REVIEW ARTICLE

Unveiling the Complexities of Rheumatoid Arthritis: A Comprehensive Pathoepidemiological Review

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Abstract

Rheumatoid arthritis (RA) is a common autoimmune disorder characterized by inflammation in the joints, affecting around 0.24–1% of the population. RA can develop through a variety of paths, resulting in a nonspecific clinical appearance. It progresses from preclinical to chronic disease, with pathogenic mechanisms that may differ across people, confounding therapy efforts. Numerous factors have been found to be associated with RA, including lifestyle-related risk factors like smoking and obesity, which are modifiable, as well as advancing age and female gender, which are nonmodifiable. RA pathophysiology is an intricate interaction between different genetic and immunological variables resulting in disease progression. With a better knowledge of the pathophysiology of RA, new therapeutic approaches are being developed for effective management of RA. This review article summarizes epidemiology, pathogenesis, and diagnostic options for RA.

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Introduction and Background

The autoimmune inflammatory illness rheumatoid arthritis (RA), which primarily impacts the joints, is characterized by autoantibodies that target a variety of molecules, including modified self-epitopes.[1] Approximately 0.24–1% of the population experiences RA, and it is twice as common in women compared to men.[2]

Rheumatoid arthritis may occur *via* several different pathways to a nonspecific clinical presentation, advancing from preclinical to chronic disease.[3,4] Although a variety of adverse long-term implications occur in RA cases, they have been substantially alleviated using intensive treatment strategies and strong pharmaceutical regimens. Early signs of RA include symptoms such as exhaustion, swollen and painful joints, and early morning stiffening of joints, while untreated RA in late stages exhibits a complicated clinical picture with the development of systemic manifestations, including lymphomas, vasculitis, lung nodules, and interstitial lung disease (ILD).[5–7]

Several factors influence the risk of developing RA, including modifiable lifestyle factors such as smoking and obesity, and nonmodifiable factors like being female and aging.[8,9] The Global Burden of Disease research indicates that two-thirds of RA patients are women, with about half of these women being over the age of 55.[10] This comprehensive review article meticulously covers the epidemiological trends, pathogenesis, and novel diagnostic markers available for diagnosing and managing RA.

Epidemiology

Worldwide, prevalence of RA is relatively stable, ranging from 0.5 to 1.0%; however, it is more prevalent among certain communities, such as indigenous North American tribes such as Indian Pimas (5.3%) and Indian Chippewas (6.8%).[11] As per the findings of the Global Burden of Disease research, there are approximately 18.5 million RA cases worldwide, and it is estimated that new cases detected per year will increase by 40% from 1.07 million in 2019 to around 1.5 million by 2040.[12] The prevalence of RA in India as reported by various studies ranged from 0.28 to 0.7%.[13] Multiple risk factors that have been associated with RA are discussed below:

Gender and Family History

Rheumatoid arthritis can manifest at any age, though it is typically identified during the third to fifth decades, and it is twice as prevalent in women as in men.[14,15] Early menopause, polycystic ovarian disease, and a history of preeclampsia have been linked to an increased risk of developing RA in women, whereas breastfeeding, hormone replacement medication, and oral contraception usage are associated with a lower risk.[16] Studies have also shown that first-degree relatives of RA patients are four times more likely to get the disease.[17]

Infectious Agents

The development of RA has been associated with various viral and bacterial pathogens. These include bacteria such as *Mycoplasma* species, *Porphyromonas gingivalis*, and *Prevotella* species, as well as viral agents like Epstein–Barr virus (EBV) and retroviruses.[18–20] Banaei et al. reported in their study the presence of bacterial superantigens in the plasma and synovium of individuals with RA, with their findings suggesting that staphylococcal superantigen could increase expression of the CD18 molecule, which is an immune mediator associated with RA.[21]

Dietary Factors

Various studies have been done to determine the association of diet with RA. They have shown that foods that either increase or decrease inflammation may be a "moderator" of the disease or a "trigger" of it. Although a variety of foods and dietary patterns have been examined for potential linkages to the risk of RA, the data are still debatable because it is challenging to determine each factor's unique influence.[22] Salgado et al., in their study, showed that a higher risk of RA has been linked to a diet that contains excessive dietary sodium.[23] The National Health Service (NHS) of England study showed that regular use of soda with added sugar was linked to a higher chance of developing seropositive RA.[24] The diets that were found to decrease the risk of RA included food rich

