

Literature Review

An Updated Review on Rheumatoid Arthritis (RA): Epidemiology, Pathophysiology, Diagnosis, and the Current Approaches for Its Treatment

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Received 9 November 2022

Accepted 15 July 2023

Published 29 December 2023

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Editor-in-Chief:

Prof. Nazik Elmalaika Obaid
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Abstract

Rheumatoid arthritis (RA) is a systemic self-inflicted inflammatory disease that primarily affects middle-aged women. Globally, 1% of people live with RA. This review aims to provide updated information on the different aspects of RA, including its epidemiology, pathophysiology, diagnosis, treatment, and management. A web-based literature search was conducted through various databases, including PubMed, Google Scholar, and Science Direct, to identify the most relevant studies. Epidemiological studies have suggested that the prevalence and occurrence of RA have remained inconsistent across geographical areas in different periods. Many factors such as age, gender, inheritances, and environmental exposure can contribute to the severity of the disease. The acute form of RA usually presents with pain, and if left untreated, it can result in joint deformities and influence a patient's quality of life (QoL). RA diagnosis is usually based on the manifestation of pain with inflammation. Currently, many therapeutic strategies are available for the cure of RA. The management of daily routine activities is required with treatment to curtail the damage, avoid future deformities, and ultimately minimize the aching trouble of the patient.

Keywords: arthritis, inflammation, joints, quality of life, autoimmunity

1. Introduction

Rheumatoid arthritis (RA) is a chronic heterogeneous inflammatory disorder that may arise due to autoimmunity. RA affects almost 5/1000 individuals and can progress to severe joint destruction and disability. It may develop at any age and usually, the

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dominance of the disease is more in females than males [1]. In the last 20 years, substantial progress has been made regarding the understanding of RA pathophysiology, optimal outcome measures, and successful cure approaches such as acknowledging the worth of early diagnosis and RA treatment. However, the exact cause of this disease is poorly known and besides advances in the medical field, the treatment is not identified. In Pakistan, the field of rheumatology continues to be emerging. Just a few hospitals provide their services with rheumatology clinical setups that are run by certified rheumatologists. There aren't any countrywide registries to preserve an account of the different functions of autoimmune illnesses and their treatment results. Currently, a limited number of studies are available that are conducted on residents of Pakistan. These researches provide significant insight into the information related to autoimmune ailments, including RA. The incidence rate of RA in Pakistan is approximately 5.5%. According to a study from Karachi, it is noticed that RA prevalence is quite common in females, and in 4900 study participants, the proportion of RA cases was found to be 12.9% [2–4]. RA causes joint impairment, and incapacity, cuts the health-related quality of life (HRQOL), and results in excessive mortality. RA health-related burden is very high. According to estimation, indirect cost which is calculated based on arthritis-related work disability and efficiency is four times higher in comparison to direct healthcare utilization, which marks it one of the priciest illnesses. Due to arthritis and loss of productivity, about 303.5 billion dollars per year are spent on medical expenses in the USA [5–7]. RA presents with articular degeneration and comorbidities that can upset different body systems, that is, bone functioning, psychological activities, and metabolic pathways. Worldwide, 1% of the population is suffering from RA. Risk factors associated with RA could be both genetic and environmental. The “shared epitope” of the MHC class II HLA-DR allele is a dominant element of genetics that is linked with the instigation of RA. In the majority of patients, the manifestation of auto-antibodies like anti-citrullinated (ACPA) or rheumatoid factor can result in terrible consequences [8]. It is believed that primary etiopathy is caused by malfunctioning of autoimmunity that happens during notional phases. In the early phases of RA, systemic immune mediators, including cytokines and autoantibodies, could be detected that are responsible for the inception and progression of obvious signs and symptoms related to the disease. Then, this generally progresses into established RA that is described by long-lasting inflammation that can cause joint deformities and damage the surrounding tissues. Recently, the development of specific immune-focused treatments, like kinase inhibitors and biologics, have radically reformed clinical care with better results. Further, studies of these drugs at cellular and molecular levels have also unveiled the multifaceted inflammatory complexes that are involved in

the initiation and propagation of RA [9]. Early diagnosis of RA can help in the prevention of joint damage and ultimately improve the results of the therapy. It is considered that the first two years of disease are quite decisive that can lead to everlasting joint destruction, thus early diagnosis and optimum clinical care are desired to minimize joint loss and improve a patient's QoL. To achieve this, robust biomarkers are required to ensure precise prognosis, prompt diagnosis, and better management of RA [10]. This review is intended to provide the most up-to-date information about the RA that could be used as a reference for researchers, clinicians, pharmacists and students.

