

There are many kinds of surgery for people with severe joint damage. Surgery is used to:

1. Reduce pain.
2. Help a joint work better.
3. Help people be able to do daily activities. Surgery is not for everyone. Talk about the option with your doctor.

Regular Doctor Visits Regular medical care is important so doctors can

1. See if the disease gets worse.
2. See if drugs are helping.
3. Look for drug side effects.
4. Change treatment when needed. Your care may include blood, urine, and other lab tests and x rays.

Alternative Therapies

Special diets, vitamins, and other alternative therapies are sometimes suggested to treat rheumatoid arthritis. Some therapies help people reduce stress. Many of these treatments are not harmful, but they may not be well tested or have any real benefits. People should talk with their doctor before starting an alternative therapy. If the doctor feels the therapy might help and isn't harmful, it can become part of regular care.

Current Research on Rheumatoid Arthritis

Research is being done in many areas:

1. Immune systems.
2. Genes.
3. Families with rheumatoid arthritis.
4. New drugs or drug combinations.
5. Rheumatoid arthritis and disability.
6. Preventing related health problems.
7. Quality of life for people with rheumatoid arthritis.

Current treatment of RA

1. Slow the rate of disease progression.
2. Control inflammation and pain; ideally the patients should be as free as possible from pain.
3. Design the appropriate treatment regimen for each patient.
4. Regular appointments with the clinic and the rheumatologist.
5. Regular patient monitoring for adverse effects of treatments.
6. Regular blood tests.
7. Monitor patient compliance

Treatment of Drug

1. Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

Ex: Paracetamol, opiates, Diproqualone.

2. Corticosteroids

Ex: prednisone, prednisolone, methyl prednisolone etc.

3. Disease Modifying Anti-rheumatic Drugs (DMARDs)

Ex: Methotrexate, Leflunomide, Hydroxychloroquine, chloroquine, cyclosporine, sulfasalazine, gold salts etc.

4. Immunosuppressants

Ex: Cyclophosphamide, Azathioprine etc.

5. Biological therapies in rheumatoid arthritis

Ex: Etanercept, infliximab, adalimumab, golimumab, anakinra, cetrolizumab, rituximab, abatecept etc.

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