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in docosahexaenoic acid and fruits rich in vitamin C due to the antioxidant properties of these foods.[25,26]

Obesity

The growing understanding that obesity correlates with an increased risk of RA is another notable trend, as white adipose tissue has been shown to function as a hormone-producing tissue capable of producing cytokines like C-reactive protein (CRP) and interleukin (IL) 6, which predispose people to autoimmune inflammatory disorders by aggravating inflammation.[27] Recent research indicates that individuals with a higher body mass index (BMI) are more likely to acquire RA and have a faster onset of the illness.[28]

Smoking

There are several hypotheses as to how smoking may make people more susceptible to RA. Smoking increases the peptidyl arginine deiminase (PAD) 2 enzyme's expression, which increases the lung's citrullination mechanisms.[29] Anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) are the key autoantibodies observed in RA individuals and have been linked with poor disease outcomes, and these are significantly increased in smokers, as shown by van Wesemael et al. in their study.[30] Smoking is thought to contribute up to one-third of the environmental risk, with an odds ratio of >2.[31] Smoking is more strongly linked to RA that is ACPA-positive and associated with increased levels of RF.[32]

Genetic Factors

Rheumatoid arthritis pathogenesis is also influenced by genetic variations, which are primarily represented by single nucleotide polymorphisms (SNP). Genome-wide association studies have identified >100 loci associated with RA using *in silico* imputation of SNP.[33] Certain genes in the major histocompatibility complex (MHC) express amino acid sequences similar to the human leukocyte antigen (HLA) peptide-binding groove, termed shared epitope (SE), which accounts for the majority of genes associated with RA.[34] The primary genetic contributor to the risk of RA is identified as the gene *HLA-DRB1*. Additional HLA genes, such as *HLA-DPB1*, *HLA-B*, and *HLA-A*, along with a variant in the *HLA-DOA* gene that influences the expression of various genes, also play a role in increasing the likelihood of developing RA.[4] The *PTPN22* gene, which encodes a protein tyrosine phosphatase found exclusively in immune cells, is a recognized risk factor for RA as well as other autoimmune diseases such as type 1 diabetes.[35]

Pathogenesis of Rheumatoid Arthritis

The pathophysiology of RA involves a multitude of factors such as genetics, environment, and immune response, all playing a role in the disease's development and progression. The role of various autoantibodies associated with RA is discussed below. The pathway to the development of RA is shown in Figure 1.

