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RHEUMATOID ARTHRITIS: REVIEW

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Abstract

A multifunctional autoimmune disease with an unclear cause, rheumatoid arthritis primarily affects the joints, though it can also appear extra-articularly.

Good RA care necessitates a multidisciplinary approach due to its complexity, which is based on a pathophysiological process that is not fully understood. Recent improvements in diagnosis and treatment of RA have improved the clinical condition of patients by preventing systemic consequences and reducing disease activity.

The development of disease-modifying anti-rheumatic medicines (DMARDs), which include standard synthetic, biologic, and targeted synthetic medications, has produced the most promising results.

In addition, continuous medication development has produced molecules with enhanced safety and efficacy profiles; nonetheless, additional investigation is required until RA becomes a pathology that can be treated.

Positive outcomes for RA patients need an early and precise diagnosis together with the best available personalized therapy.

Keywords:

RA (Rheumatoid arthritis), Rheumatoid factor, Autoimmune Disease, Chronic inflammation, DMARDs (Disease modifying antirheumatic drugs), Immune response, Synoviocytes.

Introduction:

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by a persistent inflammatory response that can harm extra-articular organs such as the heart, kidney, lung, digestive tract, eyes, skin, and nervous system in addition to joints. [1,2]

Rheumatoid arthritis is a chronic inflammatory disorder that can affect not only on joints but also on a wide variety of body systems, including the skin, eyes, lungs, heart and blood vessels, which could sustain harm from the illness in certain individuals.

Rheumatoid arthritis affects the lining of your joints, causing a painful swelling that can eventually lead to bone erosion and deformity, unlike the wear-and-tear damage of osteoarthritis.

Numerous types of arthritis have been studied and described in order to be divided into two categories: inflammatory arthritis (gout, pseudogout, basic calcium phosphate disease) and non-inflammatory arthritis (osteoarthritis). Inflammatory arthritis can also be caused by autoimmune processes, bacteria and viruses (Staphylococcus aureus, Neisseria gonorrhea, complications of Lyme disease, Parvovirus, Enterovirus) and crystal deposition. [3]

Risk Factors:

Factors that may increase your risk of rheumatoid arthritis include:

1. Gender: Women are more likely than men to develop rheumatoid arthritis.
2. Age: Rheumatoid arthritis can occur at any age, but it most commonly begins in middle age.
3. Family history: If a member of your family has rheumatoid arthritis, you may have an increased risk of the disease.[4]
4. Smoking: Cigarette smoking increases your risk of developing rheumatoid arthritis, particularly if you have a genetic predisposition for developing the disease. Smoking also appears to be associated with greater disease severity.
5. Excess weight: People who are overweight appear to be at a somewhat higher risk of developing rheumatoid arthritis.[5]

Epidemiology

- RA affects approximately 1% of the world population.
- The incidence varies by population. France has a low incidence rate o 8.8/100,000); rates in Scandinavian countries are higher at 24 to 36 per 100,000. The highest incidence rates (42–45/100,000) have been observed in the United States, but may be declining.
- In most populations, the incidence of RA increases with age until the eighth decade, and then declines. RA is more common in women and is uncommon in young men (<35 years). The difference between genders is not consistent and changes with increasing age.
- About 70% of people living with rheumatoid arthritis are women, and 55% are older than 55 years .[4]
- 13 million people with rheumatoid arthritis experience severity levels (moderate or severe) that could benefit from rehabilitation.
- In 2019, 18 million people worldwide were living with rheumatoid arthritis. In India Rheumatoid arthritis is 1% and annual incidence is 3 cases per 10,000 population.
- In India, it affects about 0.92% of adult population.[6]

Causes

- Rheumatoid arthritis is an autoimmune disease. In RA, your immune system attacks healthy tissue in your joints. A genetic component appears likely. While your genes don't actually cause rheumatoid arthritis, they

can make you more likely to react to environmental factors such as infection with certain viruses and bacteria that may trigger the RA

- Researchers are uncertain about the causes of RA. The probable causes of RA are as Follows:
  - Immune system issues
  - Age (40-60)
  - Smoking
  - Genetics
  - Obesity [7]

