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RHEUMATOID ARTHRITIS - CURRENT PERSPECTIVES ON EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT

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ABSTRACT

Introduction and purpose: Rheumatoid arthritis (RA) is a complex immune-mediated inflammatory disease characterized by a loss of self-tolerance and chronic systemic involvement. Its pathogenesis is driven by a sophisticated interplay between genetic predispositions and environmental triggers including gut microbiota dysbiosis. Modern diagnostic frameworks have shifted toward precision medicine, utilizing advanced biomarkers. Beyond progressive joint destruction, the clinical burden of RA encompasses debilitating pain driven by neuroimmune sensitization and a high prevalence of systemic comorbidities. Effective management now relies on a holistic "treat-to-target" strategy that integrates targeted therapies, such as JAK inhibitors and biologics, with structured physical activity to restore functional independence and improve quality of life. This review summarizes the current knowledge, focusing on pathophysiology, epidemiology, diagnosis and treatment. By integrating current knowledge and new findings, it aims to enhance and optimize patient care.

Description of the State of Knowledge: Rheumatoid arthritis (RA) is currently understood as a complex immune-mediated inflammatory disease driven by a breakdown in self-tolerance, where genetic markers like HLA-DRB1 and FCRL3 interact with environmental triggers such as gut microbiota dysbiosis. Detection of classic autoantibodies - Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA) - remains a cornerstone of clinical evaluation. Modern diagnostics have shifted toward precision medicine, utilizing synovial pathotyping and novel biomarkers like 14-3-3η to identify specific inflammatory subtypes for targeted intervention. The clinical burden extends beyond joint destruction to include neuroimmune-driven pain and systemic comorbidities, necessitating a holistic "treat-to-target" approach. Therapeutic strategies now integrate advanced JAK inhibitors and biologics with non-pharmacological pillars like physical activity to achieve remission and restore functional independence.

Conclusions: Modern RA management defines the disease as a systemic autoimmune condition triggered by genetic factors and environmental stressors like smoking or gut dysbiosis. Diagnostics have shifted toward a "treat-to-target" approach using precise indices like DAS28. Treatment has been revolutionized by JAK inhibitors, yet effective care must remain holistic. Notably, CAR T-cell therapy is becoming increasingly promising in clinical research as a potential way to "reset" the immune system. Beyond suppressing inflammation, a modern strategy must address neuroimmune-driven pain and fatigue through structured physical activity to truly restore a patient's quality of life.

Materials and methods: A review of recent clinical studies and scientific articles was conducted, focusing primarily on pathophysiology, epidemiology, clinical presentation, diagnosis and treatment, supplemented with the latest findings.

KEYWORDS

Rheumatoid Arthritis, Rheumatoid Factor, Anti-Citrullinated Protein Antibodies, Synovitis

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic immune-mediated inflammatory disease (IMID) characterized primarily by persistent synovitis and progressive joint destruction [1,2,35]. The pathophysiology of RA involves a complex interplay between genetic predisposition, environmental triggers, and a profound loss of immunological self-tolerance. Central to the disease's progression is the dysregulation of the cytokine network, with interleukin-6 (IL-6) playing a pivotal role. High concentrations of IL-6 in both the serum and synovial fluid drive the inflammatory cascade, leading to the proliferation of synovial fibroblasts and the formation of a destructive "pannus" that invades cartilage and bone [31,35]. Beyond local joint damage, the pathogenesis of RA is inherently systemic. The inflammatory environment triggers neuroimmune interactions, where pro-inflammatory mediators sensitize both peripheral and central nervous systems. This process, known as sensitization, explains why pain in RA often persists even when clinical inflammation appears controlled [28]. Furthermore, the chronic elevation of systemic inflammatory markers contributes to a wide spectrum of comorbidities, including accelerated atherosclerosis (cardiovascular disease), metabolic syndrome, and interstitial lung disease [26,35]. Modern molecular insights, particularly from precision medicine studies, reveal that the pathomechanism varies between patients, distinguishing between early-stage RA and treatment-resistant forms [31]. This heterogeneity is reflected in the diverse clinical manifestations, ranging from hematological disturbances like anaemia (often driven by IL-6-induced hepcidin production) to neuropsychiatric symptoms such as fatigue and depression [23,35]. Ultimately, RA is no longer viewed merely as a disease of the joints, but as a complex, multi-organ inflammatory syndrome requiring a targeted, mechanistic approach to therapy.

