Review Article

Rheumatoid Arthritis: A Comprehensive Review of Pathophysiology, Risk Factors, Diagnosis and Treatment

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that affects approximately 0.5% to 2% of the general population, with a higher prevalence among women and individuals with a family history of the condition. The disease is characterized by symmetric polyarticular inflammation, affecting small, medium, and large joints, and can lead to significant morbidity and mortality. Despite extensive research, the exact cause of RA remains unknown, but it is believed to involve a complex interplay of genetic and environmental factors. Recent studies have highlighted the role of citrullinated proteins, HLA class II alleles, and other genetic and environmental determinants in the development of RA. The diagnosis of RA is based on a combination of clinical, laboratory, and radiographic findings, including the presence of anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF). Treatment options for RA have expanded significantly in recent years, with disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents offering improved outcomes for patients. However, the complexity of RA requires a multidisciplinary approach to diagnosis and treatment, and further research is needed to fully understand the disease and develop effective therapeutic strategies.

Keywords: Rheumatoid arthritis (RA), ferroptosis, joint pain, inflammation, Disease-modifying anti-rheumatic drugs (DMARDs).

INTRODUCTION

In the general population, rheumatoid arthritis (RA), a prevalent systemic inflammatory disease, affects 0.5% to 2% of people. Those with a family history of the condition, smokers, and women are frequently impacted[1]. One of the most prevalent autoimmune inflammatory illnesses, rheumatoid arthritis (RA) mostly affects the synovial tissue in the tiny joints of the hands and feet, though it can sometimes have extra-articular symptoms. Ten years ago, new RA diagnostic criteria made it possible to classify patients with mono/oligoarthritis[2]. Unknown in origin, rheumatoid arthritis (RA) is characterized by inflammatory alterations of bone, cartilage, and joint synovial tissue, as well as, less commonly, extra-articular locations[3]. Because peptididylarginine deiminases (PADs) can produce citrullinated proteins, which are the targets of anti-citrullinated protein antibodies (ACPAs), they have been linked to the pathophysiology of seropositive rheumatoid arthritis (RA)[4].

The presence of HLA class II alleles that share the conserved amino acid sequence known as the common epitope is the most significant genetic risk factor for rheumatoid arthritis[5]. Symmetric polyarticular inflammation, affecting small, medium, and large joints in the upper and lower extremities, is a hallmark of rheumatoid arthritis (RA), a chronic systemic inflammatory rheumatic disease of uncertain cause[6]. Rheumatoid arthritis (RA) has no known cause. Environmental factors like nutrition and genetic predisposition are likely to have a role[7]. Assuming that stochastic processes, or random events, have occurred in a predisposed population is one way to explain why certain disorders emerge randomly in a population with weak genetic or environmental links[8]. Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that primarily affects the elderly and is more common in women than in men. There was regional variance in the 2002 prevalence rate, which varied from 0.5% to 1% of the population[9]. Red meat's cooked ingredients, including saturated fat, polycyclic aromatic hydrocarbons, and other preservatives, can have a negative impact on one's health[10].

One example of an autoimmune disease with a complicated etiology that is thought to involve several genetic and environmental variables is rheumatoid arthritis (RA [MIM 180300])[11]. There will be a greater number of older persons surviving longer years with chronic illnesses than ever before due to declining mortality rates and the massive baby boomer generation's entry into age categories at higher risk. Millions of adult Americans suffer from chronic musculoskeletal disorders, including arthritis, which are among the most prevalent chronic diseases[12]. Genetic and environmental factors interact intricately to define disease vulnerability, and both prospective and retrospective research have shown that smoking is a significant environmental component in the development of RA[13].

Rheumatoid arthritis (RA) is one among the autoimmune illnesses linked to the PTPN22 1858C/T polymorphism[14]. Joint tissues impacted by persistent synovial inflammation, synovial hyperplasia, joint cartilage, and bone loss are the main sites of disease in RA[15]. Most of the epidemiologic research suggest that the prevalence of RA is between 0.5 and 1.0 percent[16].

