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RHEUMATOID ARTHRITIS OVERVIEW: STUDY OF ETIOLOGY FACTORS, SIGNS AND SYMPTOMS

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ABSTRACT

Rheumatoid arthritis (RA) is an inflammatory illness characterized by destructive arthritis as its primary clinical manifestation. If RA is not treated, it causes early death and disability. For this reason, early detection and treatment are crucial. It is a primary cause of disability, and autoantibodies, including anti-cyclic citrullinated peptide antibodies (ACPAs) and rheumatoid factor (RF), are crucial diagnostic biomarkers. Moreover, it is challenging to distinguish RA from other forms of arthritis. New RA-specific biomarkers may increase the accuracy of diagnosis and assist differentiate RA from other forms of arthritis. Another explanation is that existing biomarkers might not be sensitive enough to identify RA in its early stages, before serious joint damage develops. In addition to facilitating earlier diagnosis and treatment, new biomarkers that can identify RA at an earlier stage may also help more precisely monitor disease activity and response to treatment, allowing clinicians to modify patient treatment plans and enhance overall results. The biomarkers of rheumatoid arthritis included in this article include both well-established and recently identified biomarkers. The current diagnostic standards and RA treatments will also be reviewed in this paper.

Keywords: Rheumatoid arthritis, Epidemiology, Pathophysiology, Treatment, Diagnosis.

1 INTRODUCTION

Arthritis is a degenerative condition that impacts people's joints. Its signs involved joint pain, swelling, increase of skin temperature and activity limitation (1, 2). Currently, arthritis is a prevalent condition that can affect people for both sex at any age that develops quickly and presents in different forms (3).

Arthritis is a disease that may lead to damage to the healthy cartilage of joints, causing function loss, degenerative changes, and joint instability (4). This condition, which affects 75% of women, results in pain, inflammation, and stiffness in different joints throughout the body, and causes the patient's movement to stop, having a substantial impact on the person's activities (5-7). In its various forms, arthritis is typically thought of as a chronic illness, considered as a life-long condition (8). The several forms of arthritis, included rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, acute arthritis ,and osteoporosis (6).

Rheumatoid arthritis (RA) is an autoimmune disease that primarily impacts synovial joints and can result in joint deformity and function loss (6, 9), in which the peripheral joints are the primary sites of inflammation, often leading to impairment of these joints (10). It is the most common form of autoimmune inflammatory arthritis and is associated with various comorbidities including cardiovascular disease (CVD)(11). The illness usually starts slowly and develops insidiously over time (12), and it needs long-term treatment to reduce inflammation (13). RA could have an effect on a person's activity and daily lifestyle (14, 15). Environmental exposures or triggers can cause RA, a pathologically varied disorder, in those who are genetically vulnerable. Most genetic associations are observed in individuals with the disease and high levels of ACPA (16). This illness is characterized by excessive amounts of autoantibodies being produced, in addition to swollen and painful joints. As of yet, the exact pathophysiology of RA is unknown. However, it is widely acknowledged that the genetics of inflammatory cytokines play a major role in the development of this complex illness (17).

RA is most commonly characterized by pain, trouble moving, and stiffness. The autoimmune and inflammatory mechanisms of RA impact cartilage, synovial cells, and various bodily systems (18). It primarily affects the synovial tissues, lead to irreversible damage, and appears clinically as progressive symmetric polyarthritis. If RA is not diagnosed and treated early, it may result in a reduced life expectancy, a decline in quality of life, morbidity ,functional disability, and mortality, all of which would raise the burden on society (19, 20). This review provides prevalence and incidence of RA Pathophysiology of Rheumatoid Arthritis of RA rheumatoid arthritis followed by Criteria for the Diagnosis of RA.

2 EPIDEMIOLOGY OF RA

A recent meta-analysis found that RA affects roughly 0.46% of the world's population epidemiologically (95% CI 0.39–0.54) (21). The Global Burden of Disease (GBD) study estimates that there were 20 million RA patients globally in 2017 and that 1.2 million new cases of RA were identified (22, 23). It affected RA elders all over the world. When the illness is severe, significant damage to the bones and ligaments causes long-term bone incapacity, which makes the bones immobile (24). Quality of life is greatly impacted by RA (25), in addition to productivity during work (26). Between 0.5% and 1% of people have RA, and the incidence appears to be declining from northern to southern nations as well as in urban areas relative to rural ones (27). An estimated 1% of Iraqis are thought to have RA (28, 29).

