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Multifactorial Pathogenesis and Epidemiological Patterns of Rheumatoid Arthritis

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Abstract:

Rheumatoid arthritis (RA) is a common chronic autoimmune inflammatory disease with a global prevalence of approximately 0.5%–1%, primarily manifesting as synovial inflammation, joint bone destruction, and systemic damage. This review, based on a systematic literature search covering 2000–2024, summarises epidemiological trends, pathogenic mechanisms, and risk factors for RA. Research indicates that RA onset is closely associated with genetic susceptibility (such as HLA-DRB1 shared epitopes), immune dysregulation, and environmental factors including smoking and chemical exposure. Health conditions such as obesity and periodontitis may also increase risk. Complex interactions between immune cells and cytokines lead to synovial hyperplasia, formation of erosive 'synovial overgrowth', and autoantibody production. Existing non-steroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying anti-rheumatic drugs (DMARDs) can alleviate symptoms, yet early recognition and precise intervention remain essential. This paper aims to provide reference for RA aetiological research, early prediction model development, and personalised treatment strategies, highlighting the need for integrative multi-omics approaches and translational studies to improve patient outcomes.

Keywords: Rheumatoid arthritis; Genetic; Environmental; Pathogenesis.

1. Introduction

Rheumatoid arthritis (RA) is the most prevalent inflammatory arthritis, leading to cartilage and bone destruction and disability [1]. Diagnostic criteria include the presence of at least one clearly defined joint swelling not attributable to another disease [2]. The pathological hallmarks of RA comprise synovial inflammation and hyperplasia, production of autoantibodies (such as rheumatoid factor RF and anti-citrullinated protein antibodies ACPA), alongside cartilage and bone deformities and multisystem involvement,

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including cardiovascular, pulmonary, psychological, cutaneous, and skeletal disorders [3]. The global prevalence of RA is approximately 0.5%–1%, exhibiting marked geographical variation: incidence rates are higher in northern and urban populations than in southern and rural areas [4]. Significant advances have been made in disease course management through the ongoing development of disease-modifying antirheumatic drugs (DMARDs) [5]. Early diagnosis and prompt treatment can prevent or substantially delay joint destruction in approximately 90% of patients, thereby averting irreversible disability [6]. Consequently, enhancing screening strategies and primary care physicians' awareness is crucial for early detection. Numerous clinical trials have explored the role of various drug classes in RA treatment, with some medications now integrated into routine clinical practice. First-line agents include non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, naproxen, ibuprofen, and etodolac, which alleviate pain and swelling while inhibiting inflammation. NSAIDs block prostaglandin (PG) synthesis by inhibiting cyclooxygenase (COX) activity. Inhibiting COX-2 reduces PG production at inflammatory sites, whereas COX-1 inhibition may cause common adverse effects such as bleeding and peptic ulcers. Glucocorticoids also exhibit potent anti-inflammatory effects by regulating gene expression through binding to glucocorticoid receptors, producing anti-inflammatory and immunosuppressive outcomes. However, their side effects include nausea, abdominal pain, ulcers, osteoporosis, and diabetes. Despite this, approximately 40%–50% of patients achieve remission or low disease activity under this regimen [6,7]. With advancing research, an increasing number of molecular targets have been identified and utilised for the prevention and treatment of RA. For instance, cytokines such as IL-4, IL-10, IL-15, IL-17, IL-18, IL-23, and IRAK-4 play crucial roles in both innate and adaptive immune responses in RA. These discoveries not only deepen our understanding of the multifactorial pathogenesis of RA but also lay the foundation for precision therapies targeting specific cytokine pathways. Moreover, small-molecule metabolites such as prostaglandins (PGs), leukotrienes (LXs), phospholipidase A2 (PAF), leukotrienes (LTs), nitric oxide (NO), and reactive oxygen species (ROS) also play vital roles in the pathological process of RA. Increasing evidence indicates that epigenetic regulation—including non-coding RNAs, DNA methylation, RNA methylation, and histone modifications—is equally critical in RA. Several novel therapeutics targeting these classical or emerging molecular targets are currently being explored and developed [7].

