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RHEUMATOID ARTHRITIS: INSIGHTS INTO INFLAMMATORY, MICROBIOTIC AND GENETIC CONTRIBUTIONS

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by polyarthritis, synovial tissue hypertrophy, infiltration of leukocytes, destruction of cartilage, formation of pannus, and tenosynovitis. It affects approximately 0.5% to 1.0% of the global population, leading to prolonged inflammation that impacts all body organs. This condition can lead to associated complications, including rheumatoid lung disease, carditis, vasculitis, cachexia, anemia, accelerated atherosclerosis, myocardial and cerebrovascular diseases, lymphoma, osteoporosis, depression, physical disabilities, and increased cardiovascular mortality linked to RA symptoms. Early diagnosis and symptom management are essential to prevent severe outcomes. Severity is evaluated using the DAS28 scale and ACR/EULAR classification, as this long-lasting inflammatory disorder is often instigated by a mix of genetic factors and environmental triggers. The presence of anti-citrullinated protein antibodies heightens the risk of recurrence from 13% to 32% within a year. The disease's pathogenesis involves autoreactive immune CD4+ T cells, B cells, macrophages, as well as inflammatory mediators, including cytokines, chemokines, and autoantibodies, with hormonal changes playing a role. Approximately 40% of severe RA patients are HLA-DR4 positive, commonly exhibiting complications like vasculitis, neuropathy (usually associated with vasculitis), serositis, interstitial lung disease, pulmonary nodules, scleritis, glomerulonephritis, and Felty syndrome. Treatment typically involves conventional DMARDs like methotrexate, hydroxychloroquine, and sulfasalazine, as well as synthetic disease-modifying antirheumatic drugs (sDMARDs), including pan-JAK and JAK1/2 inhibitors, along with biological DMARDs (bDMARDs). The microbiome plays a role in the local and systemic inflammatory immune responses, and adjuvant therapy with probiotic bacteria such as Lactobacillus casei or Lactobacillus acidophilus can alleviate symptoms and provide anti-inflammatory benefits. Genetic predispositions significantly influence RA, with heritable traits linked to specific genetic factors like HLA-DR and the "conserved shared epitope" (SE) in the third hypervariable region of the DRB1 chain being associated with a heightened risk of the disease. This review emphasizes interlink between RA, in-relation with inflammation, microbiota and the genetic factors/contributors associated, for in-depth understanding and management of RA.

KEYWORDS *Rheumatoid arthritis; Inflammation; Microbiota; Genetic predisposition; Cytokines; Autoimmunity; DMARDs*

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1. INTRODUCTION

Rheumatoid arthritis is a polyarticular, synovial hypertrophied, infiltration of leucocytes, cartilage destruction, pannus formation, and tenosynovitis chronic inflammatory autoimmune disease that affects bilaterally and symmetric joints. It harms the smaller joints of the hands and feet and larger joints of elbows, ankles, wrists, knees, and hips. In contrast to inflammatory polyarthropathy and inflammatory arthritis, RA is impacting 0.5% to 1.0% of the global population. The presence of autoantibodies, persistent pain, tenderness, and joint destruction damages bone, and assesses the disease as local or systemic autoimmunity by autoantibodies and elevated inflammatory cytokines and chemokines, leading to flares. It disturbs metabolism, causes extra-articular manifestations and articular involvement, and is closely linked to genetic, environmental, and hormonal factors. It disturbs immune tolerance, and altered innate and adaptive immunity encompasses autoimmune disorders leading to severe disability and premature mortality. Women are at higher risk than men, and the age group is between 30–60 years, increasing with age [1–3].

As current epidemiological studies vary, the range is from as low as 0.24% to as high as 2% [4]. It is mainly caused by triggers such as genetics, environmental toxins, high BMI, infections, hormonal changes, imbalanced gut microbiome, stress, diet, and vitamin deficiency. Patients with rheumatoid arthritis (RA) commonly suffer from morning stiffness. If this condition is not addressed, it may result in the development of small focal necrosis, adhesion of granulation tissue, and fibrous tissue on the joint surface, ultimately leading to progressive joint ankylosis, destruction, deformities, and disability [5,6].

Consistently elevated serum levels of inflammatory activity markers and diagnostic markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), along with the detection of autoantibodies including rheumatoid factor (RF) and anti-cyclic citrullinated-peptide antibodies (ACPA), are important indicators [7].

Prolonged inflammation impacts all organs of the body and leads to multiple comorbidities, including rheumatoid lung disease, carditis, vasculitis, cachexia, anemia, accelerated atherosclerosis, myocardial and cerebrovascular diseases, lymphoma, osteoporosis, depression, and physical disability. Rheumatoid arthritis (RA) is strongly associated with increased cardiovascular mortality; therefore, early diagnosis and timely management are essential to mitigate symptoms and prevent fatal outcomes [8,9].

