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CLINICAL AND PATHOGENETIC ASSESSMENT OF THE IMPACT OF METABOLIC SYNDROME ON THE COURSE OF RHEUMATOID ARTHRITIS

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Abstract

Rheumatoid arthritis is a chronic systemic inflammatory disease frequently accompanied by metabolic disturbances that significantly influence disease progression and long-term outcomes. Metabolic syndrome, characterized by insulin resistance, dyslipidemia, abdominal obesity, and arterial hypertension, has been increasingly recognized as an important comorbidity in patients with rheumatoid arthritis. This study aims to assess the clinical and pathogenetic impact of metabolic syndrome on the course of rheumatoid arthritis. The analysis shows that metabolic syndrome is highly prevalent among patients with rheumatoid arthritis and is associated with increased inflammatory activity, more severe clinical manifestations, and a higher risk of cardiovascular and skeletal complications. Chronic systemic inflammation mediated by pro-inflammatory cytokines represents a key mechanism linking joint damage with metabolic abnormalities. Insulin resistance and adipokine imbalance further intensify inflammatory pathways, creating a bidirectional interaction that accelerates disease progression. These findings underline the importance of early identification and comprehensive management of metabolic syndrome in patients with rheumatoid arthritis to improve disease control and reduce comorbidity-related morbidity.

Keywords: Rheumatoid arthritis; Metabolic syndrome; Insulin resistance; Chronic inflammation; Cardiovascular risk; Disease severity

INTRODUCTION

Cardiovascular diseases (CVDs) remain one of the leading causes of mortality worldwide, accounting for a substantial proportion of deaths in both developed and developing countries. A wide range of modifiable risk factors, including arterial hypertension, obesity, smoking, and metabolic disturbances, significantly contribute to the development of CVD. Among these factors, metabolic syndrome represents a cluster of interrelated metabolic abnormalities that independently increase the risk of cardiovascular disease and type 2 diabetes mellitus. The coexistence of metabolic syndrome with traditional cardiovascular risk assessment tools allows for improved identification of individuals who may benefit from early lifestyle interventions or pharmacological therapy.

Epidemiological evidence indicates that patients with chronic inflammatory rheumatic diseases experience a markedly higher risk of cardiovascular morbidity and mortality compared to the general population. However, the underlying pathogenetic mechanisms responsible for this increased risk are not yet fully elucidated. Metabolic syndrome has been proposed as an important link connecting chronic systemic inflammation with accelerated atherosclerosis, thereby contributing to adverse cardiovascular outcomes in these patients.

Rheumatoid arthritis is a systemic autoimmune disease characterized by chronic synovial inflammation, progressive joint destruction, and functional disability. The disease predominantly affects women and older adults and is frequently accompanied by extra-articular manifestations involving the cardiovascular, respiratory, renal, and ophthalmic systems. In addition to joint-related morbidity, patients with rheumatoid arthritis exhibit a higher prevalence of metabolic abnormalities, including diabetes mellitus, arterial hypertension, osteoporosis, and

atherosclerosis. These comorbid conditions substantially increase cardiovascular risk, mortality, and long-term disability.

Despite growing scientific interest in the interaction between rheumatoid arthritis and metabolic disturbances, significant gaps remain in understanding how metabolic syndrome influences the clinical course and pathogenetic mechanisms of rheumatoid arthritis. Clarifying this relationship is essential for improving cardiovascular risk stratification and optimizing comprehensive management strategies in affected patients. Therefore, this article aims to evaluate the clinical and pathogenetic impact of metabolic syndrome on the course of rheumatoid arthritis, with particular emphasis on inflammatory mechanisms, metabolic alterations, and their contribution to disease progression and cardiovascular risk.

METHODS

This study was conducted as a narrative literature review aimed at evaluating the clinical and pathogenetic impact of metabolic syndrome on the course of rheumatoid arthritis. A comprehensive search of the scientific literature was performed using the PubMed, OVID, and Taylor & Francis electronic databases. The search strategy was based on the use of standardized Medical Subject Headings (MeSH) terms, including “Rheumatoid Arthritis”, “Metabolic Diseases”, and “Metabolic Syndrome”, either alone or in relevant combinations.