Although it affects both sexes, women are more prone to develop RA disease. Small joints are first affected by RA, followed by larger joints, and then the eyes, red blood cells, hands, skin, heart, kidneys, and lungs, among other organs. Tendons and ligaments become more brittle, and joint bone and cartilage are regularly injured (30, 31). Although RA by itself seldom results in death, its side effects, like cardiac and respiratory conditions, can raise mortality rates (23, 32, 33). Deformities and bone degradation can result from joint injury caused by cartilage and bone loss (34). The patient's longevity, quality of life, and ability to work all suffer as the illness develops, as does the financial strain on their family (35, 36).

3 ETIOLOGICAL FACTORS OF RHEUMATOID ARTHRITIS

3.1 Rheumatoid Arthritis Risk Factors

Environmental and genetic factors combine to create rheumatoid arthritis, a complex condition. The genetic component known as the "shared epitope," exposure to cigarette smoke, and female sex have been found to have the highest associations (37). Rheumatoid arthritis is caused by a number of factors, including family history, genetic and serological risk factors that are more common in first-degree relatives, hormonal factors, environmental antigens, nutritional factors, exposure to infectious (and noninfectious/microbiota) pathogens on mucosal surfaces like the lung, periodontium, and gut, and urban residency (38).

3.2 Genetic Factors

First, there was evidence from twin and familial investigations that RA has a genetic component. The risk of RA among monozygotic twins of RA patients is actually 9–15%, which is significantly greater than the risk in the general population and up to 4-fold higher than that of dizygotic twins (25–35), It is the relative risk (RR). Similarly, the RR of RA for first-degree relatives ranges from 2 to 5 and is comparable for both men and women (39).

3.3 Environmental Factors

3.3.1 Smoking

RA patients smoke more often than the overall population. According to available data, smokers with RA had greater levels of erosive joint destruction, disease activity, pain and fatigue, and health-related quality of life (HR-QoL) than nonsmokers. Furthermore, smoking raises the risk of passing away (40).

3.3.2 Diet

One environmental component that can be changed is diet, which can have an impact on the microbiota's makeup and the course of arthritis (41). Food intake has been connected in a number of studies to either a higher or lower likelihood of being diagnosed with RA. A higher risk of RA has been associated with diets heavy in full-fat milk (as opposed to all dairy products), saturated fats (especially solid oils), and sugar-sweetened beverages (42, 43).

3.3.3 Obesity

In RA, obesity has been associated with a decreased likelihood of reaching and sustaining remission. those with RA who are fat have lower Disease Activity Scores or Disease Activity Scores in 28 joints than those who are not obese. Although obesity has not been associated with a higher risk of death in RA, RA outcomes and quality of life can be enhanced by therapies to prevent and reverse obesity (44). One changeable environmental element that can impact both the microbiota's makeup and the course of arthritis is diet (41).

3.3.4 Hormones

A number of female hormonal parameters some of which are connected to estrogen exposure have been found to be risk factors for the onset of RA. The higher incidence of RA in females indicates that the disease's development is influenced by female hormones (45). In the 12- to 24-month postpartum period following delivery, the risk appears to be highest during the first three months and then declines over the following nine months. This suggests that hormonal changes that take place during or after pregnancy may cause RA to develop, and that the number of pregnancies may have little effect on the likelihood of having RA (46).

3.3.5 Infection

Studies believe that changes in oral or intestinal flora could be one of the triggers for RA. There is growing evidence that gum inflammation, or periodontitis, is another risk factor (47, 48). Several exogenous viruses, such as hepatitis C, CMV, parvovirus B19, and EBV, have been found in synovial tissue; however, there is no conclusive evidence linking these infections to RA (49).

4 PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

Our understanding of the physiopathology of RA is still unknown. Numerous cells have been connected to its formation, though. T and B lymphocytes, neutrophils, and monocytes are all trafficked into the articular synovium through the action of proliferative synovial tissue fibroblasts in RA. The pro-inflammatory cytokines that these cells release into the articular canals are the primary source of inflammation (50, 51).

The pathophysiology of RA is now better understood, especially with regard to genetics and environmental variables that may influence the course of the illness. Advanced research methods have made it feasible to identify new pathways that are helpful for the creation of novel therapeutic approaches in RA and to better characterize the cellular and molecular mechanisms involved in the dysregulation of innate and acquired immune responses (52). Inflammatory cells such lymphocytes, neutrophils, macrophages, and fibroblast-like synoviocytes (FLSs) are found in the inflamed synovium of RA (53). The buildup and activation of these cells leads to the development of a pannus, which demonstrates an excessive accumulation of inflammatory cells and angiogenesis with a tumour-like nature (54).