In ACPA-seropositive RA, synovial fluid cells exhibit increased activity of the Bax and Bcl-2 families, promoting apoptosis more effectively than in other forms of arthritis [10]. The pathogenesis of RA involves a primary stage characterized by protein citrullination, antigen-presenting cell (APC) activation, and fibroblast-like synoviocyte (FLS) activation. This is followed by a secondary stage where APCs promote specific antibody production from B cells and autoreactive T cell responses [8].

Additionally, dysbiosis and inflammation in mucosal environments contribute to the autoactivation of T and B cells, leading to the recruitment of inflammatory mediators and progression of rheumatoid arthritis (RA) [11]. If treatment is neglected, damage reaches from peripheral joints to proximal joints. Inflammatory arthritis includes a group of arthritis accompanied by joint pain, swelling, warmth, tenderness, and morning stiffness that persists for an hour [12].

Tissue architecture at the physiological level is managed by tendons and ligaments, while at the cellular level it is contributed by tendon and ligament stromal cells. Protein arginine deiminases (PADs) contribute to higher pathogenesis of RA by protein modification of citrullination [13]. MHC class II molecule amino acids confer an increased risk of ACPA-positive disease [14]. In certain instances, autoimmunity may be triggered by cross-reactivity or mimicry to pathogen-specific antigens [15]. Synovial joints contain memory T cells that influence disease remission and severity [16]. Severity is assessed by DAS28 rheumatoid arthritis (RA), calculated using the number of swollen and tender joints and ESR (mm/hr), including DAS28-ESR and DAS28-CRP scores. Disease activity <2.6 is remission, ≥ 2.6 is low, ≥ 3.2–≤ 5.1 is moderate, and >5.1 is high [17]. It is also assessed using ACR/EULAR classification, including joints, disease duration, serology, and acute phase reactants [18].

A healthy diet rich in antioxidants and polyunsaturated fatty acids is beneficial for RA symptoms, whereas consumption of red meat and salt worsens the condition [19]. RA is associated with complications such as interstitial lung disease and metabolic dysregulation of several genes [20].

Extra-articular manifestations vary and include involvement of skin, lungs, eyes, heart, renal, and gastrointestinal systems. RF or HLA-DR4 positivity is commonly seen in severe cases (~40%), including vasculitis, neuropathy, serositis, interstitial lung disease, pulmonary nodules, scleritis, glomerulonephritis, and Felty syndrome [21,22]. Higher mortality is associated with cardiovascular disease mediated by oxidative stress, lipid peroxidation, endothelial dysfunction, and altered protein modification [23]. The main treatment agents, disease-modifying antirheumatic drugs (DMARDs), improve function by lowering systemic inflammation and synovitis [24]. The key pathological mechanisms involved in rheumatoid arthritis (RA) are summarized in Table 1, highlighting the major inflammatory mediators, genetic factors, microbiota interactions, autoantibodies, and immune cell contributions that collectively drive disease progression and joint damage. RA involves molecular insights affecting small and large joints bilaterally and symmetrically in the upper and lower extremities.

Table 1: Key Factors in RA Pathogenesis

Factor	Role in RA Pathogenesis
Cytokines (TNF-α, IL-6)	Promote and sustain chronic inflammation, joint destruction, and systemic immune activation
HLA-DRB1 genes	Major genetic susceptibility factors associated with increased risk of RA, especially ACPA-positive disease
Microbiota	Modulates immune responses, influences Th17/Treg balance, and contributes to disease initiation and progression
Autoantibodies (RF, ACPA)	Serve as diagnostic markers and contribute to immune complex formation and disease progression
Macrophages	Central mediators of synovial inflammation through production of pro-inflammatory cytokines and chemokines

2. PROBLEM STATEMENT

RA is a multifactorial disease influenced by immune dysregulation, genetic susceptibility, and environmental triggers such as infections, smoking, diet, and microbiome imbalance. The disease involves loss of immune tolerance, activation of autoreactive T and B cells, and production of inflammatory mediators. Protein citrullination and antigen presentation play a key role in initiating autoimmunity. Dysbiosis in mucosal environments further contributes to disease progression. Despite advances in treatment, challenges remain in early diagnosis, understanding disease mechanisms, and preventing progression and relapse.