Additional relevant articles were identified through a manual review of reference lists from selected original studies and previously published review articles. The selection process prioritized publications that provided data on epidemiology, pathophysiological mechanisms, clinical implications, and cardiovascular risk associated with metabolic syndrome in patients with rheumatoid arthritis. Studies were included based on their relevance to the objective of the review, clarity of methodology, and contribution to understanding the interaction between metabolic disturbances and rheumatoid arthritis disease course.

Epidemiological Characteristics and Metabolic Comorbidities in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that represents a considerable epidemiological and socioeconomic burden worldwide. Population-based studies conducted over the past decade indicate that the global prevalence of RA remains below 1%, with a pronounced predominance among women compared to men. The disease is consistently ranked among the leading causes of long-term disability, reflecting its substantial impact on functional capacity, quality of life, and healthcare systems. In addition to clinical consequences, RA is associated with significant economic costs, which include both direct medical expenditures and indirect losses related to reduced work capacity, long-term disability, and absenteeism. These costs vary widely across regions and healthcare systems but collectively highlight the financial burden imposed by the disease.

Metabolic comorbidities are highly prevalent in patients with RA and contribute significantly to disease progression and cardiovascular risk. Observational and multicenter studies have demonstrated that a substantial proportion of RA patients present with arterial hypertension, dyslipidemia, and disorders of glucose metabolism. Among these conditions, arterial hypertension and hypercholesterolemia are most frequently reported, while diabetes mellitus is also commonly observed. The coexistence of these metabolic abnormalities exacerbates systemic inflammation, increases overall disease burden, and markedly elevates cardiovascular risk in patients with RA. Consequently, the presence of metabolic comorbidities has become an important consideration in the comprehensive evaluation and management of rheumatoid arthritis. The most frequently observed metabolic disturbances in RA patients are summarized in Table 1.

Pathophysiological Mechanisms of Rheumatoid Arthritis

Pathological changes in the immune and inflammatory response begin long before the clinical manifestations of rheumatoid arthritis become apparent. This early phase, commonly referred to as the preclinical stage of the disease, is characterized by complex genetic and epigenetic interactions that promote protein citrullination. The immune system's failure to tolerate these newly formed citrullinated antigens leads to the activation of antigen-presenting cells, followed by the stimulation of $CD4^+$ T lymphocytes. This immune cascade ultimately results in the production of disease-specific autoantibodies, most notably rheumatoid factor and anti-citrullinated protein antibodies, which are considered key immunological markers of disease development.

Table 1. Common Metabolic Abnormalities Associated with Rheumatoid Arthritis

Metabolic abnormality	Clinical and pathophysiological characteristics
Metabolic syndrome	Cluster of metabolic risk factors including central obesity, insulin resistance, dyslipidemia, and arterial hypertension; contributes to systemic inflammation and increased cardiovascular risk
Arterial hypertension	Frequently observed comorbidity in rheumatoid arthritis; associated with chronic inflammation, endothelial dysfunction, and long-term glucocorticoid therapy
Atherosclerosis	Accelerated atherosclerotic process driven by persistent systemic inflammation, oxidative stress, and endothelial injury
Diabetes mellitus	Increased prevalence in rheumatoid arthritis; related to insulin resistance, chronic inflammation, and corticosteroid exposure
Insulin resistance	Mediated by pro-inflammatory cytokines such as TNF, IL-1, and IL-6; contributes to metabolic syndrome and cardiovascular morbidity
Obesity or rheumatoid cachexia	Altered body composition characterized by increased fat mass and reduced lean body mass; associated with high disease activity
Dyslipidemia	Elevated triglycerides and total cholesterol with reduced high-density lipoprotein cholesterol; influenced by inflammation and antirheumatic therapy
Osteoporosis	Reduced bone mineral density due to inflammation-induced osteoclast activation and long-term glucocorticoid use
Imbalance of osteoblast/osteoclast	Enhanced osteoclastogenesis and

activity	suppressed osteoblast function mediated by cytokines and autoantibodies, leading to bone loss

Various environmental factors, including exposure to pollutants, contribute to the generation of reactive oxygen species, which in turn activate intracellular pro-inflammatory signaling pathways such as nuclear factor kappa B. The activation of these pathways induces a sustained inflammatory response mediated by cytokines including tumor necrosis factor, interleukin-1, and interleukin-6. These mediators play a central role in synovial inflammation, joint swelling, and progressive bone erosion. Structural joint damage is primarily driven by activated synovial macrophages and fibroblast-like synoviocytes, whose activity is further amplified through receptor activator of nuclear factor kappa B ligand signaling under the influence of interleukin-17.