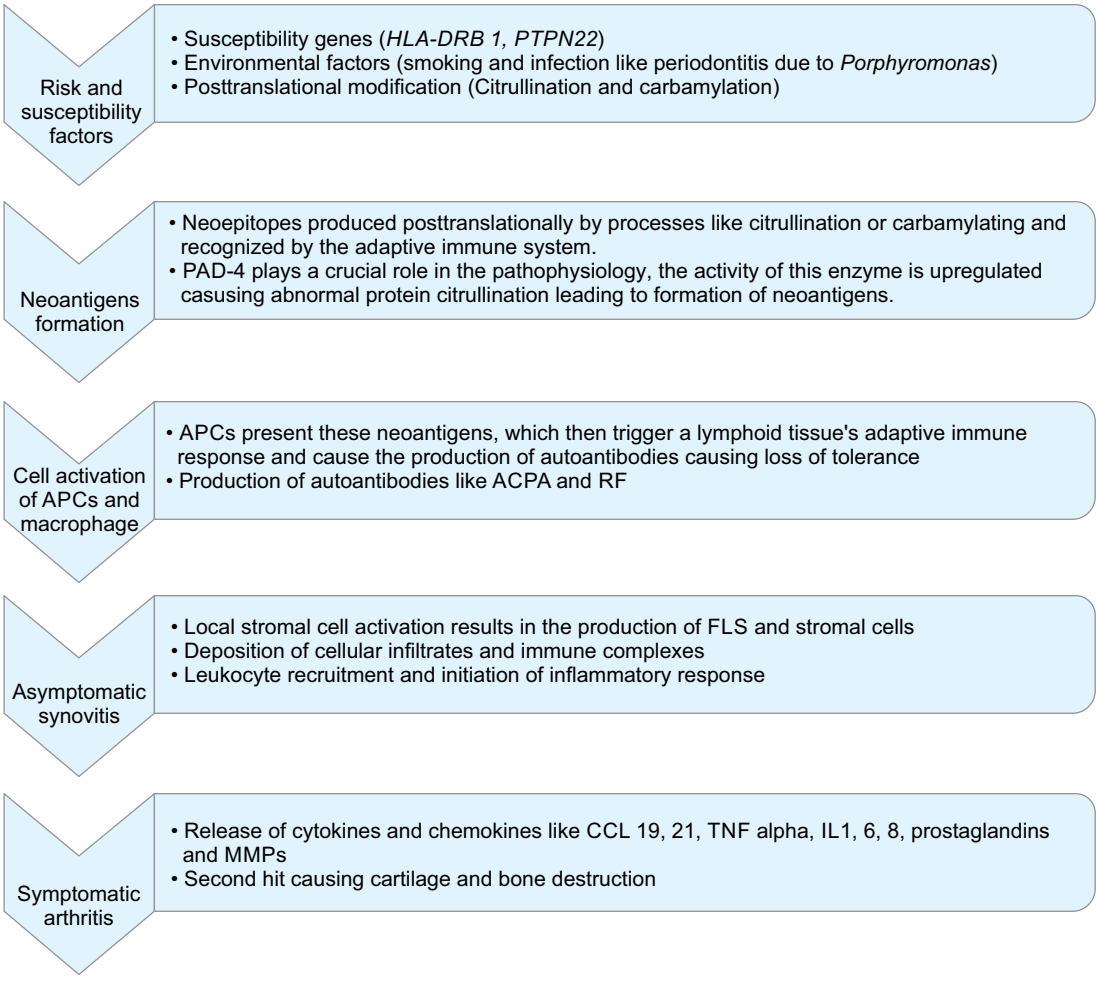

Fig. 1: Pathogenesis of RA; ACPA, anti-citrullinated protein antibodies; APCs, antigen-presenting cells; CCL, CC chemokine ligands; FLS, fibroblast-like synoviocytes; HLA, human leukocyte antigen; IL, interleukins; MMP, matrix metalloproteinases; PAD, peptidyl arginine deiminase; PTPN, protein tyrosine phosphatases; RF, rheumatoid factor; TNF, tumor necrosis factor

Role of Rheumatoid Factor Antibodies in Rheumatoid Arthritis

Rheumatoid factor within the synovium milieu significantly contributes to the inflammation process and the retention of antigens associated with RA. It produces immunological complexes in synovial inflammatory sites, complement activation, and leukocyte infiltration.[36] B-cell aggregation in inflamed synovium and lymphoid follicles is responsible for the formation of RF autoantibodies, which directly attach to the Fc region of the aggregated IgG. However, these antibodies cannot be regarded as specific, and their utility is debatable because one-third of RA patients may present as seronegative.[36] Numerous research findings indicate that the sensitivity of RF lies between 60 and 90%, while its specificity varies from 48 to 92%.[37]

Role of ACPA Antibodies in Rheumatoid Arthritis

Many proteins undergo the physiological process of citrullination, which is a common physiological phenomenon. In the context of inflammation, PAD acts to transform the proteins' uncovered arginine side chains into citrulline, which results in the citrullination of proteins.[38] Humans have 5 PAD isozymes; however, only PAD 1, 2, 3, and 4 are enzymatically active.[39] Citrullinated proteins cause B-cells to produce ACPA as a reaction when there is a breach in the tolerance of citrullinated peptides.[40] Studies have shown that in transgenic mice, citrullinated proteins can cause arthritis, and ACPAs can cause osteoclastogenesis, complement activation, and macrophage tumor necrosis factor (TNF) production.[41]

Role of Anti-carbamylated Protein Antibodies in Rheumatoid Arthritis

Rheumatoid arthritis cases may also have anti-carbamylated protein (CarP) antibodies.[42] Lysine is converted to homocitrulline during carbamylation when urea and cyanate are present. Studies have demonstrated that carbamylated proteins can initiate immune responses, attract immune cells, activate T-cells, and stimulate antibody production, leading to the release of IL, particularly IL-10 and IL-17, in susceptible individuals.[43] Additionally, the presence of these altered peptides in the synovium milieu may be facilitated by T-cell activation and a strong antibody response, which could potentially trigger the development of erosive arthritis.[44]

Diagnosis of Rheumatoid Arthritis

Clinical Assessment

To enable the timely diagnosis of RA, the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) released updated classification criteria in 2010, as outlined in Table 1.[45]

Investigational Biomarkers for Diagnosis of Rheumatoid Arthritis

At present, the ACR/EULAR guidelines recommend use of two biomarkers: RF and ACPA. RF is detected in 80–90% of cases, with a sensitivity and a specificity of 69 and 85%, respectively, while ACPA has a sensitivity and specificity of 67 and 95%, respectively.[46] After 2010, various new biomarkers have been identified for early identification of RA, which provide a "window of opportunity" to prevent joint erosion and the development of radiologic abnormalities, as discussed below and shown in Figure 2.