This review synthesizes evidence on the multifactorial pathogenesis and epidemiological trends of RA, aiming to provide a basis for early identification, prevention strategies, and innovative therapeutic approaches. In recent years, new insights and breakthroughs in rheumatoid arthritis (RA) research and clinical practice have advanced the comprehensive prevention and treatment of this disease. RA is an autoimmune disorder whose core pathological mechanisms involve not only synovial inflammation and abnormal immune cell activation, but also excessive cytokine network activation and persistent imbalance within the local joint microenvironment. Studies indicate that both B cells and T cells play pivotal roles in the pathogenesis and progression of RA. B cells generate autoantibodies (such as RF and ACPA) while promoting the release of inflammatory mediators; T cells, meanwhile, further drive abnormal proliferation of synovial cells and osteoclast activation by secreting inflammatory mediators like IL-17 and TNF-α, leading to irreversible damage to cartilage and bone tissue. Elucidation of this immunological mechanism provides a robust theoretical foundation for targeted therapies.

Therapeutically, traditional methotrexate (MTX) remains the 'gold standard' foundational medication. However, with rapid advances in molecular biology and immunology, biologics and small-molecule targeted therapies have progressively become mainstream treatments. For instance, anti-TNF-α monoclonal antibodies (e.g., etanercept, adalimumab), IL-6 receptor antagonists (e.g., tocilizumab), and JAK inhibitors (e.g., tofacitinib) are now widely employed clinically, significantly improving outcomes for many patients. By precisely intervening in key inflammatory pathways, these agents effectively reduce joint destruction and enhance quality of life. However, high treatment costs and potential infection risks continue to limit their accessibility among certain patient groups. Therefore, achieving a balance between efficacy and safety remains a key focus for future research.

Beyond pharmacological interventions, early diagnosis and standardised management are equally critical. RA often presents with non-specific symptoms in its initial stages, such as mild joint pain or morning stiffness, which are easily overlooked. Early recognition and timely intervention within the 'window of opportunity' through serological testing (e.g., RF, ACPA levels), imaging studies, and inflammatory marker monitoring can significantly improve long-term patient outcomes. Concurrently, multidisciplinary collaborative management is emerging as a trend. Collaboration between rheumatologists, orthopaedic surgeons, rehabilitation therapists, and psychiatrists enables comprehensive treatment plans encompassing medication, functional training, and psychological support.

In recent years, with the rise of epigenetics and multi-omics research, scientists have discovered that non-coding

RNAs, DNA methylation, and histone modifications play regulatory roles in the pathogenesis and progression of RA. For instance, microRNAs play a pivotal role in regulating immune cell differentiation and inflammatory cytokine expression, offering potential biomarkers and novel therapeutic targets for early RA diagnosis and personalised treatment. Concurrently, the gut microbiota is increasingly recognised as a significant external influence on RA, with its relationship to immune homeostasis providing new avenues for prevention and intervention.

Overall, the prevention and treatment of RA are progressing towards precision and individualisation. Future research must not only continue exploring novel molecular mechanisms and therapeutic targets but also focus on enhancing drug bioavailability, reducing adverse effects, and leveraging artificial intelligence and big data technologies to optimise diagnostic and therapeutic pathways. Through the deep integration of basic research and clinical application, more effective control of RA is anticipated soon, ultimately alleviating its dual burden on patients‘ quality of life and healthcare systems.