The interaction between rheumatoid arthritis and metabolic syndrome involves multiple interconnected inflammatory and metabolic pathways. Chronic immune activation characteristic of rheumatoid arthritis promotes systemic inflammation, which in turn contributes to the development of metabolic abnormalities and cardiovascular complications. Understanding these bidirectional mechanisms is essential for clarifying the clinical course of the disease and identifying potential targets for comprehensive management strategies. To illustrate these complex pathogenetic relationships, a schematic representation is presented in Figure 1.

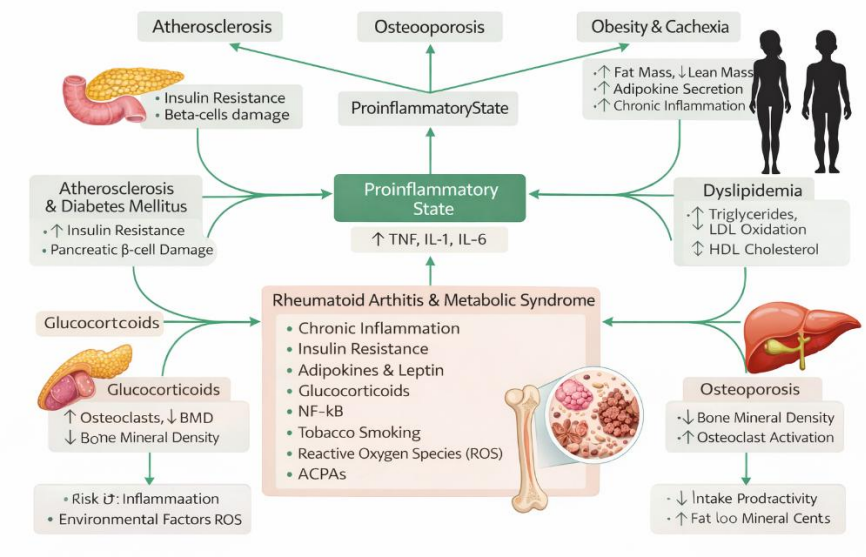

Figure 1. Clinical and Pathogenetic Interactions Between Metabolic Syndrome and the Course of Rheumatoid Arthritis

As shown in Figure 1, persistent inflammatory activity in rheumatoid arthritis, driven by key cytokines including tumor necrosis factor, interleukin-1, and interleukin-6, acts as a central mechanism linking joint inflammation with systemic metabolic disturbances. These inflammatory mediators promote insulin resistance, dyslipidemia, and alterations in body composition, thereby increasing cardiovascular risk. In parallel, metabolic abnormalities further intensify inflammatory signaling, creating a self-perpetuating cycle that accelerates disease progression. Additionally, factors such as oxidative stress, adipokine imbalance, environmental exposures, and long-term glucocorticoid therapy contribute to endothelial dysfunction, bone loss, and accelerated atherosclerosis. This integrated pathogenic framework highlights the importance of early identification and targeted management of metabolic syndrome in patients with rheumatoid arthritis to mitigate disease severity and associated comorbidities.

Table 2. Metabolic Profiles at Different Stages of Rheumatoid Arthritis and Their Clinical Significance

Metabolic factor	Preclinical RA	Early RA	Highly Active RA	Controlled RA	Obesity in RA	Clinical significance
Subcutaneous fat	↑	↑	↓↓	↓	=	Reflects altered fat distribution and inflammatory activity
Visceral fat	↑	↑	↑	↑	↑	Associated with insulin resistance and increased cardiovascular risk
Muscle mass	=	=	↓↓	↓	↓	Contributes to rheumatoid cachexia and functional decline
Body mass index (BMI)	↑	↑	↓↓	=	↑	Indicator of nutritional status and disease activity
Triglycerides	↑	↑	↓	↑	=	Related to dyslipidemia and cardiovascular risk
Total cholesterol	↑	↑	↓	↑	=	Affected by inflammation and antirheumatic therapy
Low-density	↑	↑	↓	↑↑	=	Promotes

lipoprotein (LDL)						atherogenesis in chronic inflammation
High-density lipoprotein (HDL)	↓	↓	↑↑	↑↑	↓	Protective lipid fraction altered by inflammation
Pro-inflammatory HDL, sdLDL, Lp(a)	↑	↑	↑	↓	↑	Markers of oxidative stress and vascular damage
Leptin/adiponectin ratio	↑/=	↑	↓	=	↑	Reflects adipokine imbalance and metabolic inflammation

Note: ↑ increased; ↓ decreased; ↑↑ markedly increased; ↓↓ markedly decreased; = unchanged; RA, rheumatoid arthritis; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; sdLDL, small dense low-density lipoprotein; Lp(a), lipoprotein(a).