Serum 14-3-3η

Serum 14-3-3η facilitates essential signaling cascades like the Janus kinase-signal transducer (JAK/STAT) pathways that lead to the production of proinflammatory cytokines like IL-1 and IL-6, which are associated with RA pathogenesis. Serum 14-3-3η is a chaperonin peptide; it has been recognized as a novel RA diagnostic biomarker. Its testing can improve diagnosis rates or reclassify individuals who were previously seronegative when paired with RF and ACPA.[47] Wang et al. in their study found that the 14-3-3η protein had a combined sensitivity of 73% and a specificity of 88%.[48]

Anti-mutated Citrullinated Vimentin

Citrullinated vimentin is widely produced in the synovial milieu and has been recognized as a possible self-antigen in RA pathogenesis. The anti-mutated citrullinated vimentin (MCV) antibody targets the isoform of vimentin that has arginine residues rather than glycine. When used alongside RF and ACPA testing, anti-MCV antibodies can improve the chances of diagnosing patients with nonspecific undifferentiated arthritis.[49] It has a low sensitivity of around 25% in the early stage of disease and a sensitivity of up

Table 1: Classification criteria for RA (updated in 2010) as defined by the EULAR and ACR[45]

Serial no.	*Parameter*		*Score*
1	Joints distribution	Number	(0–5)
	Major joint (including shoulders, elbows, hips, knees, and ankles)	1	0
		2–10	1
	Minor joints (excluding shoulders, elbows, hips, knees, and ankles)	1–3	2
		4–10	3
		>10	5
2	RF	ACPA	(0–3)
	Negative	Negative	Negative
	Low positive	Low positive	2
	High positive*	High positive*	3
3	Symptom duration		(0–1)
	<42 days		0
	>42 days		1
4	Acute phase reactants		(0–1)
	CRP/ESR within normal range		0
	CRP/ESR above normal limits		1

Total score ≥6 = "definite" RA. ACPA, anticyclic citrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocytic sedimentation rate; RF, rheumatoid factor; *High positive is defined as >3 times the maximum limit of normal

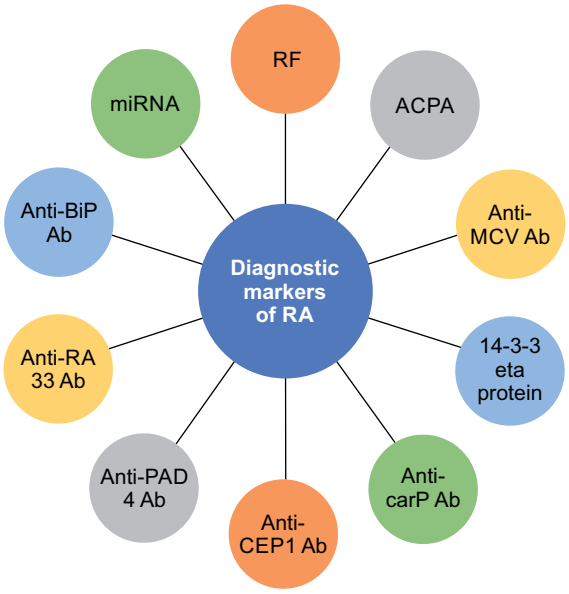

Fig. 2: Diagnostic and investigational biomarkers for diagnosis of RA; ACPA, anti-citrullinated protein antibodies; anti-BiP Ab, anti-immunoglobulin binding protein antibodies; anti-CarP Ab, anti-carbamylated protein antibodies; anti-CEP1 Ab, anti-citrullinated *α*-enolase peptide 1 antibodies; anti-MCV Ab, anti-mutated citrullinated vimentin antibodies; anti-PAD 4 Ab, anti-peptidyl arginine deiminase antibodies; anti-RA33 Ab, anti-rheumatoid arthritis 33 antibodies; miRNA, microribonucleic acid; RF, rheumatoid factor

to 46% in established RA, with a specificity of 98–100%.[50]