Stages of Rheumatoid Arthritis

Stage 1: In early stage rheumatoid arthritis, the tissue around your joint(s) is inflamed. You may have some pain and stiffness. If your provider ordered X-rays, they wouldn't see destructive changes in your bones.
Stage 2: The inflammation has begun to damage the cartilage in your joints. You might notice stiffness and a decreased range of motion.
Stage 3: The inflammation is so severe that it damages your bones. You'll have more pain, stiffness and even less range of motion than in stage 2, and you may start to see physical changes.
Stage 4: In this stage, the inflammation stops but your joints keep getting worse. You'll have severe pain, swelling, stiffness and loss of mobility. [8]

Signs and Symptoms

Signs and symptoms of rheumatoid arthritis may include:

- Swelling: Tender, warm, swollen joints
- Stiffness of Joint: Stiffness is usually worse in the mornings and after inactivity
- Pain: Inflammation inside the joints makes it painful
- Redness and warmth: Inflammation makes the joints red and warmer.
- Fatigue, fever and loss of appetite

- Early rheumatoid arthritis tends to affect your smaller joints first -particularly the joints that attach your fingers to your hands and your toes to your feet.
- As the disease progresses, symptoms often spread to the wrists, knees, ankles, elbows, hips and shoulders.

Areas that may be affected include:

- Skin
- Eyes
- Lungs
- Heart
- Kidneys
- Salivary glands
- Nerve tissue
- Bone marrow [9]

Complications

Rheumatoid arthritis increases your risk of developing:

- **Osteoporosis:** Rheumatoid arthritis itself, along with some medications used for treating rheumatoid arthritis, can increase your risk of osteoporosis - a condition that weakens your bones and makes them more prone to fracture.
- **Rheumatoid nodules:** These firm bumps of tissue most commonly form around pressure points, such as the elbows. However, these nodules can form anywhere in the body, including the heart and lungs.
- **Dry eyes and mouth:** People who have RA are much more likely to develop Sjogren's syndrome, a disorder that decreases the amount of moisture in the eyes and mouth.
- **Infections:** Rheumatoid arthritis itself and many of the medications used to combat it can impair the immune system, leading to increased infections.
- **Abnormal body composition:** The proportion of fat to lean mass is often higher in people who have rheumatoid arthritis, even in those who have a normal body mass index (BMI).
- **Carpal tunnel syndrome:** If rheumatoid arthritis affects your wrists, the inflammation can compress the nerve that serves most of your hand and fingers.
- **Heart problems:** Rheumatoid arthritis can increase your risk of hardened and blocked arteries, as well as inflammation of the sac that encloses your heart. [10]
- **Lung disease:** People with rheumatoid arthritis have an increased risk of inflammation and scarring of the lung tissues, which can lead to progressive shortness of breath. [11]
- **Lymphoma:** Rheumatoid arthritis increases the risk of lymphoma, a group of blood cancers that develop in the lymph system.
- **Employment:** RA can make work difficult. Adults with RA are less likely to be employed than those who do not have RA.
- **Obesity:** People with RA who are obese have an increased risk of developing heart disease risk factors such as high blood pressure and high cholesterol and Being also increases risk of developing chronic conditions such as heart disease and diabetes. [12]

Prevalence

- The estimated prevalence and disease burden of rheumatoid arthritis vary considerably between geographic regions, with generally higher estimates in industrialized countries and urban settings. The black people and females have more chances to get affected to RA. [13]

Pathophysiology

- RA primarily starts as a state of persistent cellular activation leading to autoimmunity and immune complexes in joints and other organs where it manifests.
- Joint damage and inflammation of the synovial membrane are the main clinical signs of the disease, and fibroblast-like synoviocytes are essential to these pathogenic processes. There are three stages in the development of RA: aninitial phase, an amplification phase and a chronic inflammatory phase, during which the cytokines IL-1, TNF-alpha, and IL-6 cause tissue damage.

