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Review Article

Rheumatoid Arthritis Epidemiology, Pathophysiology, and Management

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Abstract

Introduction: Rheumatoid arthritis is a complex autoimmune disorder that results in debilitating peripheral joint pain, and the physical disability therefrom. The prevalence of RA is heterogenous with some communities not reporting any cases while others have it in high numbers. This review will discuss the complex etiopathogenesis of the disease along with various clinical and radiological features. The review will also briefly discuss diagnostic criteria and treatment modalities.

Aim of Work: The aim of this study is to write an overview of rheumatoid arthritis epidemiology, pathophysiology, and management.

Materials and Methods: Comprehensive research of rheumatoid arthritis epidemiology, pathophysiology, and management. PUBMED search engine was the mainly used database for the search process, articles collected from the year 1997 to 2021 relating to rheumatoid arthritis. The term used in the search were: rheumatoid arthritis, HLA gene, *PTPN11* gene, citrullination, autoantibodies, ACPA, RF, periodontitis, rheumatoid nodules, DMARDs, biologics.

Conclusion: This review has briefed the basic overview of rheumatoid arthritis. RA is a complex autoimmune disease that largely affects the joints of the human body. It has some genetic predilection as well as environmental influencers in its pathophysiology.

Of particular importance is the role of autoantibodies in creating a cascade of events leading to joint inflammation. The clinical and radiological features are quite heterogenous and therefore their diagnosis depends on the clinical judgment of doctors. There also exists a diagnostic criterion that can assist in diagnosing RA, especially during patient selection in clinical studies. Pain and inflammation are generally managed by NSAIDs and steroids, while DMARDs and biologics are used to restrict the disease progression in RA.

Keywords: *Rheumatoid Arthritis; HLA Gene; PTPN11 Gene; Citrullination; Autoantibodies; ACPA; RF; Periodontitis; Rheumatoid Nodules; DMARDs; Biologics*

Introduction

Rheumatoid arthritis (RA) is a complex autoimmune disease that manifests mostly as chronic inflammation in the joints as well as some extra-articular symptoms. Inflammation in the joints can severely hamper the normal functioning of the affected individual and result in social dependency. It affects up to 1% of the adult human population and its incidence is higher in the northern hemisphere when compared to the southern. Recent discoveries in immunology and genetics have vastly improved our understanding of the pathophysiology of the disease and subsequently helped us devise novel therapeutic strategies [1].

Epidemiology

Rheumatoid arthritis (RA) generally wiggles between 0.5% to 1% in most populations, however, certain communities have a much higher prevalence. Certain native American communities namely the Pima Indians and the Chippewa Indians have a prevalence of 5.3% and 6.8% respectively. Conversely, investigators failed to find RA in any significant amount in rural African populations. Similarly, countries like China and Japan also revealed a low prevalence of RA (0.2 - 0.3% respectively) [1].

