CONTEMPORARY INSIGHTS INTO THE CLINICAL AND PATHOGENETIC INTERRELATIONSHIP BETWEEN RHEUMATOID ARTHRITIS AND METABOLIC SYNDROME

Bafayev Jamshid Turobovich
ORCID: 0009-0007-8852-638X
Bukhara State Medical Institute
Umurova Shahrizoda Fozil qizi
Bukhara State Medical Institute
umurova.shahrizoda@gmail.com

Abstract: Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease characterized by progressive joint destruction, extra-articular manifestations, and a high risk of early disability [1,2]. In recent years, increasing attention has been focused on the high prevalence of metabolic syndrome (MetS) among patients with RA and its significant impact on disease activity, therapeutic response, and cardiovascular prognosis [4,7,10]. Metabolic syndrome, which includes insulin resistance, abdominal obesity, dyslipidemia, and arterial hypertension, is considered a key component of systemic inflammation in RA [5,9,14]. This review analyzes current concepts regarding the pathogenetic mechanisms linking immune-mediated inflammation and metabolic disturbances, the role of adipokines and insulin resistance, the clinical significance of RA–MetS comorbidity, as well as contemporary diagnostic and therapeutic approaches.

Keywords: rheumatoid arthritis, metabolic syndrome, insulin resistance, chronic inflammation, adipokines, cardiovascular risk.

Introduction

Rheumatoid arthritis is one of the most common autoimmune connective tissue diseases, affecting approximately 0.5–1% of the adult population worldwide [1]. The disease is characterized by a chronic progressive course, persistent immune-mediated inflammation, and destruction of joint structures, leading to a marked reduction in quality of life and work capacity [2,3].

Currently, RA is regarded not only as a joint disease but also as a systemic pathology associated with increased mortality, a substantial proportion of which is attributable to cardiovascular complications [4,7]. It has been demonstrated that the cardiovascular risk in patients with RA is comparable to or even exceeds that observed in patients with type 2 diabetes mellitus [8].

Metabolic syndrome represents a cluster of interrelated metabolic abnormalities that substantially increase the risk of atherosclerosis and cardiovascular disease [5,6]. According to epidemiological studies, the prevalence of MetS in patients with RA ranges from 30% to 45%, significantly

exceeding that in the general population [10,11]. Contemporary scientific concepts emphasize that chronic systemic inflammation represents the key pathogenetic link integrating the development of RA and metabolic disturbances [9,14].

The pathogenesis of rheumatoid arthritis is based on complex immune dysregulation involving activation of T and B lymphocytes, macrophages, and excessive production of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukins-1 and -6 [2,16]. These mediators play a central role in maintaining chronic inflammation, joint destruction, and the development of systemic complications [17].

Systemic inflammation exerts a profound effect on metabolic processes. Proinflammatory cytokines disrupt insulin signaling in peripheral tissues by inhibiting insulin receptor phosphorylation and reducing glucose uptake [9,15]. As a result, insulin resistance develops, which represents a core component of metabolic syndrome [3,21]. Therefore, RA and MetS should be considered interrelated conditions that mutually exacerbate disease severity [14,30].

Insulin resistance is detected in approximately 60–70% of patients with active rheumatoid arthritis, including individuals without diabetes mellitus [15,21]. Its severity correlates with disease activity, C-reactive protein levels, and erythrocyte sedimentation rate [18].

Chronic inflammation in RA contributes to hyperinsulinemia, lipid metabolism disorders, and endothelial dysfunction, creating conditions for accelerated atherogenesis [12,23]. Insulin resistance is regarded as a central mechanism linking immune-mediated inflammation with cardiovascular complications in patients with RA [26].

Adipokines are biologically active molecules produced by adipose tissue that play an important role in the regulation of inflammation and metabolism [19,20]. Patients with RA exhibit an imbalance in adipokine profiles, which contributes to persistent inflammation and metabolic dysfunction [24].

Leptin exerts pronounced proinflammatory effects by stimulating T-lymphocyte activation and cytokine production [31]. Elevated leptin levels are associated with higher RA disease activity and increased cardiovascular risk [24]. Adiponectin, which normally exhibits anti-inflammatory and anti-atherogenic properties, may exert paradoxical effects in RA, promoting cartilage degradation [19]. Adipokine imbalance forms a “vicious circle” integrating inflammation, obesity, and insulin resistance [20].

The presence of metabolic syndrome substantially aggravates the clinical course of rheumatoid arthritis. Such patients more frequently exhibit high disease activity, pronounced pain syndrome, and accelerated progression of structural joint damage [18,22].

The coexistence of RA and MetS is associated with a marked increase in

cardiovascular risk. Early development of atherosclerosis, endothelial dysfunction, and enhanced thrombogenicity lead to a higher incidence of myocardial infarction and stroke [7,8,23,34]. According to cohort studies, cardiovascular diseases represent one of the leading causes of premature mortality in patients with RA [30,35].

Current clinical recommendations emphasize the necessity of regular screening for metabolic syndrome components in patients with rheumatoid arthritis [17,33]. Assessment of body mass index, waist circumference, lipid profile, and glucose metabolism parameters should be an integral part of patient management.