Objective of the work

The aim of this study is to provide an overview of rheumatoid arthritis, focusing primarily on its pathophysiology, etiology, and clinical presentation, as well as on diagnosis and a critical analysis of the effectiveness of treatment and maintance of the remission.

Materials and Methods

A review of clinical studies and scientific articles published between 2024 and 2026 was conducted. The source of these materials was the PubMed database. The reports were compared, focusing primarily on pathophysiology, epidemiology, clinical presentation, diagnosis and treatment.

Pathophysiology

The pathophysiology of rheumatoid arthritis (RA) is a sophisticated, multi-stage process that originates from a profound dysregulation of the immune system, characterized by the early breakdown of self-tolerance and abnormal interactions between T-cells and B-cells [1,2]. This immunological failure is heavily influenced by specific genetic predispositions, most notably polymorphisms in the FCRL3 gene on chromosome 1q23, which lead to increased B-cell receptor signaling and a concurrent impairment of regulatory T-cell (Treg) suppressive functions, thereby creating a fertile ground for chronic autoaggression [3,31]. A crucial element in the disease’s initiation is the mucosal-origin hypothesis, specifically the gut-joint axis, where intestinal dysbiosis and increased epithelial permeability (often involving zonulin) trigger the activation of self-reactive lymphocytes that subsequently migrate to the synovial compartment [20,29]. Once established in the joints, the inflammatory environment is sustained by a potent cytokine cascade dominated by IL-6, which utilizes both "classic" and "trans-signaling" pathways to drive the proliferation of synovial fibroblasts. This results in the formation of an invasive, tumor-like pannus that secretes matrix metalloproteinases, leading to the irreversible degradation of articular cartilage and bone tissue [34,35]. Beyond localized damage, this chronic inflammation facilitates complex neuroimmune crosstalk, where pro-inflammatory mediators and autoantibodies directly sensitize the nervous system, explaining the persistence of pain even during clinical remission [5,28]. Ultimately, the systemic reach of these pathways, particularly IL-6-induced hepcidin production, results in widespread comorbidities, ranging from anaemia of chronic disease to accelerated cardiovascular and metabolic disturbances, underscoring RA as a holistic, multi-organ inflammatory syndrome [23,26,28].

Epidemiology and Clinical Presentation

Rheumatoid arthritis is a globally prevalent autoimmune condition affecting approximately 0.5% to 1% of the adult population [9,17]. The disease exhibits a significant gender disparity, being two to three times more common in women than in men, though this ratio can increase to as much as 4-5:1 in individuals diagnosed before the age of 40 [13,17]. While RA can manifest at any age, its peak incidence is typically observed in the sixth decade of life [17]. Geographically, prevalence rates are highest in Western populations, often exceeding 300 cases per 100,000 inhabitants, while in Northern Europe, the prevalence remains around 0.4% [13]. Interestingly, modern epidemiological trends show a relative rise in seronegative RA cases, which can account for up to 30% of all RA diagnoses, alongside a decline in seropositive forms-a shift potentially influenced by demographic aging and changing environmental exposures [9,13,19,25]. The disease's impact is also age-dependent: young-onset RA (YORA), occurring before age 60, often correlates with a higher frequency of the HLA-DRB1 shared epitope, whereas elderly-onset RA (EORA) is frequently associated with different genetic markers and a more acute clinical presentation [13,18]. Furthermore, RA is a major risk factor for systemic complications, such as a twofold increased risk of hip fractures and higher rates of cardiovascular and pulmonary comorbidities, which significantly contribute to its overall global burden [14,15,17].

The clinical spectrum of RA is defined by a debilitating combination of localized joint destruction, systemic complications, and a profound erosion of the patient's overall quality of life. At the forefront of the disease is chronic, multi-faceted pain, which arises not only from active synovial inflammation but also from complex neuroimmune crosstalk and central sensitization, leading to persistent discomfort even when clinical remission appears to be achieved [7, 28]. The clinical manifestation of RA is primarily characterized by symmetrical polyarthritis, predominantly affecting the small joints of the hands and feet [16]. The hallmark symptom is persistent joint pain accompanied by swelling and significant morning stiffness that typically lasts for more than 30 to 60 minutes, which is a key clinical indicator of inflammatory as opposed to degenerative joint disease [16]. As the disease progresses, patients often experience a reduced range of motion and functional impairment, leading to difficulties in performing daily activities. This inflammatory environment is a primary driver of systemic bone loss, which, when coupled with long-term corticosteroid use, results in a significantly increased risk of osteoporotic fractures, particularly of the hip and vertebrae [14,17]. Beyond the skeletal system, RA manifests through various extra-articular symptoms, including IL-6-induced anaemia of chronic disease, cardiovascular acceleration, and pulmonary involvement, all of which contribute to a heightened mortality risk [26,35]. These physical burdens are inextricably linked to neuropsychiatric symptoms, such as profound pathological fatigue, sleep disturbances, and depression, which are frequently cited as the most significant factors reducing Health-Related Quality of Life (HRQoL) [11,23,30]. To mitigate these effects, physical activity and structured exercise are highlighted as essential therapeutic components, as they help to suppress systemic inflammation, improve joint functionality, and counteract the sedentary lifestyle often adopted by patients due to fear of pain [8]. Ultimately, the management of RA requires a holistic approach that addresses both the measurable clinical markers and the subjective, patient-reported outcomes to restore functional independence [23,31].