Pathophysiogy:

Personalized dietary practices are supported when treatments are tailored to the pathophysiological processes that people prioritize. Therefore, the results of this research advance our knowledge of how vitamin D supports individualized dietary practices in the treatment of RA[17]. Numerous theories have been proposed, despite the fact that the pathophysiological processes underlying RA remain incompletely understood. According to reports, immunological processes might take place years before joint inflammatory symptoms appear; this is known as the "pre-RA phase"[18]. The accuracy of a patient's prognosis is impacted by the significant clinical variability in RA. Thus, assessing the variety present in the pathophysiology of RA and determining the mechanisms of action in significant cell subsets represent our most pressing challenges[19]. One of the structural remodeling characteristics of atrial fibrillation (AF) is the hypertrophy of atrial myocytes, which has been linked to the JAK signaling pathway, which is significant in cardiac pathophysiology. JAK inhibitors may have an impact on the incidence and progression of AF in RA[20].

Risk factor:

Patients with immunocompromising diseases are more likely to get HZ in addition to being older. This covers immunosuppressive drugs as well as immunocompromising illnesses. According to a recent German claims data analysis, patients with rheumatoid arthritis (RA), depression, asthma, chronic heart disease, or chronic obstructive pulmonary disease (COPD) had an average 30% increased risk of developing acute HZ when compared to those without any underlying conditions. With chances ratios ranging from 1.37 to 1.57 for all age categories, RA had the greatest odds ratio among these conditions[21]. The most frequent main causes of CRPS in a recent review of 1043 individuals were carpal tunnel syndrome (7%), blunt traumatic injuries other than fractures (e.g., sprains) (21%), fractures (42%), and surgery (12%). A definite triggering event was found in 7% of cases. Still, there is a very low overall frequency of CRPS linked to these triggering events. According to Crijns et al., 0.19% of the 59,765 patients who had treatment for distal radius fractures also had CRPS[22]. Numerous studies on the genesis of RA have been conducted in recent decades, and the information that is now available suggests that both genetic and environmental variables play a significant role in causing RA. In fact, the incidence of RA is intimately linked to the susceptibility genes PTPN22, TNFRSF14, and HLA-DRB1[23]. Male sex, age, duration of RA, age at onset, smoking history, rheumatoid factor positivity and titre, anti-cyclic citrullinated peptide positivity and titre, higher c reactive protein, and higher erythrocyte sedimentation rate (ESR) were risk factors linked to the presence of ILD in ⩾5 studies. Positive anti-Scl70 antibody and negative anti-centromere antibody were consistently found to be risk factors for ILD in SSc, diffuse SSc subtype (found in around five investigations)[24]. One of the best examples of how RA's systemic inflammation can affect an organ system other than the musculoskeletal system is cardiovascular disease (CVD). inflammatory in RA, which is defined by an increase in certain inflammatory indices, cytokines, and antibodies, predisposes patients to acquire various comorbidities and raises the risk of death and disability in addition to conventional risk factors. Numerous environmental and genetic variables that might lead to endothelial dysfunction are shared by atherosclerosis and RA[25].

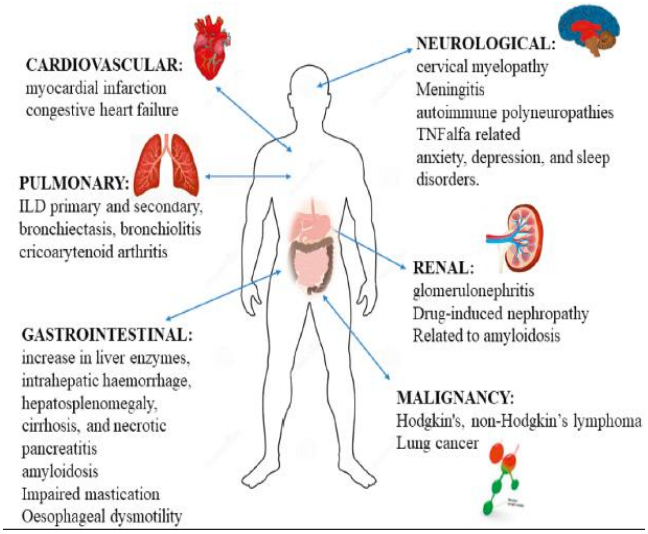

Figure 1: The most frequent extra-articular manifestations and comorbidities of patients with rheumatoid arthritis[25].