Non-specific inflammation

- Once an aberrant immune response is triggered, certain factors make it persistent and permanent. These are hereditary conditions that alter how the adaptive immune system is regulated. For RA, environmental and genetic risk factors interact, with cigarette smoking being the most well-established risk factor
- Higher risks for women may be explained by additional hormonal and environmental factors, such as onset after childbirth and hormonal medications. Increased susceptibility could result from negative feedback mechanisms, which are typically responsible for maintaining tolerance.
- Surpassing certain antigens through positive feedback mechanisms, like IgG Fc bound to rheumatoid factor and citrullinated fibrinogen bound to antibodies to citrullinated peptides (ACPA – Anti–citrullinated protein antibody).
- The only signs for RA are autoantibodies to IgGFc, also referred to as rheumatoid factors and ACPA, which has an 80% specificity for RA diagnosis. People with RA have abnormally glycosylated antibodies, as with other autoimmune diseases, and it is thought that these antibodies contribute to joint inflammation. [14]

Amplification in the synovium

- After the establishment of the generalized abnormal immune response, which may take years before symptoms appear B lymphocyte-derived plasma cells generate large amounts of ACPA of the IgG and IgM classes as well as rheumatoid factors. Complement binding and the Fc receptor cause these to activate macrophages, contributing to the severe inflammation associated with RA.

- The altered N-glycans of an autoreactive antibody facilitate its binding to the Fc receptors, thereby inducing inflammation in RA patients. This leads to edema, vasodilation, and the entry of activated T-cells, mostly CD4 in microscopically nodular aggregates and CD8 in microscopically diffuse infiltrates into the synovium, which is responsible for local inflammation in a joint. By expressing MHC class II molecules, synovial macrophages and dendritic cells serve as antigen-presenting cells, determining the tissue's immune response. [15]

Chronic inflammation

- Granulation tissue forms at the synovial lining's margins as the disease worsens, accompanied by pannus with significant angiogenesis and tissue-damaging enzymes.These pathogenic processes heavily involve the fibroblast-like synoviocytes. The raised calprotectin levels act as a biomarker of the degenerative processes that cause the synovium to thicken, the cartilage and underlying bone to disintegrate, and the joint to deteriorate.
- Crucially, it appears that inflammatory events are not restricted to the synovium but rather appear to be systemic. Evidence points to changes in the T helper profile that promote inflammation, such as

inflammatory T helper cells that produce IL-17A and pathogenic T17 cells that originate from the memory and effector compartments in the peripheral blood of RA patients.

- Cytokines and chemokines attract and accumulate immune cells, i.e. activated T- and B cells, monocytes and macrophages from activated fibroblast-like synoviocytes, in the joint space.

- Through RANKL and RANK signaling, they ultimately cause osteoclast synthesis, which weakens bone tissue.

- When compared to the cells found in normal tissues, the fibroblast-like synoviocytes found in the synovium during rheumatoid arthritis exhibit a different phenotype. The features that set rheumatoid arthritis fibroblast-like synoviocytes apart from healthy ones can be used to characterize the aggressive phenotype of these cells and the impact they have on the joint microenvironment.

- These hallmark features of fibroblast-like synoviocytes in rheumatoid arthritis are divided into seven cell-intrinsic hallmarks and four cell-extrinsic hallmark. Reduced apoptosis, decreased contact inhibition, increased migratory invasive potential, altered epigenetic landscape, temporal and spatial heterogeneity, genomic instability and mutations, and reprogrammed cellular metabolism are the hallmarks of cell-intrinsic traits.

- The cell-extrinsic features of FLS in RA include: promoting bone erosion and osteoclastogenesis; degrading cartilage; inducing synovial angiogenesis; and recruting and activating immune cells. [16]

Diagnosis

Blood Tests-

- People with rheumatoid arthritis often have an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, which may indicate the presence of an inflammatory process in the body.
- Other common blood tests look for rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Following Tests are performed:
  1) RA test
  2) ASO Titer test
  3) ANA (Anti-nuclear antibody) Test

Imaging Tests:

X-rays are recommended to help track the progression of rheumatoid arthritis in your joints over time. MRI and ultrasound tests can help your doctor judge the severity of the disease in your body. It observe following:

1) Reduction of joint space
2) Nodule formation at joint
3) Osteoporosis at joint [17]

Reasons for Proliferating RA:

- Fault in the immune system that causes the body to attack its own tissues in joints.
- Wear and tear of joints over time.
- Abnormal metabolism.