3. RA RELATED AUTOIMMUNITY AND INFLAMMATORY INSIGHTS

RA condition is a long-lasting inflammatory disorder that is often triggered by the interplay of genetic predispositions and environmental influences and primarily affects the synovial joints. A consistently elevated serum biomarker indicating inflammation in patients who test negative for anti-citrullinated protein antibodies raised the recurrence risk from 13% to 32% within a year. Furthermore, the likelihood of relapse rose significantly to 76% among patients who had both anti-citrullinated protein antibodies and a persistent positive serum biomarker for inflammation [25].

The pathogenesis involves immune autoreactive CD4+ T cells, B cells, macrophages, inflammatory mediators like cytokines, chemokines, autoantibodies, and hormonal fluctuations. T helper 1 (Th1) cells promotes secretion of tumour necrosis factor-α (TNF-α), interleukin (IL)-2, interferon-γ (IFN-γ) function as proinflammatory to damage bone, while IL-4, IL-5, and IL-13 are implicated in anti-inflammatory responses. IL-22 works on synovial fibroblast cell proliferation via chemokine C-C ligand 2 (CCL2), and

T follicular helper (Tfh) cells release IL-21, inducing B cell activation via CXCR5. Participation of inflammatory cytokines and chemokines such as IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, G-CSF, TNF-α, CCL2, CCL3, and CXCL10 is well documented. Joint architecture including ligaments and tendons experiences mechanical force accompanied by chronic inflammation [26 -29].

Periodontitis is a persistent inflammatory condition that results in heightened bone resorption and systemic inflammation, contributing to anti-citrullinated peptide autoantibody formation. Osteoclast activity differs under inflammatory conditions [30]. Asymptomatic rheumatoid arthritis immune system remodelling culminates in tissue-invasive effector T cells and stromal cell activation leading to inflammation. Faulty DNA repair pathways may be associated with T cell tolerance decline including telomere fragility and mitochondrial DNA instability. Regulatory T cells inhibit effector T cell proliferation and protect against RA. RA is subdivided into ACPA-positive and ACPA-negative disease. The shared epitope alleles in MHC class II region predispose individuals mainly to ACPA-positive RA. Transport proteins OCTN1 and OCTN2 regulate metabolic and inflammatory responses [31].

Macrophages play a central role in synovial inflammation through cytokine and chemokine production. IL-18 promotes Th1 differentiation and is associated with IL-12, IL-15, TNF-α, and IFN-γ. IL-1β is highly expressed in RA synovium. CD14+ myelomonocytic cells differentiate rapidly into HLA-DR+ cells in RA patients [32, 33]. Macrophage imbalance between M1 and M2 phenotypes contributes to chronic inflammation through Notch, JAK/STAT, NF-κB, and MAPK signalling pathways. Synovial macrophages and fibroblasts undergo metabolic reprogramming sustaining chronic inflammation [34]. NF-κB activation promotes dendritic cell maturation and antigen presentation, triggering autoimmunity. NF-κB regulates cytokines such as IL-1β, TNF-α, IL-6, IL-8, ICAM-1, and VCAM-1 [35]. T cell activation involves NF-κB-dependent gene expression including IL-2 and IFN-γ. NF-κB and c-Myc interactions promote synovial hyperplasia and inhibit apoptosis, while PDGF and MMPs contribute to tissue destruction and angiogenesis [36].

HIF-1α mediates metabolic shift toward glycolysis and promotes angiogenesis and cartilage damage. PHD2 regulates HIF-1α degradation in synovial fibroblasts. TNF-α and PI3K/Akt pathways regulate HIF-1α expression, while IL-1β further enhances HIF-1α activity and VEGF production [37, 38]. HIF regulation involves PHD/VHL and NF-κB pathways influencing inflammatory cytokines. HMGB1 enhances VEGF production via HIF-1α signaling in endothelial cells [39]. The JAK-STAT pathway regulates inflammation, immunity, and autoimmunity gene expression. Circadian rhythm disruption increases inflammatory markers [40, 41]. RA is associated with systemic comorbidities including cardiovascular disease due to shared inflammatory pathways [42].

Early diagnosis and treatment within 3–6 months is critical to achieve remission. NSAIDs, glucocorticoids, and DMARDs including methotrexate, hydroxychloroquine, and biologics are standard therapies. Moxibustion and traditional therapies reduce HIF-1α and VEGF-mediated inflammation [43, 44]. Natural compounds such as aminoflavone, vorinostat, acriflavine, and herbal agents also show anti-inflammatory effects [45].

