World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 7.409

REVIEW ON RHEUMATOID ARTHRITIS AND AWARENESS ON MULTIPLE CATEGORIES

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Article Received on 05/02/2025 **Article Revised on 25/02/2025** **Article Accepted on 17/03/2025**

ABSTRACT
Rheumatoid arthritis (RA), a chronic inflammatory autoimmune disorder, is characterised by persistent synovial inflammation, erosion of bones and cartilage, leading to joint destruction. Clinical manifestations are morning stiffness, pain in shoulder, neck and pelvic girdle, loss of mobility with fever, fatigue, malaise, loss of body weight, and development of rheumatoid nodules. Environmental and genetic factors are important contributors in its susceptibility. Association between RA and diet, cigarette smoking, hormones, alcohol, microbiota, infection, and coffee have also been reported. To diagnose patients with RA, American college of rheumatology (ACR, 2010) criteria, developed by European league against rheumatism (EULAR). Inflammation produced in RA patients is due to cell-mediated immune response. The rheumatoid synovium consists of a large number of CD_4^+ T cells suggesting pathogenic nature of T cells in this disorder. B-cells may also participate in the pathogenesis by several means such as autoantibodies, by instigation of T-cells through expression of co-stimulatory molecules, by generating pro-inflammatory and anti-inflammatory cytokines and by organisation of other inflammatory cells. The conventional management of RA usually focuses over reducing pain and limiting the disability by medical therapies which include a number of classes of agents such as non-steroidal anti-inflammatory drugs (NSAIDs), non-biological and biological agents, disease-modifying anti rheumaticdrugs (DMARDs), immunosuppressants, and corticosteroids. However, only proper rehabilitation can promote the objective to achieve the joint functionality and ease of motion which improves independence as well as quality of life in patient suffering from Rheumatoid Arthritis.

KEYWORDS: rheumatoid arthritis, joints deformity, autoimmune disorder, NSAIDs and DMARDs.

Significance of the Study
Rheumatoid arthritis not only affects the joints but can also affect internal organs, thus causing permanent disability in many instances. Currently, there is no cure for this autoimmune disease, rather, symptoms are addressed on an individual basis. Here, we succinctly summarize the classic and current treatment options available for the management of patients suffering from this complex disease.

INTRODUCTION
Rheumatoid arthritis (RA) is a chronic, symmetrical, inflammatory autoimmune disease that initially affects small joints, progressing to larger joints, and eventually the skin, eyes, heart, kidneys, and lungs. Often, the bone and cartilage of joints are destroyed, and tendons and ligaments weaken.[1] All this damage to the joints causes deformities and bone erosion, usually very painful for a patient. Common symptoms of RA include morning stiffness of the affected joints for > 30 min, fatigue, fever, weight loss, joints that are tender, swollen and warm, and rheumatoid nodules under the skin. The onset of this disease is usually from the age of 35 to 60 years, with remission and exacerbation. It can also afflict young children even before the age of 16 years, referred to as juvenile RA (JRA), which is similar to RA except that rheumatoid factor is not found.[2, 3, 4, 5] In the West, the prevalence of RA is believed to be 1–2%[5, 6], and 1% worldwide.[7]

Clinically, the diagnosis of RA can be differentiated from osteoarthritis (OA) as the affected areas in RA are the proximal interphalangeal (PIP) and metacarpophalangeal (MP) joints; OA typically affects the distal interphalangeal (DIP) joint. OA is the most common type of arthritis and is caused by wear and tear rather than an

autoimmune condition. It has no effects on the lungs, heart, or immune system. In addition, OA typically affects only one side of the body, as opposed to the symmetrical nature of RA. Another differentiating factor is that RA patients suffer from persistent morning stiffness for at least ≥1 h. Patients with OA may have morning stiffness, but this typically resolves or decreases within 20–30 min.[8, 9] The goals of treatment for RA are to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Treatment regimens consist of combinations of pharmaceuticals, weight-bearing exercise, educating patients about the disease, and rest. Treatments are generally customized to a patient's needs and depend on their overall health. This includes factors such as disease progression, the joints involved, age, overall health, occupation, compliance, and education about the disease.[10] This review briefly highlights the classic and current treatment options available to address the discomfort/complications of RA. An exhaustive review was recently published by Smolen et al.[11]

PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

RA, in some patients, is triggered by some sort of environmental factor in a genetically predisposed host. The best example is tobacco use in a patient with the HLA-DRB1 "shared epitope" gene and the development of ACPA-positive RA.[12] RF and ACPA antibodies are the best-known autoantibodies in RA, but several other autoantibodies are relatively specific for RA. The presence of antibodies in rheumatoid arthritis is referred to as seropositive RA. RF is an antibody of any isotype that binds to the Fc portion of IgG RA patients often have antibodies to citrullinated proteins. These antibodies have been identified in patients with RA since 1964 (antiperinuclear factor)[13] and were also described in 1979 (anti-keratin antibodies)[14] by different assays. In the 1990s, these antibodies were determined to be the same antibodies with high specificity for RA.

[15]The antibodies were found to have specificity for filaggrin, a citrullinated peptide.[16][15] The epitope for these antibodies is citrullinated peptides. A cyclic citrullinated peptide (CCP) was synthesized, which could be used in an ELISA to test for these antibodies in patients in a clinical situation.[17] These antibodies are called anti-cyclic citrullinated peptide antibodies (ACPA). Citrulline is derived from the post-transcriptional modification of arginine by peptidyl arginine deiminase (PAD).[18]

The immune response in RA starts at sites distant from the synovial joints, such as the lung, gums, and GI tract.[12] In these tissues, modified proteins are produced by biochemical reactions such as citrullination. The mechanism behind environment-triggered RA is thought to be due to the repeated activation of innate immunity.

Etiology: The etiology of RA has a significant basis in genetics. It is thought to result from the interaction between patients' genotypes and environmental factors. In a nationwide study of 91 monozygotic (MZ) and 112 dizygotic (DZ) twin pairs in the United Kingdom, the overall MZ concordance rate was 15%, and in dizygotic twins, 5%.[19] The heritability of rheumatoid arthritis is approximately 40% to 65% for seropositive rheumatoid arthritis and 20% for seronegative rheumatoid arthritis.[19] The risk of developing rheumatoid arthritis has been associated with HLA-DRB1 alleles: *HLA-DRB1*04*, *HLA-DRB1*01*, and *HLA-DRB1*10*. These HLA-DRB1 alleles contain a stretch of a conserved sequence of 5 amino acids referred to as the "shared epitope" (SE) in the third hypervariable region of their DRB1 chain, which has been associated with the risk of developing RA.[20][21][22][23]

Polymorphisms in other genes are associated with RA, including *PAD14*, *PTPN22*, *CTLA4*, *IL-2RA*, *STAT4*, *TRAF1*, *CCR6*, and *IRF5*.[24][25][26] Single nucleotide polymorphism (SNP) in *PSORS1C1*, *PTPN22*, and *MIR146A* genes are associated with severe disease.[27] Some genetic polymorphisms are associated with RA in different ethnic groups.[25][27]

The term epigenetics refers to heritable changes without altering the DNA sequence. These changes may be present in chromatin or the DNA. These include DNA methylation, histone modification, and non-coding RNA-mediated regulation. RA-FLS (fibroblast-like synoviocytes) overexpress tyrosine phosphatase SHP-2, coded by gene PTPN11, compared to synoviocytes from osteoarthritis (OA) patients, promoting the invasive nature of RA-FLS. The enhancer region of the PTPN11 intron contained two hypermethylated sites, resulting in abnormal epigenetic regulation of the gene and alteration of the function of RA-FLS.[28]

Cigarette smoking is the strongest environmental risk factor associated with rheumatoid arthritis. Studies have shown in anti-citrullinated protein antibody (anti-CCP) positive individuals, there is an interaction between the shared epitope (SE) and smoking that increases the risk of RA.[29][30][31][32][33][34][35]

Other environmental triggers may play a role as a trigger for RA, which is more closely associated with seropositive RA. These include silica, asbestos, textile dust, and *P gingivalis.*[36] This suggests that external exposure to various antigens in parts of the host distant from the joints then triggers an autoimmune inflammatory response in the joints. These distant locations include the lungs, oropharynx, and GI tract.[36] Changes in the composition and function of the intestinal microbiome have been related to rheumatoid arthritis as well. The composition of the gut microbiome becomes altered in patients with rheumatoid arthritis (dysbiosis), where rheumatoid arthritis patients have decreased gut microbiome diversity compared with healthy individuals.