- Injuries due to accidents or sporting activities.
- Infections.
- Degradation of joints.
- Muscle weakness.
- Obesity [18]

Management of RA

Treatment:
There is no cure for rheumatoid arthritis. But clinical studies indicate that remission of symptoms is more likely when treatment begins early with medications known as disease modifying antirheumatic drugs (DMARDs).

- **Medications:**

The types of medications recommended by your doctor will depend on the severity of your symptoms and how long you've had rheumatoid arthritis.

➢ **NSAIDs**: Nonsteroidal anti-inflammatory drugs (NSAIDs) can relieve pain and reduce inflammation. Over-the-counter NSAIDs include ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve). Stronger NSAIDs are available by prescription. Side effects may include stomach irritation, heart problems and kidney damage.

➢ **Steroids**: Corticosteroid medications, such as prednisone, reduce inflammation and pain and slow joint damage. Commonly used corticosteroid is Dexamethasone.

➢ **Conventional DMARDs**: These drugs can slow the progression of rheumatoid arthritis and save the joints and other tissues from permanent damage.
Common DMARDs include
- Methotrexate (Rheumatrex, Trexall)
- Hydroxychloroquine (Plaquenil)
- Sulfasalazine (Azulfidine)
- Leflunomide (Arava)
- Tumor Necrosis Factor Inhibitors-etanercept (Enbrel, adalimumab (Humira) and infliximab (Remicade), certolizumabpegol (Cimzia), golimumab (Simponi)
- T-cell Costimulatory Blocking Agents - abatacept (Orencia)
- B cell Depleting Agents - rituximab (Rituxan)
- Interleukin-6 (IL-6) Inhibitors -tocilizumab (Actemra)
- Interleukin-1 (IL-1) Receptor Antagonist Therapy-anakinra (Kineret)
- Intramuscular Gold
- Other Immunomodulatory and Cytotoxic agents - azathioprine (Imuran) and Cyclosporine A (Neoral, Sandimmune) [19]

➢ **Biologic agents:** Also known as biologic response modifiers, this newer class of DMARDs includes:
- Abatacept (Orencia)
- Adalimumab (Humira)
- Anakinra (Kineret)
- Certolizumab (Cimzia)
- Etanercept (Enbrel),
- golimumab (Simponi),
- Infliximab (Remicade),
- rituximab (Rituxan)

- Sarilumab (Kevzara)
- Tocilizumab (Actemra).

Biologic DMARDs are usually most effective when paired with a conventional DMARD, Such as methotrexate. [20]

➢ **Targeted synthetic DMARDs.**

- Baricitinib (Olumiant)
- Tofacitinib (Xeljanz)
- upadacitinib (Rinvoq)

It may be used if conventional DMARDs and biologics haven't been effective. Higher doses of tofacitinib can increase the risk of blood clots in the lungs, serious heart-related events and cancer.[21]

▪ **Physical Therapy and Occupational Therapy:**

- Doctors may recommend physical therapy and occupational therapy.
- Physical therapy can help you regain and maintain overall strength and target specific joints that bother you.
- Occupational therapy can help develop, recover, improve, as well as maintain the skills needed for daily living and working.
- Sometimes, assistive devices or braces may be helpful.
- Optimize movement, reduce pain, and help you maintain the ability to work. [22,23,24]

▪ **Surgery:**

Doctors may recommend surgery if you have permanent damage or pain that limits your ability to perform day-to-day activities. Surgery is not for everyone. You and your doctor can discuss the options and choose what is right for you.

Your doctor will consider the following before recommending surgery:

• Your overall health.

• The condition of the affected joint or tendon.

• The risks and benefits of the surgery.

Types of surgery may include

- Joint repairs
- Joint replacements. [25,26,27]

Side Effects of Medicines:

➢ **NSAIDs:**

- The most common toxicity of NSAIDs is gastrointestinal disturbance which may clinically include burning, belching, or irritation, but which can represent irritation of the lining of the stomach, erosions, and even ulcerations that can result in bleeding.
- NSAIDs, which block the inflammation of RA, can be present in both prescription drugs and over-the-counter drugs like ibuprofen. The most common side effects are stomach problems like heartburn and belching.

➢ **Steroids :**
Steroids in RA management may also cause high blood pressure, weight gain, high blood sugar and decreased bone health.