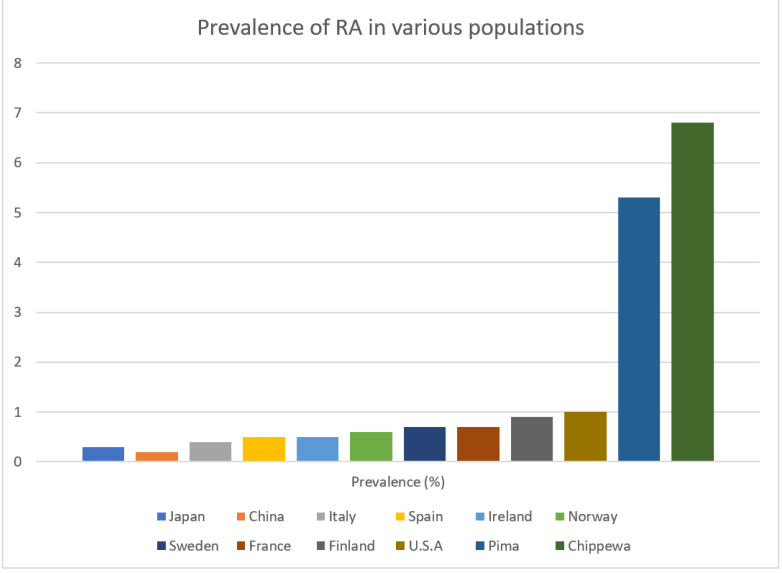

Chart 1: *Prevalence of RA in various populations [1].*

Some migrant epidemiological studies have suggested the possibility of genetic factors playing a role in the prevalence of RA. There was a low occurrence of RA in a black Caribbean population living in the UK in one study compared to whites [2]. Another study revealed that Pakistanis living in the UK have a lower prevalence of RA when compared to ethnic English, but higher than that of Pakistanis living in Pakistan [3].

Etiology

Rheumatoid arthritis is thought to be caused by a complex interplay of the environment and the patient's genotype. RA has been associated with human leukocyte antigen (HLA) genes for a long time and, more specifically, with DR4 allotypes. Also, most RA patients were also found to be sharing 5 amino-acid sequence motifs called the shared epitope [4]. Another gene, known as *PTPN11* was found to be overexpressed in fibroblast-like synoviocytes in RA patients when compared with Osteoarthritis (OA) patients [5].

Smoking has been considered the most decisive environmental risk factor for RA. One study performed on 14 healthy smokers and 16 healthy non-smokers revealed the upregulation of citrullinated proteins in bronchoalveolar lavage cells in the former group. This was also linked with higher expression of peptidylarginine deiminase (PAD)2 enzyme [6].

Both oral and gut microbiomes have been associated with integral players in the development of rheumatoid arthritis. X Zhang., *et al*. (2015) performed metagenomic sequencing from the dental, salivary, and fecal matter of RA patients and non-RA controls. They found alterations in the microbiome of RA individuals compared to controls. They noticed an increase in *Lactobacillus salivarius* and reduced *Haemophilus* spp in RA subjects [7].

Of particular importance is the association between RA and periodontitis (PD). Patients suffering from periodontitis are at an increased risk of getting RA and vice versa [8]. Severe gingivitis is caused by a bacterium called *Porphyromonas gingivalis,* which may explain some pathophysiology behind RA. *P gingivalis* produces peptidyl-arginine deiminase (PAD) enzyme, which may provide a source of citrullinated antigens and, in turn, anti-citrullinated protein antibodies (ACPA). Unfortunately, the antigen citrullinated by the PAD enzyme of *P gingivalis* differs significantly from citrullinated self-antigens. Therefore, this hypothesis is debatable. The role of ACPA in RA is explained in the next section [9].

Auto-antibodies

The sera of RA patients contain many autoantibodies, and they help us provide clues to the pathophysiology of RA. Rheumatoid Arthritis can be divided into seropositive and seronegative types based on the presence of autoantibodies whereas most cases of RA are seropositive. The common autoantibodies found are rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), anti-carbamylated protein antibodies (anti-CarP), and more recently anti-acetylated protein antibodies. Of these, ACPA has become popular in research, which are antibodies targeting citrullinated proteins. The process by which the peptidyl-arginine deiminase (PAD) enzyme converts the amino acid arginine to citrulline is called citrullination. Citrulline amino acid is not among the naturally occurring 20 amino acids in humans and thus, it triggers antibodies against it [10].

Rheumatoid factor (RF) is another autoantibody which is a pentameric IgM molecule that acts against Fc regions of IgG antibodies. This presence of these autoantibodies in elevated amounts in the sera of patients is suggestive of a more severe disease of RA. Also, people who have RF in their blood are likely to get RA and have a poorer prognosis [11].