There is an increase in these genera: *Actinobacteria, Collinsella, Eggerthalla, and Faecalibacterium*. *Collinsella* alters gut mucosal permeability and has been related to increased rheumatoid arthritis disease severity.[35]

Mechanism of Action

By inhibiting fatty acid COX enzyme, trolamine salicylate inhibits the production of prostaglandins and thromboxanes in inflammatory cells involved in generating pain and inflammation.[17]

Inflammation

Inflammation (Latin, inflammo, "I ignite, set alight") is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants (Fig.8). Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. Inflammation is not a synonym for infection, even in cases where inflammation is caused by infection. Although infection is caused by a microorganism, inflammation is one of the responses of the organism to the pathogen. However, inflammation is a stereotyped response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen.

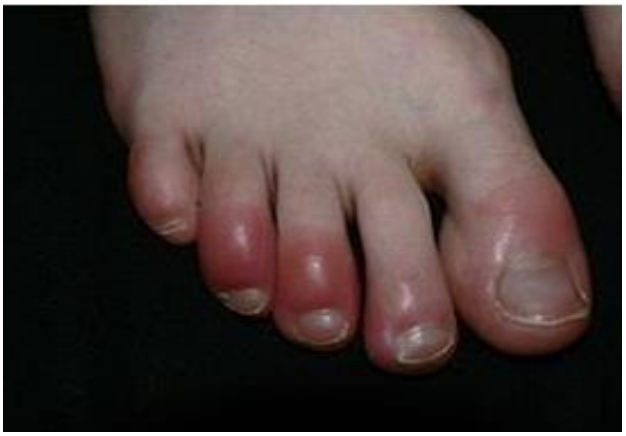

Fig. 8: Inflammation

Classification of Inflammation

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.[45]

Signs and symptoms

Signs and symptoms of RA usually occur in the wrists, hands, or feet and include:

- pain, swelling, and stiffness in more than one joint
- a low-grade fever
- appetite loss
- weight loss
- tiredness
- dry eyes
- chest pain.

Risk Factors for RA

The cause of RA is unknown, but certain risk factors are associated with an increased likelihood of developing RA, including a family history of RA or other autoimmune diseases, smoking, poor dental health, and viral infections.

Diagnosis of RA

- **Medical history:** The doctor will ask about joint symptoms (pain, tenderness, stiffness, difficulty moving), when they started, if they come and go, how severe they are, what actions make them better or worse and whether family members have RA or another autoimmune disease.
- **Physical examination:** The doctor will look for joint tenderness, swelling, warmth and painful or limited movement, bumps under the skin or a low-grade fever.
- Rheumatologists use physical examination, blood tests, and x-ray scans to diagnose RA. Most patients with RA have blood test results that are positive for antibodies called rheumatoid factor (RF), anticyclic citrullinated protein (CCP) antibodies, or both. Rheumatologists can help differentiate RA from other diseases that may cause similar symptoms but require different treatment.

Treatment and Prognosis of RA

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs do not have any disease-modifying effects but are commonly used to relieve symptoms related to joint inflammation and pain. There are about 20 such drugs (depending on what country you are in) that are all effective at full doses. There is some variation in side effects and toxicities. There is a class Black Box warning for cardiovascular disease, although there is variation in the cardiovascular effects among NSAIDs.[37][38]

❖ **Corticosteroids**

Corticosteroids are commonly used in patients with RA. There are several situations in which corticosteroids should be considered. In a new patient with very active RA, corticosteroids can be used as bridge therapy while DMARD therapy is instituted. Some studies show that using corticosteroids early in RA patients improves outcomes and has disease-modifying effects, including radiographic progression.[39][40]

TNF inhibitors

The TNF inhibitors include etanercept, infliximab, adalimumab, certolizumab, and golimumab. The ACR does not recommend using TNF inhibitors until a nonbiologic DMARD has been tried.[41]

Rituximab

Rituximab is a biologic DMARD that can be added for treating RA if patients have uncontrolled RA and who did not respond to TNF inhibitors.[42] Rituximab is given as an intravenous infusion; it depletes CD20+ B-cells and decreases the immune response to vaccines in patients receiving rituximab.