Diagnosis

The diagnostic approach to RA has transitioned from traditional clinical assessments to a sophisticated, multi-dimensional strategy aimed at early detection and precision medicine. Central to the diagnostic process is the identification of systemic inflammatory markers, specifically IL-6, which acts as a key orchestrator of the acute-phase response; its levels correlate strongly with disease activity and the elevation of traditional reactants like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [24,35]. While the detection of classic autoantibodies - Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA) - remains a cornerstone of clinical evaluation, they are often absent in nearly 30% of patients [19]. It was observed that joint pain occurred more frequently in individuals who tested positive for both markers, compared to those with a single positive result for either of these markers [22]. To address this "seronegative" gap, modern diagnostics utilize supplemental markers such as 14-3-3η protein, a specialized chaperone protein that, when elevated, indicates active joint-tissue destruction and helps predict a more aggressive disease course [24,31,34].

Furthermore, the diagnostic field is expanding into neuroimmune monitoring, where the presence of specific autoantibodies is analyzed alongside the patient's pain profile to identify central sensitization status, ensuring that pain is not misattributed solely to active inflammation [7,28]. On a cellular level, advanced molecular profiling of synovial tissues-known as pathotyping—allows clinicians to categorize the disease into

distinct inflammatory subtypes, such as lympho-myeloid (high B-cell/T-cell infiltration) or pauci-immune (fibroblast-dominant), which is crucial for selecting the most effective targeted therapy from the outset [31].

Emerging research highlighted in the preclinical phase suggests that the "origin" of RA markers may be found in gut microbiota dysbiosis and increased mucosal barrier permeability (leaky gut); markers of intestinal inflammation and specific microbial signatures serve as early red flags of impending autoimmunity before irreversible joint erosion occurs [20,29]. Finally, the integration of Multi-Biomarker Disease Activity (MBDA) scores, which synthesize data from multiple serum proteins, alongside multi-omics (genomics and transcriptomics), provides a high-resolution map of tissue degradation and structural risk. This holistic data integration ensures that medical interventions are not only timely but precisely targeted to the individual's unique molecular signature [21,31,34].

Management

The modern management of RA follows a "treat-to-target" principle, aiming for clinical remission or low disease activity through an integrated approach of pharmacological and non-pharmacological interventions [31]. The pharmacological cornerstone remains Disease-Modifying Anti-Rheumatic Drugs (DMARDs), which have evolved from traditional agents like methotrexate to highly targeted therapies. This includes JAK inhibitors (targeted synthetic DMARDs), which effectively suppress multiple intracellular cytokine signaling pathways simultaneously [4], and biological DMARDs that neutralize extracellular mediators such as TNF and IL-6 to halt osteoclast activation and joint destruction [5,35]. Early aggressive intervention is critical, as the initial "window of opportunity" allows for the modulation of the immune system before irreversible structural damage occurs [6,21]. However, for patients experiencing persistent pain despite well-controlled inflammation, standard DMARD therapy often proves insufficient, necessitating specialized pain management strategies [33].

The treatment of RA has been significantly advanced by the introduction of targeted therapies, which offer high efficacy for patients who do not respond to conventional treatments. JAK inhibitors (such as upadacitinib) are highly effective targeted synthetic DMARDs that work by blocking intracellular signaling for multiple cytokines, leading to rapid clinical improvement and high rates of clinical remission [4,12]. On the other hand, biological DMARDs (bDMARDs), including TNF inhibitors and IL-6 receptor antagonists (like tocilizumab), neutralize specific extracellular inflammatory mediators to halt joint destruction and reduce systemic symptoms [5,35]. While both classes are potent, their safety profiles require careful monitoring. Common side effects of JAK inhibitors include an increased risk of herpes zoster (shingles), upper respiratory tract infections, and potential alterations in lipid profiles or blood counts [4,12]. Biological therapies are primarily associated with an increased risk of serious infections and injection-site or infusion reactions [5,35]. Furthermore, some biologics, especially those targeting IL-6, may require monitoring for gastrointestinal perforations or neutropenia, depending on their specific molecular target [35]. The choice between these therapies is increasingly guided by personalized medicine, taking into account the patient's specific inflammatory phenotype, comorbidities, and prior treatment responses [31].