2. Literature Search and Inclusion Criteria

This study primarily obtained data through systematic literature searches. The databases searched included the U.S. National Library of Medicine (PubMed) and Google Scholar, with a search time frame from January 2000 to December 2024. The search strategy combined Medical Subject Headings (MeSH) with free-text keywords, with primary keywords including ‘Rheumatoid Arthritis,’ ‘RA,’ ‘risk factors,’ ‘genetics,’ ‘environment,’ ‘hormones,’ ‘prevalence,’ and ‘incidence,’ among others. Boolean logic operators (AND/OR) were used to combine these keywords to ensure the comprehensiveness of the search.

The inclusion criteria for literature were as follows: 1) Peer-reviewed articles published in English-language journals; 2) Studies involving the epidemiological characteristics, pathogenesis, or clinical management of rheumatoid arthritis; 3) Studies including content related to genetic susceptibility, environmental exposure, immunological mechanisms, or hormone levels; 4) Cohort studies, case-control studies, cross-sectional studies, and clinical trials. Exclusion criteria were: 1) non-peer-reviewed literature, conference abstracts, reviews, or news reports; 2) Pure case reports and studies with methodological deficiencies; 3) Studies focusing on paediatric RA (unless they have significant reference value for the overall mechanism).

During the screening process, two researchers independently read the titles and abstracts to exclude irrelevant literature. Subsequently, the full texts of potentially relevant studies were reviewed, and discrepancies were resolved through discussion. The final included literature was categorised into three types based on the research focus: 1) Epidemiological trends; 2) Pathogenesis factors (genetic, immunological, environmental, hormonal); 3) Treatment implications.

3. Pathogenesis and Multifactorial Risk Landscape of Rheumatoid Arthritis

3.1 Pathogenesis

The synovial pathological changes in rheumatoid arthritis (RA) primarily manifest in two aspects. Firstly, the synovial intima exhibits marked thickening, attributable to the increased number and activation of two types of synovial cells: macrophage-like synoviocytes (MLSs) and fibroblast-like synoviocytes (FLSs). These cell types serve as major sources of diverse cytokines and proteases, including integrins, selectins, and members of the immunoglobulin superfamily. MLSs secrete multiple pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α), which directly drive inflammatory responses and tissue destruction. Concurrently, FLSs not only produce IL-6 but also release substantial amounts of matrix metalloproteinases (MMPs) and small-molecule inflammatory mediators, such as prostaglandins and leukotrienes, thereby further promoting cartilage matrix degradation and sustaining the inflammatory environment. Notably, FLSs also promote the formation of ectopic lymphoid structures (ELSs) within synovial tissue through interactions with immune cells, thereby amplifying local immune responses.

Secondly, the infiltration of adaptive immune cells into the synovial sublining represents another hallmark feature of RA. This process leads to the characteristic formation of ‘pannus’ at the cartilage-bone interface. Comprising MLSs, FLSs, dendritic cells, plasma cells, and mast cells, pannus constitutes the key pathological basis for joint damage and erosion in advanced RA. Nearly half of the cells within the sublining layer are $CD4^+$ memory T cells, which can either diffusely infiltrate tissues or form germinal centre-like structures. Within these ectopic ‘germinal centres’, mature B cells proliferate, differentiate, and produce antibodies. Concurrently, substantial numbers of B cells, plasmablasts, and plasma cells are present, with a significant proportion secreting rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), thereby further driving the immunopathological process of RA (Fig.

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1) [3].