Diagnosis:

External triggers, including smoking, have been found to be risk factors for the formation of these autoantibodies and may play a role in an early breach of tolerance. Additionally, the prevalence of ACPA rises with age, especially in postmenopausal women, among healthy first-degree relatives of RA patients. ACPA is linked to the severity of the illness, has a detrimental effect on the likelihood of achieving long-term drug-free remission, and increases the probability of chronicity if it is present at diagnosis (that is, while there is clinically evident arthritis)[26].

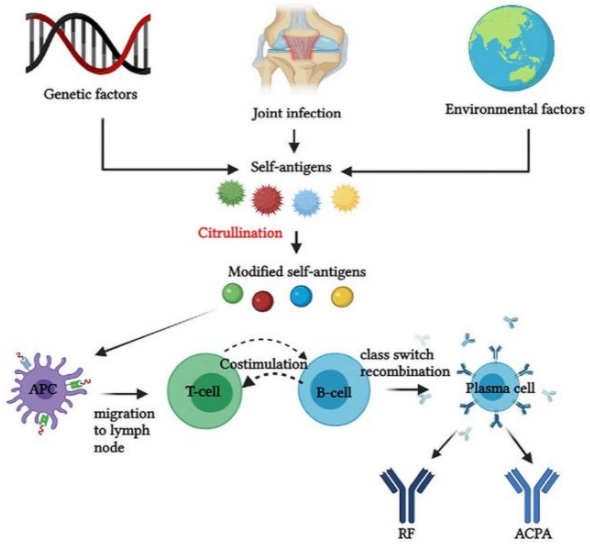

Figure 2: Immunological processes in the pre-RA phase[28].

New treatment techniques are accessible as a result of significant advancements in the pharmaceutical sector. Finding a cure, however, is made more difficult by our incomplete knowledge of the molecular processes controlling the destiny of antibodies. Early diagnosis and the best possible non-pharmacological and pharmaceutical therapy, together with regular assessments of therapeutic efficacy and safety, are necessary for the most successful therapeutic strategy. Remission and minimizing negative effects are the goals of treatment[27].

Furthermore, RF plays a significant role in prognostication and differential diagnosis for arthritis patients. Years before RA manifests, the RF isotypes may already be in the pre-clinical stage[28].Closely linked to RA, serum rheumatoid factor (RF) can either confirm a clinically suspected diagnosis or describe the severity of the illness. An IgM antibody that binds to the Fc portion of IgG is often used to test RF. Up to 80% of RA patients who have been diagnosed have RF, while 50% of people may have it within the first six months of their illness. Since RF affects up to 15% of the elderly and 5% of the general population, it is not exclusive to RA[29]. The definition of chronic rheumatic arthritis of the temporomandibular joint is "active (pathogen-independent) inflammation of the temporomandibular joint," under the worldwide expert consensus (TMJaw). It is diagnosed based only on the evidence of inflammatory alterations in soft tissue using contrast-enhanced magnetic resonance imaging (MRI) and is not influenced by subjective symptoms or clinical indicators[30]. A collaborative multidisciplinary approach involving expert input from radiology, pathology, rheumatology, and pulmonology is necessary for the diagnostic approach of patients with ILD in the context of known or suspected RA. This approach should also evaluate for other potential causes of ILD, such as HP, pneumoconiosis, connective tissue diseases (CTD) other than RA, or iatrogenic causes, such as drug toxicity[31].