Pathophysiology

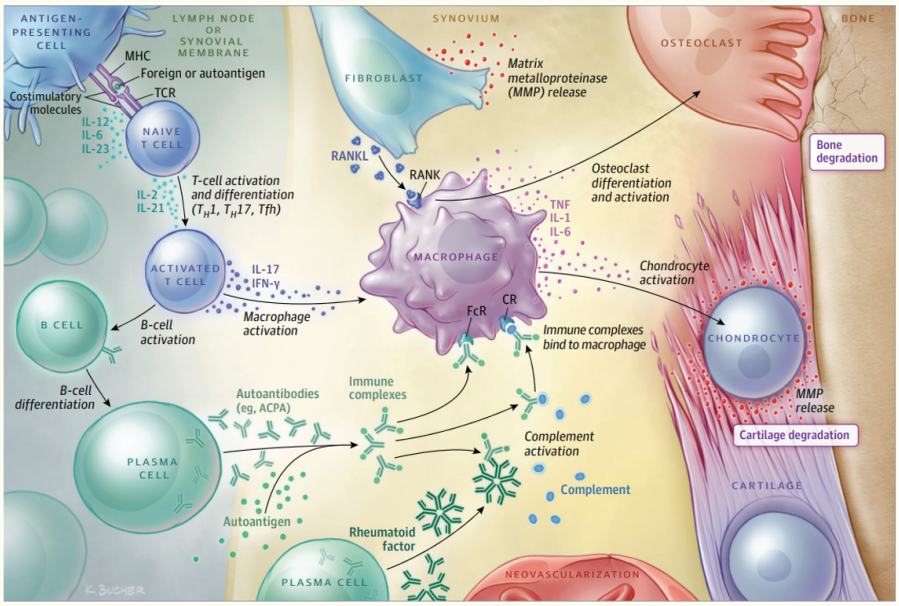

Figure 1: *Pathophysiology of rheumatoid arthritis [12].*

Citrullinated proteins act as autoantigens, along with foreign proteins such as viruses or bacteria may cross-react and behave as autoantigens.

↓

These autoantigens can be presented by antigen-presenting cells via major histocompatibility complex II to T cells.

↓

T cells release various lymphokines that attract macrophages and instigate B cells to produce autoantibodies.

↓

These autoantibodies form immune complexes of IgG immunoglobulins which get bound to IgM RF, thus causing the immune complex to grow and activate the complement system.

↓

Immune complexes, along with the activated complement system activates macrophages to secrete proinflammatory cytokines.

↓

In the presence of proinflammatory cytokines, fibroblasts with a RANK ligand can activate macrophages to differentiate into osteoclasts

↓

These osteoclasts resorb the bony regions of the joint cavity, along with inflammatory destruction of joints leading to symptoms of Rheumatoid Arthritis [12].

Figure

Clinical features

The common presenting clinical feature in RA is joint pain with stiffness, especially in the morning. Small, peripheral joints of the hands are usually affected, whereas axial joint involvement like that of the lumbar region is uncommon. Some long-standing cases may also present with cervical joint symptoms. Most patients present with multiple small joint involvements, although few patients show monoarticular involvement as well [13].

On a clinical examination, the joints will feel boggy and soft as compared to hard in osteoarthritis. Palpation will lead to tenderness and so will any movements. When several joints are involved, there will be a marked reduction in the grip strength of the individual. metacarpophalangeal joint subluxation, ulnar deviation, swan neck deformity, Boutonniere deformity, and the "bowstring" sign are common findings in the advanced stages of the disease [13].

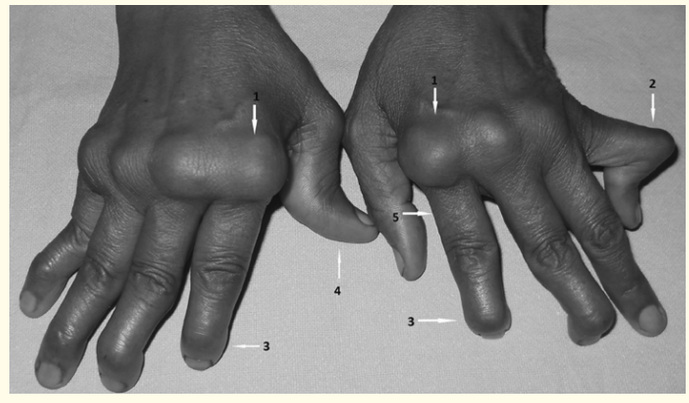

Figure 2: *(1) dorsal subluxation of metacarpal heads, (2) boutonniere deformity, (3) swan neck deformity, (4) hitchhiker's thumb, (5) ulnar deviation of fingers [14].*

People with RA may also suffer from extra-articular symptoms such as rheumatoid nodules (firm subcutaneous lumps), rheumatoid vasculitis, and necrotizing inflammation of blood vessels. Cardiovascular and interstitial lung diseases may be more frequent in RA-affected individuals. Physical functioning and quality of life may be harshly compromised in severe and advanced cases [15].