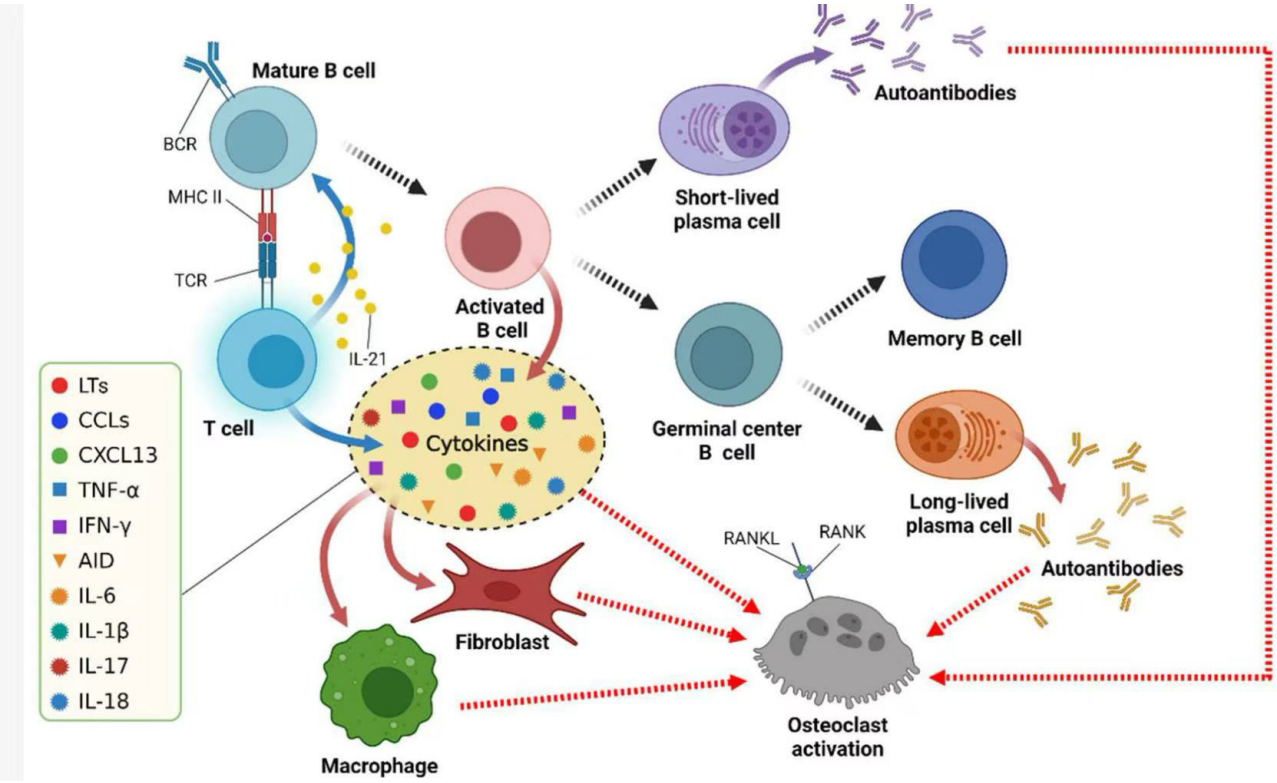

Fig. 1 The multiple functions of B cells in RA. BCR = B cell receptor; TCR = T cell receptor; MHC = major histocompatibility complex; RANKL = receptor activator of NF-κB ligand; RAN receptor activator of NF-κB [3]

3.2 Genetic Factor

Early studies revealed a significant genetic association between rheumatoid arthritis (RA) and polymorphisms within the human leukocyte antigen (HLA) locus. With increasing understanding of the HLA locus, particularly the structure of HLA-DRB1, researchers have progressively clarified that this genetic susceptibility is primarily concentrated in a class of alleles termed shared epitopes (SE), exhibiting the most pronounced expression in anti-citrullinated protein antibody (ACPA)-positive RA patients. To elucidate this phenomenon, scholars proposed the SE hypothesis, which seeks to identify common features among different HLA-DRB1 alleles or haplotypes. Initially, a homologous sequence was identified within amino acids 69–74 of the HLA-DRB1 β-chain, posited as a key protein structure closely linked to RA pathogenesis. Building upon this hypothesis, multiple studies categorised several DRB1 haplotypes into SE allele clusters and compared them with control populations. Results indicated that most haplotypes derived from DRB101, 04, and 10 belonged to SE alleles, while DRB114:02 was proposed as a potential major risk factor in the American population. Conversely, the HLA-DRB1*13 allele has been demonstrated to confer significant protection against RA. Further stratified analysis by autoantibody subtype revealed the strongest genetic association occurred in autoantibody-positive RA patients. Both early rheumatoid factor (RF) and subsequently acquired anti-citrullinated protein antibodies (ACPA) were closely linked to SE alleles. This series of findings not only illuminates the molecular aetiology of RA but also provides deeper insights into understanding its genetic susceptibility mechanisms [7] (Figure 2).