Treatment:

Better long-term patient outcomes may result from changing the course of RA, according to insights from the early arthritis framework. The idea of RA's "window of opportunity" refers to a crucial early stage of the illness when starting disease-modifying anti-rheumatic medication (DMARD) treatment can have a major influence on prognosis. Early intervention at this stage can avoid irreversible joint injury and result in remission or minimal disease activity[32]. Non-steroidal anti-inflammatory drugs (NSAIDs) are not usually the first-line treatment option in the early stages of managing EORA because seniors are more likely to experience NSAID side effects and because most seniors should not take NSAIDs due to comorbidities. As soon as the diagnosis is determined, disease-modifying antirheumatic medications (DMARDs), most often methotrexate, are administered. The introduction of biological or targeted synthetic DMARDs becomes a feasible therapeutic option when aged individuals show resistance to traditional DMARD therapy[33]. The quality of life for RA patients is often reduced by complications, which may also increase their mortality rate. Since consequences are frequently closely associated with prognosis and need early detection and timely therapy, the main therapeutic goals for RA are reducing disease activity and treating extra-articular damage[34].

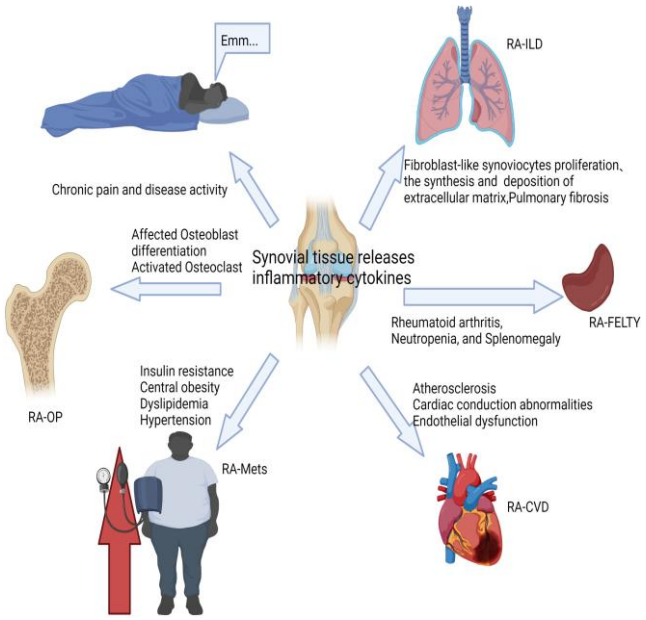

Figure 3: The complications of RA are usually closely related to disease activity and inflammation levels[34].

The internal connection between ferroptosis and RA has not yet been thoroughly investigated. People who have a thorough awareness of the connections between ferroptosis and other biological processes will discover that the laws governing ferroptosis, apoptosis, autophagy, and other cell death patterns share some traits. The link between these many forms of cell death is still unclear, despite the fact that treating RA requires the simultaneous modulation of several cell death pathways[35]. Currently, the most popular medication for RA that targets B cells is Rituximab, which depletes B cells. Specifically, 95% of human B lymphocytes have CD20 expressed on their surface. With the exception of pro-B cells and plasma cells, rituximab that targets CD20 can decrease all B cells[36]. Understanding the distinctions between seronegative and seropositive RA and further characterizing clinical phenotypes among the heterogeneous seronegative group will aid in the stratification of patients into discrete clinical endotypes and enable the implementation of targeted treatment in the pursuit of precision medicine[37].

CONCLUSION

Rheumatoid arthritis is a complex and multifactorial disease that requires a comprehensive understanding of its pathophysiology, risk factors, diagnosis, and treatment. The disease is characterized by chronic inflammation and joint damage and can lead to significant morbidity and mortality. Recent advances in our understanding of the genetic and environmental factors that contribute to RA have led to the development of new therapeutic strategies, including DMARDs and biologic agents. However, further research is

needed to fully understand the disease and develop effective treatment. A multidisciplinary approach to diagnosis and treatment, involving expert input from rheumatology, radiology, pathology, and pulmonology, is essential for optimal patient outcomes. By advancing our understanding of RA and developing effective therapeutic strategies, we can improve the quality of life for patients with this debilitating disease. Ultimately, the goal of RA treatment is to reduce disease activity, prevent joint damage, and improve patient outcomes, and this can be achieved through a combination of early diagnosis, aggressive treatment, and careful monitoring of disease activity.

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