Radiological features

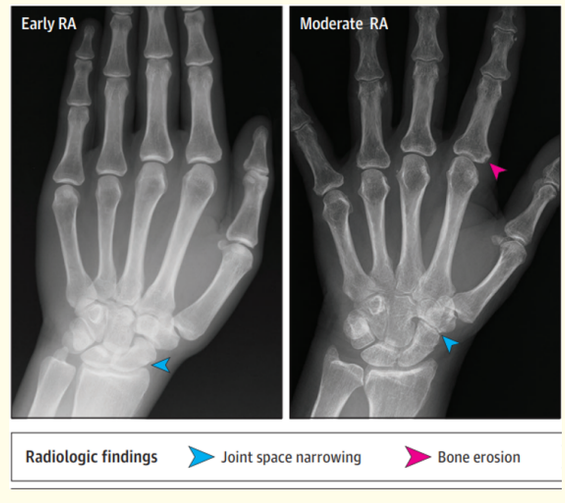

Figure 3: *Early RA showing narrowing of joint spaces, while moderate RA showing bony erosions additionally [16].*

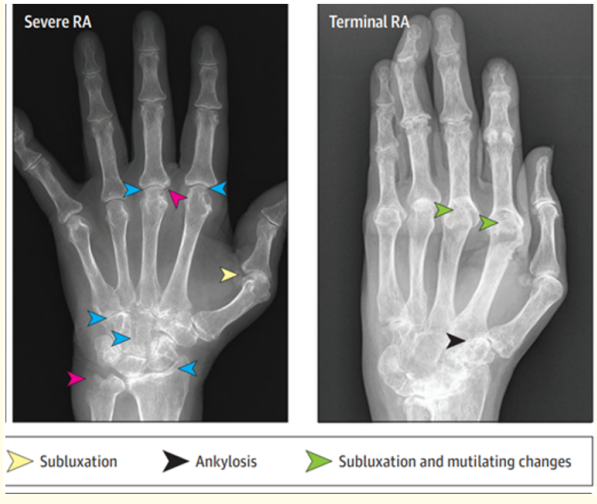

Figure 4: *Severe and terminal RA showing subluxation, multiple bony erosion, and mutilating changes in the joint [16].*

Conventional radiography

Plain X-rays are still important in diagnosing RA and assessing disease severity and prognosis. Plain X-rays of hands can provide a lot of bony changes such as erosions, subluxations, and ankylosis of joints. Their advantages include ease of use, being cheaper, and being very reliable. They do have certain drawbacks such as low sensitivity of early disease, soft tissue changes that cannot be visualized, and are 2-dimensional representations of the 3-dimensional problem [17].

Ultrasound

When it comes to the assessment of soft tissue joints, ultrasound can be cheap and valuable imaging technique. Synovial thickening, the presence of fluid in joints, and abnormalities of tendons and ligaments can easily be appreciated on high-resolution ultrasound. Joint access to either aspirate fluid or infiltrate medications via an ultrasound guide is very helpful. Despite several advantages, they cannot be used for visualizing deeper joints [17].