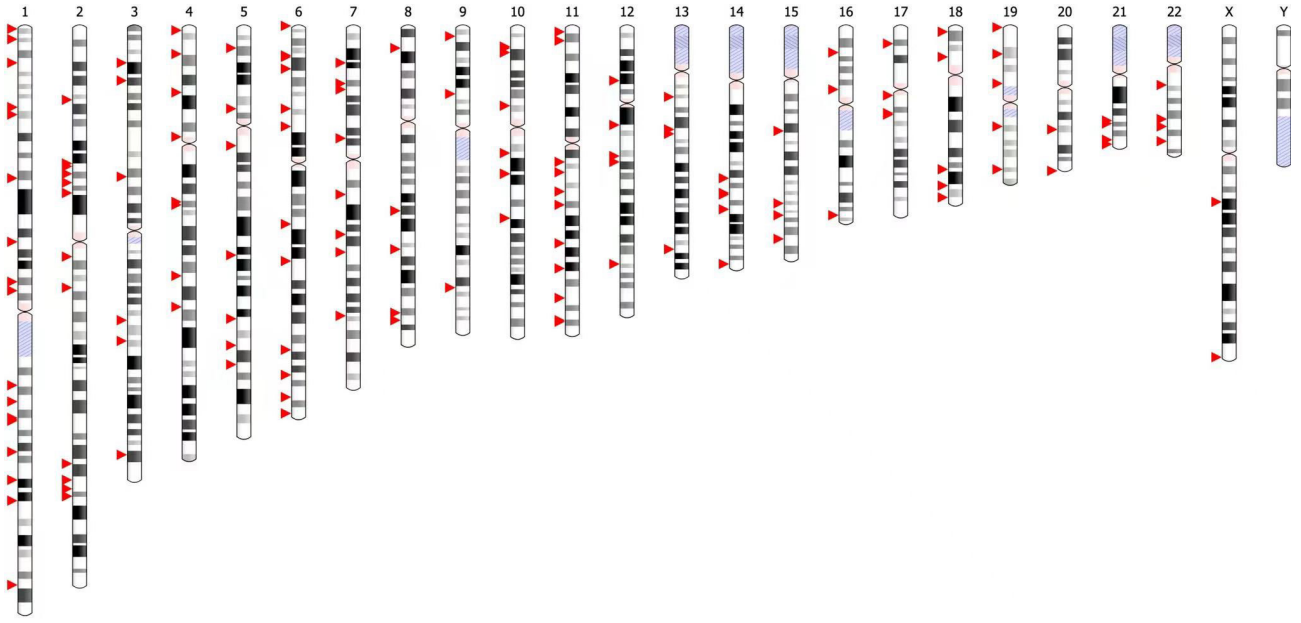

Fig. 2 Related genes of RA [7]

3.3 Environmental Trigger

Therefore, environmental triggers also play a role of inducing the RA. For example, smoking is an important trigger, the detailed process of the reaction is smoking activates PAD2/PAD4 enzymes in lung tissue; these enzymes transform arginine to citrulline, altering protein structure; the immune system mistakes these modified proteins as foreign invaders and leads to production of anti-citrullinated protein antibodies (ACPAs) that attack the body‘s own tissues [8]. There is evidence to support the opinion that smoking cessation lowers RA risk by 37% after 5 years.