The primary location of the inflammatory process is the synovial membrane. It is believed that the pathophysiology of RA, which results in complete tissue damage, is caused by the infiltration of T cells and B cells (inflammatory cells) into the pannus and synovial fluid (55). Increased cytokine production brought on by inflammation causes synovitis, edema, and joint injury. Monocytes and mast cells make up the majority of the immune cells present in synovial fluid. A small number of adaptive immune cells, including as B cells, Th1 (T-helper type 1), Th17, and plasma cells, also contribute to inflammation. Furthermore, there are significant levels of antibodies against citrullinated proteins in the joint fluid, which triggers the release of complement proteins and initiates the inflammatory response (56).

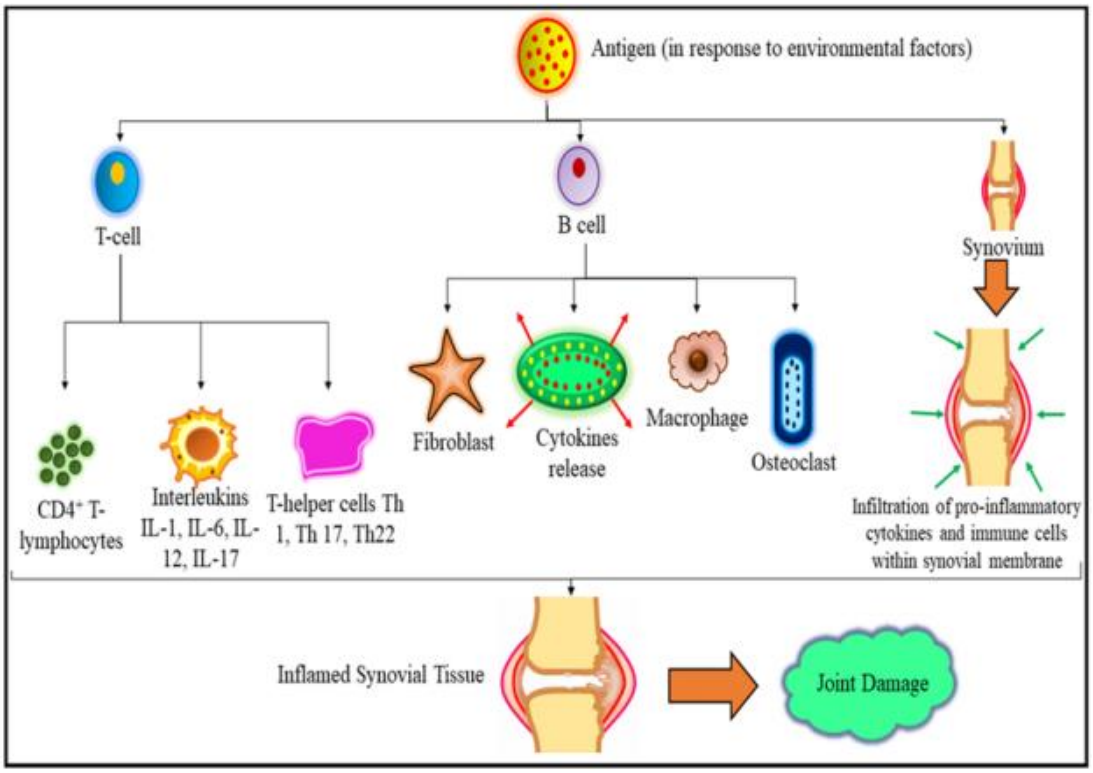

Figure 1: Pathophysiology of rheumatoid arthritis (57).

5 ROLE OF CYTOKINES IN RHEUMATOID ARTHRITIS

Signaling cells release small proteins called cytokines to regulate inflammatory and immune responses (58). Cytokines play a crucial role in the development of rheumatoid arthritis; therfore cytokines have an essential contribution to the inflammatory response and the emergence of chronic inflammation (59). In rheumatoid arthritis (RA), cytokines are the primary component of the immune system that facilitate communication. Although the precise involvement of some interleukins in the pathophysiology of RA is yet unknown, interleukins and RA have a close association (60). Cytokines in RA can be divided into four groups:

- Cytokines that cause inflammation in joints.
- Cytokines that promote inflammation.
- Cytokines that reduce inflammation
- Antagonists of natural cytokines.

In RA, the balance between pro-and anti-inflammatory cytokines determines the intensity and extent of inflammation, and thus can have a variety of clinical implications (61, 62). Cytokines are crucial for communication between the various immune system components at each stage of the pathophysiological process of RA after the first stressors have taken place (63). Joint damage and impairment are brought on by the release of pro-inflammatory cytokines and other pro-inflammatory substances (64-66). In RA, the main involved players are IL-1, TNF-, IL-6, and IL-18 cytokines (67). Interlukine-6 and TNF-α, are crucial to the pathophysiology and progression of RA .Biological treatments that target have revolutionized these cytokines However, approximately work for about 50% of the patients are non-responders to these therapies (68, 69).