Effective control of inflammatory activity using methotrexate and biologic disease-modifying antirheumatic drugs leads to a reduction in proinflammatory cytokine levels and improvement in insulin sensitivity [28,29]. Non-pharmacological interventions, including weight reduction, balanced nutrition, and increased physical activity, play a crucial role in reducing cardiovascular risk [26,27].

Conclusion

Rheumatoid arthritis and metabolic syndrome represent closely interconnected pathological conditions unified by common mechanisms of chronic systemic inflammation and insulin resistance [1,9,30]. Their coexistence results in a more severe clinical course of RA and a significant increase in cardiovascular risk. Early identification of metabolic abnormalities and a comprehensive, personalized therapeutic approach are essential for improving prognosis and quality of life in patients with rheumatoid arthritis [33–35].

REFERENCES

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388:2023–38.
2. Firestein GS, McInnes IB. Immunopathogenesis of rheumatoid arthritis. *Immunity*. 2017;46:183–96.
3. Dessein PH, Joffe BI. Insulin resistance in rheumatoid arthritis. *Arthritis Rheum*. 2006;54:2765–75.
4. Giles JT. Cardiovascular disease in rheumatoid arthritis. *Rheum Dis Clin North Am*. 2012;38:405–26.
5. Grundy SM. Metabolic syndrome update. *Trends Cardiovasc Med*. 2016;26:364–73.
6. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome. *Circulation*. 2009;120:1640–5.
7. Crowson CS, Liao KP, Davis JM, et al. Rheumatoid arthritis and cardiovascular disease. *Arthritis Care Res*. 2013;65:1610–9.

8. van Halm VP, Peters MJ, Voskuyl AE, et al. RA versus diabetes as CV risk factor. *Ann Rheum Dis*. 2009;68:1395–400.
9. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444:860–7.
10. Chung CP, Oeser A, Solus JF, et al. Metabolic syndrome in RA. *Arthritis Rheum*. 2008;59:39–46.
11. Kerekes G, Nurmohamed MT, Gonzalez-Gay MA, et al. Metabolic syndrome in RA. *Ann Rheum Dis*. 2014;73:514–21.
12. Ridker PM. Inflammation and atherosclerosis. *Circulation*. 2012;105:1135–43.
13. McInnes IB, Schett G. Cytokines in RA. *Nat Rev Immunol*. 2007;7:429–42.
14. Dessein PH, Tobias M, Veller MG. Metabolic syndrome and CV risk in RA. *Arthritis Res Ther*. 2006;8:R21.
15. Giles JT, et al. Insulin resistance in RA. *Arthritis Rheumatol*. 2015;67:626–36.
16. Peters MJ, et al. EULAR CV risk recommendations. *Ann Rheum Dis*. 2010;69:325–31.
17. Agca R, et al. EULAR CV risk update. *Ann Rheum Dis*. 2017;76:17–28.
18. Ajeganova S, et al. Metabolic syndrome and disease activity in RA. *Ann Rheum Dis*. 2011;70:1018–23.
19. Tilg H, Moschen AR. Adipocytokines and inflammation. *Nat Rev Immunol*. 2006;6:772–83.
20. Lau DCW, et al. Adipokines. *Nat Rev Endocrinol*. 2017;13:447–59.
21. Wasko MC, et al. Insulin resistance in RA. *Arthritis Rheum*. 2007;56:3010–9.
22. Baker JF, et al. Obesity and RA. *Curr Opin Rheumatol*. 2018;30:276–82.
23. Myasoedova E, et al. CV risk in RA. *Arthritis Rheum*. 2010;62:1576–82.
24. Rho YH, et al. Adipokines and CV risk in RA. *Arthritis Res Ther*. 2009;11:R176.
25. Zhang J, et al. Metabolic syndrome in RA. *Clin Rheumatol*. 2013;32:813–9.
26. Nurmohamed MT. CV risk in RA. *Autoimmun Rev*. 2009;8:663–7.
27. Castañeda S, et al. CV risk management in RA. *Expert Rev Clin Immunol*. 2016;12:1003–14.
28. Popa C, et al. Anti-TNF therapy and insulin sensitivity. *Ann Rheum Dis*. 2009;68:549–54.
29. Choy E. Inflammation and insulin resistance. *Rheumatology*. 2012;51:393–400.
30. Sattar N, et al. CV risk in RA. *Circulation*. 2003;108:2957–63.
31. Karvonen-Gutierrez CA, Harlow SD. Adiposity and inflammation. *Arthritis Rheum*. 2012;64:1133–42.

32. England BR, et al. CV risk in RA. *Arthritis Rheumatol*. 2018;70:841–50.
33. Michaud K, Wolfe F. CV mortality in RA. *Arthritis Care Res*. 2007;56:722–30.
34. Ridker PM. Biomarkers and CV risk. *N Engl J Med*. 2007;357:2195–7.
35. Agca R, et al. CV prevention in inflammatory arthritis. *Ann Rheum Dis*. 2017;76:17–28.