4. MICROBIOTA IMPACT ON RA

Microbiota resides in humans and plays a valuable role in maintaining homeostasis and health. It is implicated in gut, gingival, and respiratory mucosal sites, where microbiome alterations are associated with local and systemic inflammatory immune responses. Probiotic bacteria used as adjuvant therapy may relieve symptoms. Microbiome imbalance is an important environmental factor contributing to autoimmune disorders. The gut microbiota influences both the quantity and functionality of circulating Th17 and Treg cells, and imbalance between Th17 and Treg leads to surplus TNF-α and elevated pro-inflammatory cytokines along with the presence of ACPAs [46, 47].

RA is caused not only by immunological factors but also by microbiome and structural components. Periodontitis-associated dysbiosis promotes bone resorption in distant joints. Autoantigens in rheumatoid

arthritis undergo post-translational modifications during microbe–immune interactions, contributing to autoimmunity initiation. Dysbiosis is linked with autoimmune pathogenesis and is influenced by stress, smoking, and alcohol consumption [48-50].

Gut microbiota and serum CCP protein interactions remain under investigation. Gut epithelial damage allows pathogen entry, disrupting tight junctions and activating dendritic cells and macrophages. Microbial antigens at mucosal surfaces contribute to immune dysregulation in RA development [51, 52]. Oral microbiome studies show correlation between *Porphyromonas gingivalis* presence and RF/CCP levels. Citrullination-inducing bacteria such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* link periodontitis and RA. *Prevotella copri* is enriched in RA patients and promotes Th17/IL-17 mediated inflammation through molecular mimicry. *Fusobacterium nucleatum* contributes to synovial inflammation via macrophage activation and Rab5a signalling [53, 54].

Microbiota influences drug response and toxicity, affecting RA therapy outcomes. Probiotic strains such as *Lactobacillus casei* and *Lactobacillus acidophilus* reduce inflammation and improve symptoms. *Parabacteroides distasonis* metabolites regulate inflammatory rhythms via SIRT5–NF-κB axis. High-fiber diets alter microbiota and increase succinate production, contributing to inflammation [55-58]. Antibiotics, prebiotics, probiotics, and fecal microbiota transplantation may modify disease progression. Microbial imbalance disrupts Th1/Th2/Th17/Treg balance. Genetic contribution to RA is significant, with heritability estimated at ~60%. HLA-DRB1 and non-HLA genes contribute to susceptibility [59]. Twin studies show higher concordance in monozygotic twins compared to dizygotic twins. Shared epitope (SE) alleles in HLA-DRB1 are strongly associated with RA risk. Specific motifs such as QKRAA and DERAA determine susceptibility or protection [60, 61].

HLA-DRB1*04 and related alleles increase RA risk significantly. Smoking interacts with HLA-DR shared epitope to increase disease risk. HLA-DRB1 explains approximately 11% of genetic variance in RA [62]. Autoantibody-positive RA is strongly associated with HLA-DRB1 variants, especially valine at position 11, while HLA-DRB1*13 is protective [63]. GWAS studies identify additional susceptibility genes including PADI2, SPRED2, TRAF1, and others [64]. Regulatory T cells are considered therapeutic targets for autoimmune diseases using ex vivo gene therapy approaches [65].

5. CONCLUSION

RA is a multifactorial chronic autoimmune disorder characterized by persistent synovial inflammation, immune dysregulation, and progressive joint destruction. The disease arises from a complex interplay of inflammatory mediators, including cytokines, chemokines, and immune effector cells such as CD4+ T cells, B cells, macrophages, and synovial fibroblasts, which collectively drive tissue damage and systemic manifestations.

Genetic susceptibility plays a central role in RA pathogenesis, particularly involving HLA-DRB1 shared epitope alleles and other non-HLA genetic variants identified through genome-wide association studies. These genetic factors contribute significantly to disease risk, especially in autoantibody-positive RA, and interact with environmental triggers to initiate immune activation.

Emerging evidence highlights the critical contribution of microbiota dysbiosis in RA development and progression. Alterations in gut and oral microbial communities influence immune balance, particularly the Th17/Treg axis, promote citrullination, and enhance systemic inflammatory responses. Specific microbial species, such as *Porphyromonas gingivalis* and *Prevotella copri*, have been strongly associated with disease onset and severity.

Therapeutic advances, including conventional DMARDs, biologic agents, and JAK inhibitors, have significantly improved disease outcomes by targeting key inflammatory pathways. However, early diagnosis within the therapeutic window remains essential to prevent irreversible joint damage and long-term disability. Additionally, emerging approaches such as microbiome modulation and personalized medicine offer promising avenues for future RA management.

Overall, a comprehensive understanding of inflammatory mechanisms, microbial influences, and genetic predisposition is crucial for the development of more precise and effective therapeutic strategies, ultimately aiming to achieve sustained remission and improved quality of life in RA patients.

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