Beyond medication, a holistic treatment plan must incorporate lifestyle and supportive interventions. Physical activity is a cornerstone of non-pharmacological therapy, as regular exercise helps to suppress systemic inflammation through the release of anti-inflammatory myokines, improves joint range of motion, and counteracts the muscle wasting (sarcopenia) often associated with chronic autoimmunity [8,10]. Moreover, structured exercise programs are vital for reducing the cardiovascular risks prevalent in RA patients and helping them overcome the "fear of movement" caused by joint pain [10]. Parallel to physical rehabilitation, addressing the psychological aspect is essential for long-term success, as RA is frequently linked to high levels of fatigue, sleep disturbances, and secondary depression [23]. These neuropsychiatric symptoms are major determinants of a patient's HRQoL and can exacerbate the perception of pain, making psychological support and stress management indispensable tools for improving overall functional independence and treatment adherence [23].

Furthermore, nutritional modulation, such as anti-inflammatory diets or plant-based interventions, plays a significant role in altering the gut microbiota, which can further suppress autoimmune triggers [32]. Effective long-term management also requires continuous monitoring of disease activity using standardized scores and imaging, ensuring that therapy is personalized to the patient's specific molecular and clinical profile [12,31].

Monitoring disease activity is the cornerstone of the "treat-to-target" strategy, which aims to achieve clinical remission through a standardized, multimodal assessment [31]. Clinical status is primarily evaluated using composite indices such as the DAS28 (Disease Activity Score 28), which integrates the count of tender

and swollen joints with patient-reported health assessments and inflammatory markers like CRP or ESR [24]. For more immediate, point-of-care decisions, clinicians frequently employ the SDAI (Simplified Disease Activity Index) and CDAI (Clinical Disease Activity Index), the latter of which provides a purely clinical score without the need for immediate laboratory results [24]. Furthermore, cutting-edge diagnostic tools like the Multi-Biomarker Disease Activity (MBDA) score - which analyzes 12 distinct serum proteins - and the measurement of serum calprotectin offer a more objective, molecular-level view of subclinical inflammation that traditional physical exams might overlook [12,24].

A revolutionary frontier in the treatment of RA involves the adaptation of Chimeric Antigen Receptor (CAR) T-cell therapy, a technology originally perfected in oncology, to reset the dysfunctional immune system [27]. According to recent research, the efficacy of this approach lies in the engineering of specialized T-cells-specifically CAR-Tregs (Regulatory T-cells - designed to recognize specific joint-related antigens and suppress localized inflammation without compromising systemic immunity [27]. Preliminary studies have demonstrated significant potential in achieving long-term drug-free remission by selectively depleting pathogenic B-cells or neutralizing the auto-reactive T-cell clones that drive chronic synovitis [27]. While still in the experimental stages, the clinical effectiveness observed in early models suggests that CAR T-cell therapy could overcome the limitations of traditional DMARDs, offering a "one-time" precision intervention that targets the root cause of the immune breakdown rather than merely managing its downstream symptoms [27,31].

Conclusions

Based on the comprehensive data, the modern understanding of RA defines it as a complex, systemic autoimmune disease where genetic predispositions, such as HLA-DRB1 and FCRL3 polymorphisms, interact with environmental triggers like gut microbiota dysbiosis and smoking to drive a profound breakdown in self-tolerance. Current epidemiological shifts reveal that the seronegative form of the disease now accounts for up to 30% of cases, a trend potentially influenced by demographic aging and necessitating more precise diagnostic tools. Management has transitioned to a rigorous "treat-to-target" strategy, utilizing composite indices such as DAS28, SDAI, and CDAI to achieve clinical remission, often through the rapid action of JAK inhibitors or the revolutionary potential of CAR T-cell technology. Ultimately, effective care must be holistic, moving beyond the suppression of inflammatory markers to address persistent neuroimmune-driven pain and systemic fatigue through structured physical activity, which serves as a critical non-pharmacological pillar for improving overall Health-Related Quality of Life.

Disclosure

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