On the basis of this, a significant amount of scientific research has been devoted to the identification of specific biomarkers for this disease, both for the goal of diagnosis and prognosis prediction. Particular focus has been placed on cytokines, which are tiny proteins that play a role in immune system signaling and have been shown to play a role in the pathogenesis of rheumatoid arthritis. Immune cells like T-cells and B-cells create cytokines, which infiltrate the synovial fluid that coats and lubricates joints and mediates the erosion of bone and cartilage, resulting in inflammation and pain (70, 71).

6 MEASURE OF RHEUMATOID ARTHRITIS SEVERITY

In order to reliably assess the disease activity of RA at any particular time point during the disease course, Various instruments have been developed (72). The DAS28 is calculated using the following four factors: The patient's overall

health score (as assessed by the VAS), the number of swollen and painful joints, and the erythrocyte sedimentation rate (ESR). The ESR may be substituted with the serum C-reactive protein (CRP) (73, 74).

The primary criterion used to inform therapy decisions is the disease activity score (DAS28) based on C-reactive protein (DAS28-CRP), which is used to assess disease activity in RA patients (75). inflammation may play a role in the pathophysiology behind poor bone metabolism, higher levels of bone loss are indicated by rising CRP levels over time (76). A DAS28 of 2.6–3.2 indicates low disease activity, 3.2–5.1 indicates moderate disease activity, and >5.1 indicates significant disease activity (77, 78).

The Clinical Disease Activity Index (CDAI) is a composite index for measuring disease activity that excludes acute-phase reactants. The bigger benefit of CDAI is its ability to be used in patient evaluation; as a result, it can essentially be used everywhere and anytime for RA patients to assess disease activity (79). A clinical composite score known as CDAI can be used to measure the RA's disease activity. It is a more recent tool, therefore it does not require any prerequisites like the DAS28, like calculators, computers, or measurements of acute phase reactants. The concept of CDAI was created as a sum of swollen/tender joints (out of the 28), which also incorporates the patient's and doctor's overall evaluation on the visual analogue scale (VAS), which has a scale that spans from 1 to 10 and is useful for forecasting the disease status (80), the following are CDAI's advantages:

- Its capacity to operate without the aid of calculators or normograms.
- Addresses how simple it is to implement this measure anywhere and at any time (80).

The Clinical Disease Activity Index(CDAI) is indicated by the following scores were given 0-2.8 remissions, 2.9-10 low, 10.1-22 Moderate, 22.1-76 High (81, 82).

SDAI is a scale that Smolen et al. (83) suggested, and the outcome is the simple sum of the following: the number of swollen joints (28), the number of painful joints (28), the CRP (mg/dL), the patient's and the doctor's evaluations of the disease activity on a visual analogue scale from 0 to 10 cm (83, 84).

7 DIAGNOSIS OF RHEUMATOID ARTHRITIS

Laboratory tests, especially those for rheumatoid arthritis, anti-citrullinated protein antibodies (ACPAs), and X-rays, come after the history and physical examination, which form the basis of the first diagnosis (85).

7.1 Physical Examination

The doctor looks at the joints to check for inflammation or stiffness. Finding out how many joints are affected and how long they have been inflamed is crucial. The doctor also looks for rheumatoid nodules or inflammatory tear ducts, two other signs of rheumatoid arthritis (86). The proximal interphalangeal joints, metacarpophalangeal (MCP) joints, carpus, elbows, shoulders, and knees are the joints that are most crucial to the articular exam for RA. As a result, the disease usually affects these joints, which are crucial to the techniques used to evaluate and monitor the patient's disease activity on a number of measurement scales (87). Some patients may present with mono articular joint involvement. The majority of the time, joint engagement develops slowly over several months, although in some circumstances, joint Participation could start right away or take weeks or overnight (88).

7.2 ACR/EULAR Criteria for the Diagnosis of RA

Clinical and serological characteristics that are exclusively relevant to individuals with at least one swollen joint were among the classification criteria proposed by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) (89, 90).

The most recent criteria for diagnosing RA were proposed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) in 2010. A thorough physical examination and patient history must be used to establish a high index of suspicion in order to diagnose RA (89). According to these guidelines, patients who have recently appeared with synovitis in at least one joint, no other diagnosis that more adequately explains the synovitis, and a total score of at least 6 (out of 10) from four categories are likely to be diagnosed with RA. They consist of the following:

The number and site of involved joints.