Janus kinase (JAK) Inhibitors

JAK is a group of tyrosine kinases that participate in intracellular signal transduction for haematopoiesis and immune cell function. JAK inhibitors (such as tofacitinib) are oral agents that reduce the production of cytokines and are approved as second-line agents for the treatment of RA.[43]

PREVANTION

Several key prevention strategies have been proposed to prevent rheumatoid arthritis and control the disease progression. In particular, reducing exposure to inhaled silica, dusts and occupational risks, and lifestyle related behaviours (e.g., prevention of/stop smoking, healthy nutrition, physical activity, maintaining a normal body weight, maintaining good dental hygiene) play an important role. Some evidence also suggests breastfeeding may be protective to the mother

ANNEXURE

SURVEY QUESTIONNAIRE

1.Name:
Age:
Gender:
Working:
2. What is the past history of the rheumatoid arthritis in your family?
3. Which type of diet you're taking after suffering?
4. If you have any other disease along with rheumatoid arthritis?
5. When was this condition first diagnosed?
6. Which type of drugs your using?
7. From how many years you're suffering from rheumatoid arthritis?
8. Are you suffering difficulty while holding objectives?
9. What did you think the cause of rheumatoid arthritis

10. You taking prescribed medicines or medications?
A) Yes
B) No
11.Did you skip any medications in last few days during disease period?
A) Yes
B) No
12. Did you stop taking your medications or medicines when you drink alcoholic beverages?
A) Yes
B) No

RESULT

We limited analysis to individuals 20 years and older and excluded those who did not have a medical exam because this provided BMI data. Respondents were asked if they had arthritis, and if so, was it OA, RA, psoriatic arthritis (PA), other arthritis, and whether they did not know what kind. While it is likely that most who reported that they did not know what kind had OA, we excluded these from further consideration because our goal was a comparison of risks for confirmed OA and RA. We also lumped those with PA in with "other" because those numbers were small. Over the full period there were 47,031 persons who had the medical exam and were included in our study. Of these there were 4,298 reported cases of OA, 2,482 reported case of RA, 1,337 individuals with other types of arthritis, and 4,218 individuals who did not know what type of arthritis they had. A total of 34,696 persons reported that they did not suffer from arthritis.

DISCUSSION

Prevalence of both increases with age, although it rises more steeply at older age for OA as would be expected due to wear and tear. Both occur more frequently in women than men. However, the sex difference we find using NHANES data is not nearly as large as literature reports of a three-fold difference (Wolfe et al., 1968). The reasons for this are unclear. One possibility is that the random survey used by NHANES provides a more accurate distribution than seen in a hospital or clinicbased study, which often reflects greater use of medical care by women than by men. Nevertheless, we do find rates in women to be higher than men.

CONCLUSION

RA is a debilitating, chronic, inflammatory disease, capable of causing joint damage as well as long-term disability. Early diagnosis and intervention are essential

for the prevention of serious damage and loss of essential bodily functions. The treating physician should consider adhering to treat-to-target (T2T) recommendations [44], by first outlining the aims and then implementing the protocols to achieve and assess them. Furthermore, early referral to a specialist can help to ensure better treatment outcomes. With advances in the field of molecular medicine, we have a better understanding of disease mechanisms which can aid in the designing of more effective treatments. Old treatment modalities have been optimized and new ones have been produced. Gene array analysis is proving beneficial in finding out which patients will be more responsive to specific medications. This customization will allow for more rapid treatment as well as decrease the likelihood of disease progression during the experimental phase to seek an appropriate treatment for a particular patient. Gene array analysis is also being used to determine which patients are at greater risk for more aggressive forms of RA. It is foreseen that treatment methods will face tremendous improvements in the management of RA.

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