2. Methods

A web search of various databases, including PubMed, Google Scholar, Scopus, and Springer Link, was conducted to determine the most appropriate studies. Keywords such as "arthritis", "joint pain", "inflammation", "epidemiology", "etiology", "pathophysiology", "diagnosis", and "treatment" were used to find relevant publications. Only research publications, literature reviews, and systematic reviews published in the English language between 2010 and 2022 were considered for this study. Only 35 articles were used in this review after a full-text review. The articles included focused on the current study's objectives and provided a critical perspective on arthritis. Articles were excluded if they lacked detailed information and did not meet the study's objectives, which included epidemiology, pathophysiology, diagnosis, and treatment of arthritis.

3. Results and Discussion

3.1. Epidemiology

The prevalence of RA differs among communities. According to estimation, 20–50 cases per 100,000 individuals are reported from Northern America and Northern Europe. Although a lower prevalence of RA, 9–24 cases per 100,000 persons has been documented in Southern Europe. There is hardly any epidemiological information on developing countries. Several studies have shown a significant decline in the incidence of RA over time, with a trend shifting toward older age [11]. The epidemiological studies of African countries have revealed the occurrence of RA in: South Africa and Congo at 0.9%, Egypt at 0.2%, Algeria at 0.13%, and Nigeria at <0.5%. Altogether, available data on RA occurrence is quite heterogeneous and limited which may be due to large regional variations and methodological discrepancies. Further, some small studies that

were conducted in Africa (South Africa, Nigeria, and Liberia) have demonstrated that the prevalence of RA is higher in males compared to females, and it is incompatible with existing literature. It is suggested that geographical variations in RA manifestation could be due to genetic and environmental factors. In Asia, the incidence of RA is recorded as follows: South Korea 0.26%, India 0.75%, Japan 0.6-1%, and Karachi (Pakistan) 0.142%. RA occurrence rate varies from 0.2% to 0.3% between China and Japan, respectively. This information led to the thought that dissimilarities in genetic makeup could influence the incitement and development of disease. To date, epidemiological studies from different cities in Pakistan except Karachi have not been reported yet [12].

3.2. Pathophysiology

The pathogenesis of RA is linked to various factors, including genetic, epigenetic, and environmental. In genetic factors, a group of predisposing genes called Human leukocyte antigen (HLA) class II with more than a 100 susceptible loci such as CTLA4, TRAF1, PTPN22, and PADI4 are mainly responsible for the commencement of the inflammatory process. Further, nonimmune cells (chondrocytes and fibroblasts), immune cells (mast cells, T cells, B cells, dendritic cells, and macrophages), inflammatory mediators (proteases, cytokines autoantibodies and chemokines), and various nongenetic factors (smoking and sex hormones) are also jointly involved in the inflammatory reactions that target the bone and cartilage, resulting in impaired joint function [9, 13]. In RA, the synovium is the main target tissue. Fibroblast-like synoviocytes (FLS) and macrophage-like synoviocytes (MLS) are multiplied during joint inflammation to form pannus, which subsequently attacks the cartilage and destroys it. FLS and MLS are the main factors that can contribute to joint inflammation and demolition [14].

Depending on how long the illness lasts, almost 50–80% of patients suffering from RA develop autoantibodies. These autoantibodies can trigger the effector phase of the inflammatory response which can discharge the extracellular matrix (ECM) components by disrupting the chondrocytes and cartilage. Moreover, the glycosylation of autoantibodies is critical in this situation. Increased sialylation of IgG-Fc is helpful in reducing bone loss due to inflammation while decreased sialylation will cause osteoclastogenesis and development of RA [15]. In the early phase of RA, bone attrition with diminution of physical activity first appears then the severity of the disease is gradually increased as the disease progress. The key stimuli of bone destruction include autoantibodies, inflamed synovium, proinflammatory cytokines, and receptor activator of nuclear factor κ B ligand (RANKL). Various inflammatory mediators are developed due to eliciting

the immune and non-immune cells. At the intersection of bone and cartilage, the differentiation of preosteoclasts into osteoclasts (bone-resorbing cells) is supported by macrophage colony-stimulating factor (M-CSF) and fibroblasts expressing RANKL [16].