Serologic abnormalities such as the presence of anti-citrullinated peptide /protein antibodies(Anti-CCP) or rheumatoid factor(RF).

Increases in inflammatory indicators (such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

The duration of symptoms as represented in table (1).

Table 1: The 2010 ACR-EULAR classification criteria for rheumatoid arthritis. A patient must receive a score of 6/10 in order to be diagnosed with RA (91) (89).

No	Criteria	Joint involvement	Points (need-6 total)
A	**Joint involvement** (swollen or tender joint on examination)	1 large	0
		2–10 large	1
		1–3 small	2
		4–10 small	3
		>10 (at least 1 small)	5
B	**Serology**	Negative RF and ACPA	0
		Low positive RF or low positive ACPA	2
		High positive RF or high positive ACPA	3
C	**Acute phase reactants**	Normal CRP and normal ESR	0
		Abnormal CRP or abnormal ESR	1
D	**Duration of symptom**	< 6 weeks	0
		≥ 6 weeks	1

7.3 Radiological Investigation

The most reliable imaging method for RA early identification is MRI. Joint effusion and synovitis can be differentiated using contrast-enhanced MRI (92).Benefits of an ultrasound include its low cost, wide availability, lack of contraindications, and capacity to deliver noninvasive real-time imaging. While magnetic resonance imaging (MRI) techniques (preferably contrasted), when used routinely in the diagnosis of RA because they are considered sensitive diagnostic tool for detecting, considered as an operator-dependent technology are constrained by cost factors when used to detect, for example, pannus formation or synovial hypertrophy before the occurrence of bone erosion. MRI evaluation of numerous joints is time-consuming and expensive (93).

When it comes to identifying and diagnosing inflammation, imaging techniques such as MRI and ultrasound are more sensitive than clinical evaluation (94-98). In this sense, novel techniques that provide quick, automated identification of subclinical inflammation could improve the evaluation of inflammation in clinical practice. Thermography is a rapid, non-invasive imaging technique that gauges how much long wave infrared radiation from bodies increases with temperature (98-101). Since warmth is one of the primary indicators of inflammation, thermography may be helpful in the early detection of arthritis (102, 103). Furthermore, bone erosions can be detected by ultrasound (9, 104), as well as subclinical synovitis, which may cause radiographic disease progression even if the patient seems to be in clinical remission (105, 106). Because of these properties, ultrasonography is commonly used in clinical practice and clinical trials for RA diagnosis and disease state monitoring (9, 93). Both MRI and ultrasonography have been recommended for RA patients in order to diagnose and monitor disease activity (9, 107).

8 TREATMENT OF RHEUMATOID ARTHRITIS

Disease-modifying anti-rheumatic medications (DMARDs) are the first line of treatment for rheumatoid arthritis in order to reduce its aggressiveness. Since biological therapy targets multiple molecules, including interleukin-6 (IL-6) and tumor necrosis factor (TNF-a), it should be initiated if a patient does not react to synthetic DMARDs (108, 109). In order to treat rheumatoid arthritis (RA), the EULAR developed guidelines in 2010 for the use of disease-modifying anti-rheumatic medications (DMARDs) (16). Treatment should begin after RA diagnosis and first assessments. The patients with RA are treated in a variety of ways, In order to address the various issues with function and psychosis (110). Although there is no known cure for RA, therapies can lessen symptoms and halt the disease's progression. Early and

aggressive disease-modifying treatment gives the best outcomes when applied (111). There are efficient RA treatments available, but they can be expensive (25). The most recent 2019 recommendations from the European League Against Rheumatism (EULAR) emphasise the need of maintaining a balance between efficacy, costs and safety is important (25). In Japan, The Japan College of Rheumatology released the country's most recent RA treatment recommendations in 2020 (112) , and its overarching principles of RA are in line with the EULAR recommendations. Both of these recommendations and the American College of Rheumatology's (ACR) guidelines for treating RA stress that the aim of treatment should be remission or low disease activity (113, 114).

9 CONCLUSIONS

In conclusion, according to recent research's, the prevalence of RA in Iraq is moderate to high and has recently dramatically increased. Early RA diagnoses and treatment are essential to prevent irreversible joint degeneration and improve long-term outcomes. Early diagnosis and treatment of RA may be made easier by new biomarkers that can identify the disease early. They may also help more precisely track disease activity and response to treatment, allowing doctors to modify patient treatment plans and enhance overall results.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

No conflicts of interest pertaining to this work are disclosed by any of the authors.

Authors' contribution

All authors took equal part in the conduct of the study and in the preparation of this manuscript.

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