Chemical substances sometimes also lead negative impacts to RA. It mainly involves long-term exposure to certain occupational or environmental chemicals, which may increase the risk of developing the disease by inducing immune abnormalities or inflammatory responses. Firstly, Asbestos, which is a long-term exposure to asbestos (such as workers in construction, shipbuilding, mining and other industries) may increase the risk of RA. When asbestos fibers enter the human body, they may trigger chronic inflammation and immune activation, disrupting the balance of the immune system. Secondly, Silica dust (silicon dioxide) which is a inhalation of silica dust by workers in mining, quarrying, glass manufacturing and other industries may induce autoimmune responses by activating inflammatory pathways in the body (such as the NLRP3 inflammasome), thereby increasing the risk of RA. Thirdly, Solvent substances, such as benzene, toluene, and xylene (commonly used in painting, printing, chemical and other industries). They may affect the function of the immune system, and studies have shown a certain association with an increased risk of RA. [9]. At last, Pesticides and insecticide would increase the risk of contracting RA. Some studies have found that long-term exposure to pesticides in agricultural environments (such as organophosphates and carbamates) may be related to the risk of RA, possibly due to their potential interference with the immune system. However, the current evidence needs further verification [10].

3.4 Other Medical Condition

Obesity may indirectly increase the risk of developing RA by affecting inflammatory responses and immune function. Specifically, adipose tissue in obese individuals secretes various inflammatory factors (such as TNF-α and IL-6). These factors can keep the body in a state of chronic inflammation for a long time, which in turn abnormally activates the immune system, prompting it to attack the body‘s own joint tissues and increasing the possibility of RA onset [11].In addition, obesity may also affect hormone levels and metabolic functions, further disrupting immune balance, exacerbating inflammatory responses, and having an adverse impact on the occurrence and development of RA [12].

Periodontitis in oral health (especially that associated with Porphyromonas gingivalis infection) may be related to the onset of RA. Porphyromonas gingivalis, one of the main pathogenic bacteria causing periodontitis, produces certain substances (such as peptidylarginine deiminase) that may induce the body to produce autoantibodies and trigger immune response disorders [13]. This immune

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abnormality may interact with the pathogenesis of RA, prompting the immune system to mistakenly attack joints, thereby increasing the risk of RA.

Beyond genetic factors, mounting evidence indicates that lifestyle and environmental exposures play equally pivotal roles in the onset and progression of rheumatoid arthritis (RA). Obesity and periodontitis are two widely recognised contributors, potentially promoting RA development and advancement through pathways involving chronic inflammation and immune dysregulation.

Firstly, the association between obesity and RA extends beyond increased secretion of inflammatory cytokines. In an obese state, adipose tissue is regarded as an 'endocrine organ' capable of secreting multiple hormone-like substances such as leptin and adiponectin. These molecules directly influence the differentiation and function of immune cells. For instance, leptin promotes the activation of T cells and B cells, causing them to produce more pro-inflammatory cytokines and thereby amplifying the inflammatory response. Concurrently, obesity is closely linked to insulin resistance. Metabolic dysfunction can exacerbate abnormal immune cell activity by altering glucose and lipid metabolic pathways, creating a dual 'metabolic-immune' imbalance. This imbalance not only perpetuates chronic inflammation but may also compromise self-tolerance, thereby increasing the risk of immune attacks on joint tissues [11,12]. Moreover, obesity correlates with altered oestrogen levels in females. Some studies suggest aromatase in adipose tissue converts androgens into oestrogens; abnormally elevated oestrogen levels may disrupt immune homeostasis, thereby increasing susceptibility to RA.

Secondly, the association between periodontitis and RA has garnered significant academic attention. Periodontitis is a common chronic inflammatory oral disease, with Porphyromonas gingivalis considered a key pathogenic bacterium. This microorganism secretes the citrullinase-related enzyme peptidyl arginine deiminase (PAD), which induces citrullination modifications in host proteins. This modification alters the structure of self-proteins, rendering them more readily recognised as 'non-self' by the immune system and thereby inducing the production of anti-citrullinated protein antibodies (ACPA). Extensive research indicates that ACPA are among the most RA-specific autoantibodies, closely associated with the early onset and severity of the disease [13]. Consequently, periodontitis may provide an 'inflammatory source' for RA development through the interaction between microorganisms and immune responses.