Cytokines play a major role in the development of several events related to inflammation such as synovitis, destruction of the joints, and response to autoimmunity. In this regard, four families of chemokines, including C, CC, CXC, and CX3C and numerous cytokines, including TGF β , TNF- α , IL-1, IL-6, IL-10, IL-12, IL-15, IL-18, IL-23, etc., are causative elements of joint inflammation [17]. Recently, patients suffering from arthritis are treated with TNF- α neutralizing mediators, and therapy found to be effective in the reduction of RA signs and symptoms. In many clinical trials, TNF inhibitors have shown promising activity against RA. It is expected that this approach can open new avenues in the treatment of arthritis by making mediators against other cytokines such as IL-1, IL-6, and IL-17. Nevertheless, cytokines directing remedies must be carried out with caution because they are capable of performing multiple functions, demonstrating the pleiotropic nature, can escalate joint inflammation, and might be redundant. Targets like cells (T and B), signaling molecules, and synovium-directing targets can be considered while developing novel compounds for the treatment of RA [18].

3.3. Clinical presentation and associated comorbidities

RA is a long-lasting heterogeneous inflammatory disease of joints that leads to stiffness, pain, and swelling of the joints called synovitis. It also causes wasting of the muscles that surround the defective joints. Clinical presentation of chronic RA may include fatigue, soreness, inflammation, stiffness, and deformities of joints. RA-diagnosed patients are unable to perform physical activities, have poor mental strength, and their social life is badly affected [19]. Chronic RA classically presents as pain in multiple joints of hands and feet with a symmetrical distribution. The affected joints are not only sore but also usually burning and distended. One of the classical symptoms of RA is morning stiffness of the joints that can persist for more than thirty minutes. In the acute phase of RA, ACPA and rheumatoid factor (RF) are observed with elevated levels of C-reactive protein and sedimentation rate. It is noted that nearly 50–80% of the patients with RA have ACPA, RF, or both which make the prognosis worse. If the patient remains untreated, extra-articular symptoms can appear that include scleritis, rheumatoid nodules, vasculitis, interstitial lung disease, and mononeuritis multiplex [20].

RA raises the chance of stroke and myocardial infarction that may happen due to the activation of systemic immunity and inflammation. The risk of cardiovascular events and atherogenesis increases in patients who have persistently raised serum concentrations of proinflammatory cytokines (TNF and IL-6) and C-reactive protein [21]. Further, the risk of increased cardiovascular events in RA patients can be linked with glucocorticoid intake to treat the ailment, disease-associated functional disability, and severity and duration of disease [22]. In addition, proinflammatory cytokines (TNF and IL-6) can alter the CNS activity and may cause depression and increase the sensitivity of pain in RA patients. It is believed that anti-TNF therapy not only reduces brain pain sensitivity but also improves serotonin homeostasis in RA patients [9].

3.4. Diagnosis

A prompt, accurate diagnosis is important in the treatment of RA. In 90% of patients, early diagnosis is not only helpful in halting disease progression but also minimizes joint destruction and avoids disability. Patients suffering from RA present with painful and inflamed joints and feel stiffness in joints particularly in the morning [2]. Usually, RA diagnosis is made based on a doctor's assessment, the presence of typical RA signs and symptoms, family history, laboratory tests, and joint examination by imaging techniques (i.e., ultrasound sonography). In RA patients to assess the severity of inflammation, elevated levels of ESR and CRP, and the presence of RA-specific autoantibodies are commonly used biomarkers. CRP is an acute-phase protein, a member of the protein family known as pentraxin that consists of five subunits of 23-kDa. CRP concentration in serum can rise by ≥ 3 folds in case of inflammation, infection, or tissue injury, and it is not affected by factors such as gender and age. CRP serum concentration has demonstrated a positive correlation with the development of disease, changes in radiological parameters, alteration in synovium histological features, and clinical factors, including pain, joint stiffness in the morning, fatigue, disability, and articular index. Thus, CRP has proven to be a useful marker in RA diagnosis and in the surveillance of disease evolution and the prognosis of joint lesions [23].

Ultrasonography and MRI have been suggested to diagnose and track disease activity in patients with RA. Ultrasound analysis not only provides useful information about synovial proliferation but is also found to be helpful in the evaluation of bone erosion and subclinical synovitis even if the clinical manifestation of the patient's condition appears to decrease [24]. There are many benefits of using ultrasound. It is a robust noninvasive technique, easily accessible, produces real-time results, and is comparatively

economical. The drawbacks are that ultrasound is considered an operator-dependent technology and needs expertise in terms of measurement and quality assessment [25].