➢ **Methotrexate: Liver Damage :**
The most serious side effect of methotrexate is liver damage. That's why people with existing liver disease aren't good candidates for this medication. Liver function should be checked prior to initiation of methotrexate and then again two to three weeks after starting the medication.

➢ **Triple Therapy and Eye Damage**

- Combining methotrexate with two other DMARDs may be an option if methotrexate alone isn't enough to achieve good RA management.
- One of the drugs used in this triple therapy is hydroxychloroquine, a malaria drug that's effective for some cases of RA. For this particular DMARD, the most serious possible side effect is eye damage. [28,29]

▪ **Meftal Spas**

- The mefanamic acid was used to treat Rheumatoid arthritis, osteoarthritis, dysmenorrhoea, mild to moderate pain, inflammation, fever, dental pain.
- The Indian Pharmacopoeia Commission (IPC) issued a drug safety alert about Meftal, a commonly used non-steroidal anti-inflammatory drug (NSAID), saying that its constituent, mefenamic acid, triggers drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, a severe allergic reaction. [30]

Lifestyle Changes

Certain activities can help improve your ability to function on your own and maintain a positive outlook.

➢ **Rest and exercise:**
Balance your rest and exercise,take more rest when your RA is active and do exercise when it is not. Rest helps to decrease active joint inflammation, pain, and fatigue. Exercise is important for maintaining healthy and strong muscles, preserving joint mobility, and maintaining flexibility.

Exercise can help to:
• Improve your sleep.
• Decrease pain.
• Keep a positive attitude.
• Maintain a healthy weight.

➢ **Stress managemen**t:
You may feel fear, anger, and frustration, along with any pain, physical limitations, which can increase your stress level. Stress also may affect the amount of pain you feel. Ways to cope with stress can include:

- Regular rest periods.
- Relaxation techniques such as deep breathing, meditating, or listening to quiet sounds or music.
- Movement exercise programs, such as yoga.

➢ **Mental health management:**
If you feel alone, anxious, or depressed about having the disease, talk to your doctor, an RA support social worker, or mental health professional. Keep the lines of communication open. Talk to family and friends about your RA to help them understand the disease. You may find it helpful to join an online or community support group.

- **Healthy diet:**
  A healthy and nutritious diet that includes a balance of calories, protein, and calcium is important for maintaining overall health.

- **Apply heat or cold:**
  Heat can help ease your pain and relax tense, painful muscles. Cold may dull the sensation of pain. Cold also has a numbing effect and can reduce swelling. [31,32]

Diet:

- **Fish oil:**
  Some preliminary studies have found that fish oil supplements may reduce rheumatoid arthritis pain and stiffness.

- **Plant oils:**
  The seeds of evening primrose, borage and black currant contain a type of fatty acid that may help with rheumatoid arthritis pain and morning stiffness.

- **Fruits and veggies:**
  Fruits and vegetables are rich in antioxidants, which help stabilize molecules called free radicals that can trigger inflammation and damage cells. They're also packed with vitamins and minerals the body needs and in polyphenols, all of which may help lower C-reactive protein (CRP), a marker of inflammation.

- **Peas and beans:**
  These legumes are a great source of protein, which is important for muscle health and people with RA are prone to muscle loss. [33]

Conclusion

RA is a severe, inflammatory, chronic illness that can lead to long-term disability and joint damage. The avoidance of severe harm and the loss of vital physiological functions depends on early diagnosis and treatment. The treating physician ought to think about following the treat-to-target (T2T) recommendation, which involves defining the goals and then putting the procedures and controls to reach and evaluate them.
Better treatment results can also be ensured with an early referral to a specialist. The understanding of disease mechanisms has improved due to developments in the field of molecular medicine, which may help in the development of more potent treatments. Both new and improved versions of existing treatment modalities have been developed. The use of gene array analysis is showing promise in identifying the patients who will respond best to particular treatments. In order to find the best treatment for a patient, this customization will enable faster treatment and reduce the chance that the disease will progress during the experimental phase. Additionally, gene array analysis is being used to identify patients who may be more susceptible to more severe forms of RA.
It is anticipated that RA management techniques will see significant advancements.

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