More significantly, obesity and periodontitis may exhibit synergistic effects in RA pathogenesis. Obese individuals are often more susceptible to periodontitis due to dietary and immunoregulatory abnormalities, while periodontitis further promotes RA development through systemic inflammation and autoimmune dysregulation. This interplay renders the body more prone to breach immune tolerance against the backdrop of chronic inflammation and immune disorder, leading to autoattack on joints. In summary, the aetiology of RA is not solely determined by genetic predisposition; factors such as obesity and periodontitis that alter inflammatory responses and immune homeostasis also play significant roles. Future research should focus more intently on the synergistic mechanisms linking metabolic health and oral health in the RA pathogenesis, with the aim of providing novel intervention strategies for early prevention and comprehensive management of the disease.

4. Summary

RA is a typical multifactor-driven disease, and the interaction between genetic and environmental factors should be considered. This article briefly introduces the clinical hazards and epidemiological characteristics of rheumatoid arthritis. Based on the research results, we can summarize that genetic factors, environmental triggers, hormones and gender differences, as well as health conditions are all causes of this disease. Secondly, it also sorts out the pathogenesis, aiming to provide a theoretical basis for non-early identification and prevention strategies. Future research should focus on strengthening the integration of mechanisms, developing early prediction models and individualized intervention strategies. Furthermore, from an epidemiological perspective, RA exhibits significant heterogeneity across gender and age strata: women generally face a higher risk than men, while increased incidence during perimenopause and later life suggests hormonal fluctuations and compromised immune tolerance may be pivotal links. Urban-rural disparities and latitudinal gradients across populations imply that lifestyle, occupational exposures, and climatic factors collectively shape disease distribution. At the aetiological level, a 'two-hit' model exists between genetic susceptibility and exogenous triggers: individuals carrying HLA-DRB1 shared epitopes are more prone to protein citrullination and immune epitope expansion when exposed to stimuli such as smoking, silica dust, or chronic oral infections, subsequently inducing a cascade of autoantibodies including ACPA/RF. Obesity-associated adipokines and cytokine network dysregulation further exacerbate inflammation and angiogenesis within the synovial microenvironment. Histologically, synovial fibroblast-like cells exhibit tumour-like proliferation and invasive phenotypes. In concert with macrophages, plasma cells, and the Th17 axis, they drive

the formation of erosive pannus and trabecular bone destruction. Imbalances in the osteoclast-osteoblast coupling mechanism explain the continuum from early bone demineralisation to subsequent deformity fixation. Regarding interventions, traditional csDMARDs and glucocorticoids remain cornerstone therapies. Molecularly targeted drugs against TNF, IL-6, and JAK significantly reduce disease activity and delay radiographic progression. However, therapeutic responses vary across different phenotypes (ACPA-positive/negative, early-onset/late-onset, coexisting metabolic syndrome or interstitial lung disease). Looking ahead, risk stratification integrating multi-omics and deep phenomics holds promise for pre-clinical identification of 'high conversion' populations. Traceable exposure studies and oral-pulmonary microbiome assessments may emerge as novel entry points for primary and secondary prevention. 'Cure-oriented' management targeting minimal residual inflammation will rely on reproducible composite biomarkersto guide dose reduction and personalised sequential strategies. Concurrently, enhanced lifestyle interventionsalongside vaccination and bone health maintenance can reduce the burden of complications and improve long-term functional outcomes at the population level. In summary, the multifactorial aetiology and phenotypic diversity of RA necessitate a precision-oriented, integrated evidence-based approach to its prevention and management.

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