In 2010, ACR–EULAR (American College of Rheumatology–European League against Rheumatism) devised criteria for the diagnosis of RA. For RA diagnosis, the 2010 EULAR criteria include the following indicative factors: duration of symptoms appearance, number of joints involved, the manifestation of RA-specific autoantibodies, and changes in serum concentration of CRP and ESR. EULAR 2010 has graded various parameters as follows: involvement of joints is graded from 0 to 5 subject to the size and number of the involved joints (at least one inflamed joint must be present as per criteria), levels of RF autoantibodies and ACPAs are graded up to three scores, and one mark each for the duration of disease symptoms, altered CRP serum concentration, and raised ESR. According to EULAR 2010, the maximum score would be 10 for disease, and a RA diagnosis is made if the total score of the patient is more than 6, and other reasons for synovitis such as infections and trauma, etc., can be excluded [26]. Various factors can influence RA diagnosis and management. These factors may include patients' ignorance of symptoms, lack of skilled personnel, insufficient diagnostic facilities, inadequate access to medicines and increased incidence of infectious diseases, for example, HIV, tuberculosis, and hepatitis. In a poor healthcare setup, management and early diagnosis of the disease can be made by maintaining registries that will provide sufficient evidence to rheumatologists about the usage of medication, pattern, and outcome of the disease [7].

3.5. Treatment and management

Many therapeutic approaches, including IL-1 and IL-6 inhibitors, blockade of TNF- α , angiogenesis-inhibiting agents, and B-cell therapy are currently being used for RA treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARD), for example, cyclophosphamide, methotrexate, sulfasalazine, and intramuscular gold, are commonly available synthetic medicines that are used for RA treatment. However, these drugs should be used with caution as they may cause gastric ulcers and hypertension, and induce hostile hepatorenal effects [27, 28]. The combination of DMARD and corticosteroids is used as a primary treatment for RA. For faster relief and prevention of disease progression, this combination of drugs should start as soon as the diagnosis of RA has been made. In addition, NSAIDs and corticoids are commonly used as adjuvant therapy in RA to gain more benefits by decreasing inflammation and pain caused by inflamed joints [29]. The ACR 2015 guidelines have

recommended the use of glucocorticoids (GCs) with DMARDs at the lowest dose and for the shortest duration for premature and established RA to treat disease flares. Contrary to the European guidelines, depending on disease activity, GCs can be added to treatment when a csDMARD is started [30]. Since patients with RA are expected to receive a therapeutic combination, awareness of adverse events and the balance between benefits and risks while suggesting antirheumatic medications could be the main element in improving results. In the future, drug utilization and safety studies for antirheumatic drugs are required. Moreover, traditional medicines can offer a better option for RA treatment as these are safe, easily available, and economical. Around 60–90% of arthritis patients use traditional drugs. In the future, it is suggested to perform more research on traditional medicines to validate their efficacy and safety [31, 27].

Besides pharmacological treatment, management of the disease also plays an imperative role in managing symptoms. In rheumatology, with the advent of novel therapeutic strategies and the modernization of healthcare facilities, more trained healthcare professionals are required so that RA patient symptoms can be managed efficiently [19]. Further, other therapies, for example, massage, heat therapy, cold therapy, hydrotherapy, transcutaneous electrical nerve stimulation, yoga, and exercise will prove beneficial in the reduction of disease severity and will improve the patient's QoL [32]. Recently, mesenchymal stem cell (MSC) therapies have been introduced for RA treatment. This MSC therapy is based on the cell-based treatment that is quite useful due to its immunomodulatory, anti-inflammatory, and regenerative properties. However, more research is needed to study its applicability in clinical settings. Several pieces of research have shown positive results in the case of osteoarthritis, that is, decreased severity of pain, boosted function of joints, and improved QoL. However, a few clinical trials have been conducted on RA and still many clinical trials are in progress with the expectation that this therapy could prove favorable for the cure of RA with minimum side effects [33]. Early diagnosis, optimal treatment strategies, access to medicines, decreased exposure to risk factors, patient awareness, development of vigorous prophylactic measures, and modification of lifestyle are prerequisites for the RA cure and its management, improve patient's QoL, and curtail RA global health burden [34, 35].

4. Conclusion

RA pathophysiology and several risk factors are well identified and significant development in its cure and management has been made. In the existing literature, little information about epidemiology is available. Further, the data on RA mortality rate and its

association with other comorbidities are insufficient. In the future, more epidemiological studies are required to understand RA distribution across geographical regions and the role of ethnicity in developing the disease. The possibility of remission in patients suffering from RA can be improved by prompt diagnosis and adherence to a treat-to-target approach with close monitoring and management.

Acknowledgements

None.

Ethical Considerations

Not applicable.

Competing Interests

None.

Availability of Data and Material

Not applicable.

Funding

None.

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