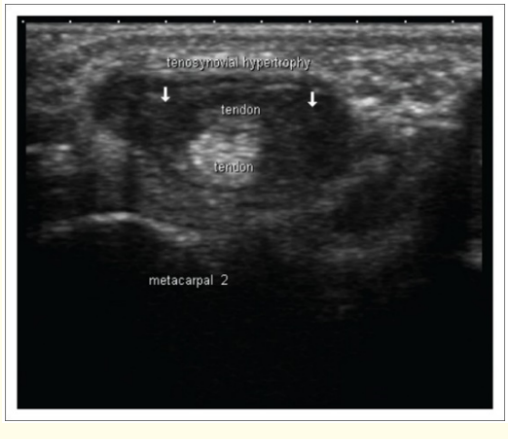

Figure 5: *Ultrasound showing tenosynovitis of metacarpals [17].*

Magnetic resonance imaging (MRI)

MRIs are good at examining bones, cartilage, and associated soft tissues. When compared to plain X-rays, they are very sensitive to early disease changes. For imaging, the anatomy of the hand, T1-weighted (T1W) imaging is used whereas T2-weighted (T2W) imaging and proton density-weighted fat-saturated (PDW-FS) are used to identify regions of inflammation [17].

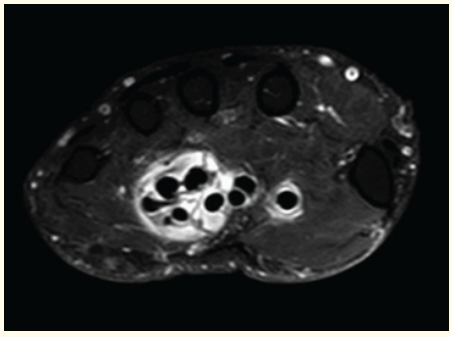

Figure 6: *MRI (PDW-FS) of metacarpal showing tenosynovitis [17].*

Diagnostic criteria

Due to so much heterogenicity in the clinical presentation, it is difficult to diagnose Rheumatoid arthritis. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have come up with diagnostic criteria for RA. The diagnostic criteria include scoring of joint distributions, serology, symptom duration, and acute phase reactions. A total score of ≥ 6 is classified as definite rheumatoid arthritis [18].

Joint distribution		**Serology**	
1 large joint	0	Negative RF and negative ACPA	0
2 - 10 large joints	1	Low positive RF and low positive ACPA	2
1 - 3 small joints (Large joint not counted)	2	High positive RF or high positive ACPA	3
4 - 10 small joints (Large joint not counted)	3		
> 10 joints (At least 1 small joint)	5		
Symptom duration		**Acute phase reactions**	
< 6 weeks		Normal CRP or normal ESR	
≥ 6 weeks		Abnormal CRP or abnormal ESR	

Table: *American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) Diagnostic criteria (2010). ACPA: Anti-Cyclic Citrullinated Protein Antibody; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; RF: Rheumatoid Factor [18].*

Treatment

The first line of treatment in rheumatoid arthritis includes the management of pain and inflammation. Nonsteroidal anti-inflammatory drugs such as naproxen and aspirin are commonly used. Steroidal drugs are more potent than non-steroid anti-inflammatory drugs, but

they come with the severe side effects of prolonged use. Opioid analgesics such as codeine and tramadol can be used to manage severe pain [19].

The second line of treatment involves either slowing down or arresting the progression of RA where disease-modifying antirheumatic drugs are used. Methotrexate, Hydroxychloroquine, and Sulphasalazine are commonly used disease-modifying antirheumatic drugs. Their effects are usually slow and they also help in reducing the risk of lymphoma associated with RA [19].

Newer medications such as biologics, also known as biological DMARDs, are more rapid and targeted effect on slowing the progression of the disease. Etanercept, Infliximab, and Adalimumab are some TNF (tumor necrosis factor) inhibitors that come under biological DMARDs. These drugs are only considered if conventional DMARDs such as methotrexate fail to achieve desired results as they are expensive [19].

Conclusion

This review has briefed the basic overview of rheumatoid arthritis. RA is a complex autoimmune disease that largely affects the joints of the human body. It has some genetic predilection as well as environmental influencers in its pathophysiology. Of particular importance is the role of autoantibodies in creating a cascade of events leading to joint inflammation. The clinical and radiological features are quite heterogenous and therefore their diagnosis depends on the clinical judgment of doctors. There also exists a diagnostic criterion that can assist in diagnosing RA, especially during patient selection in clinical studies. Pain and inflammation are generally managed by NSAIDs and steroids, while DMARDs and biologics are used to restrict the disease progression in RA.

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