Anti-carbamylated Protein Antibody

Anti-carbamylated protein antibodies have emerged as a novel biomarker for RA. These antibodies strongly correlate with radiological progression of disease, offering crucial prognostic information for more effective therapy. Li et al.'s 2016 meta-analysis demonstrated the sensitivity and specificity of this biomarker at 42 and 96%, respectively.[51]

Anti-citrullinated *α*-enolase Peptide 1 Antibody

Peptides such as *α*-enolase, generated following citrullination, have been recognized as autoantigens contributing to the development of RA. Citrullinated *α*-enolase peptide-1 (CEP-1) was first identified in the RA synovial milieu by Kinloch et al.[52] Rheumatoid synovial fluid has *α*-enolase, and synovial fluid has higher anti-CEP-1 levels than serum, indicating the development of local antibodies. When anti-CCP and anti-CEP-1 antibody analysis are combined, the anti-CEP-1 antibody may provide additional diagnostic value in RA patients.[53] Studies have shown that compared to individuals with anti-CCP antibody-positive RA, those with anti-CEP-1 antibody-positive RA are more likely to experience bone erosions or ILD. The anti-CEP-1 antibody has a high specificity of up to 97% and a low sensitivity of 44%.[54]

Anti-peptidyl Arginine Deiminase 4 Antibodies

Three of the five PAD enzymes that have been reported in human beings are PAD 2, 3, and 4, which are autoantigens in RA.[41] With a specificity of >95%, anti-PAD4 antibodies are detected in up to 18% of RF- and ACPA-seronegative people. A more severe disease phenotype and joint erosions are linked to anti-PAD4 antibodies, and it may be useful for prognostic and diagnostic purposes.[55]

Anti-rheumatoid Arthritis 33 Antibodies

Heterogeneous A2 nuclear ribonucleoprotein (hnRNP-A2), commonly referred to as rheumatoid arthritis 33 (RA33), is a ubiquitous nuclear peptide involved in mRNA processing, transportation, and translation. It is produced in most organs and tissues; however, abnormal accumulation has been identified in inflamed synovial tissue of RA patients.[56] Anti-RA33 antibodies are found in approximately 33% of RA patients, with a 90% specificity.[57]

Anti-immunoglobulin Binding Protein Antibodies

Immunoglobulin binding protein (BiP) is an endoplasmic reticulum (ER)-localized protein essential for the assembly of polypeptide chains and preventing cells from apoptosis when a cell is stressed. During the development of RA, BiP arises as a result of stress response, and individuals with RA are likely to generate autoantibodies against BiP. Anti-BiP antibodies are autoantibodies that attach to the stressed BiP. Anti-BiP antibodies are found in around 60% of RA patients, with a specificity reaching up to 96%.[58]

Microribonucleic Acid: An Emerging Biomarker for Rheumatoid Arthritis

Microribonucleic acid (miR) is a small endogenous noncoding ribonucleic acid (RNA) made up of around 20 nucleotides that contribute to control of gene expression at the posttranscription level. Few studies have addressed the potential of miR in the synovial milieu and blood as a novel biomarker to differentiate healthy people from RA cases.

In their research, Elsayed et al. showcased a notable rise in miR-146a levels in the blood of individuals with RA. They also noted that miR-146a exhibited superior diagnostic utility compared to ACPA and RF. Specifically, miR-146a enabled the differentiation of RA patients from healthy individuals with a specificity and sensitivity of 100 and 96%, respectively.[59]

Murata et al.'s research investigation reported that miR-125a-5p, miR-26a, and miR-24 had a diagnostic sensitivity of 53.9, 89.5, and 63.7%, respectively, as well as a specificity of 94.3, 64.7, and 89.5%, respectively. They suggested that miR-125a-5p, miR-26a, and miR-24 can be used, with these miRs showing 78.4 and 92.3%.[60]

Conclusion

The focus of this narrative review was to understand the pathogenesis and development of RA and highlight the diagnostic utility of traditional as well as new biomarkers. The new biomarkers are helpful for diagnosis at an early stage and for predicting the progression of RA. However, more research studies are needed to discover novel biomarkers for evaluating therapeutic response. RA pathophysiology is a complicated interaction of various immunological, environmental, and genetic factors contributing to disease development and progression. With an improved understanding of the pathophysiology of RA, new therapeutic approaches are being developed for effective management of RA.

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