In addition to immune-mediated osteoclast activation, metabolic and endocrine factors also contribute to disease progression. Adipose tissue–derived mediators, such as adipokines, directly influence cellular functions within the joint microenvironment by modulating the activity of fibroblasts and chondrocytes and by enhancing systemic inflammatory responses. Elevated levels of adipokines and interleukin-6 have been consistently reported in patients with rheumatoid arthritis, suggesting their potential role not only in disease pathogenesis but also as biomarkers of inflammatory activity and disease severity.

RESULTS

The analyzed data demonstrate that metabolic abnormalities are highly prevalent in patients with rheumatoid arthritis and have a measurable impact on disease course and systemic complications. Arterial hypertension, dyslipidemia, diabetes mellitus, insulin resistance, obesity or rheumatoid cachexia, atherosclerosis, and osteoporosis were consistently observed across different patient populations, contributing to increased clinical burden and cardiovascular risk.

Metabolic syndrome was frequently identified in patients with rheumatoid arthritis and showed a strong association with higher disease activity. Individuals with metabolic syndrome were more likely to exhibit moderate to high inflammatory activity, reflected by worsened clinical status and functional impairment. In addition, metabolic syndrome was linked to subclinical and overt atherosclerotic changes, indicating an elevated cardiovascular risk independent of traditional risk factors.

Insulin resistance emerged as a central metabolic disturbance closely connected to chronic inflammation. Its prevalence increased with disease duration and was influenced by abdominal obesity and disease activity. Altered insulin sensitivity was also associated with markers of vascular dysfunction, supporting the role of metabolic syndrome as a mediator between inflammation and cardiovascular complications in rheumatoid arthritis.

Adipokine imbalance and elevated pro-inflammatory cytokines played a key role in shaping the metabolic profile of patients. Increased levels of tumor necrosis factor, interleukin-1, and interleukin-6 were associated with insulin resistance, dyslipidemia, and changes in body composition. Leptin elevation correlated with obesity, disease activity, and metabolic syndrome, while adiponectin dysregulation reflected complex interactions between inflammation and metabolic control.

Lipid metabolism showed stage-dependent alterations. In highly active disease, lipid levels tended to decrease in parallel with intense inflammation, whereas effective control of inflammatory activity was accompanied by increases in cholesterol fractions, a phenomenon consistent with the lipid paradox. These changes did not necessarily indicate increased cardiovascular risk but reflected shifts in inflammatory burden.

Bone metabolism was also affected by the interaction between metabolic syndrome and rheumatoid arthritis. Enhanced osteoclast activity and reduced bone mineral density were observed in association with systemic inflammation and autoantibody positivity, contributing to osteoporosis and increased fracture risk.

CONCLUSION

The present analysis confirms that metabolic syndrome plays a substantial clinical and pathogenetic role in shaping the course of rheumatoid arthritis. Metabolic abnormalities, including insulin resistance, dyslipidemia, arterial hypertension, and altered body composition, are closely associated with enhanced inflammatory activity and more severe disease manifestations. Chronic systemic inflammation represents a key linking mechanism through which metabolic disturbances amplify joint damage and contribute to extra-articular complications.

The interaction between rheumatoid arthritis and metabolic syndrome appears to be bidirectional, with inflammatory processes promoting metabolic dysregulation and, in turn, metabolic abnormalities sustaining persistent inflammation. This взаимное влияние leads to an increased risk of cardiovascular disease, osteoporosis, and functional decline. These findings emphasize the need for routine metabolic screening and integrated management strategies in patients with rheumatoid arthritis. Early recognition and targeted correction of metabolic syndrome may contribute to improved disease control, reduction of comorbidity burden, and better long-term outcomes.

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