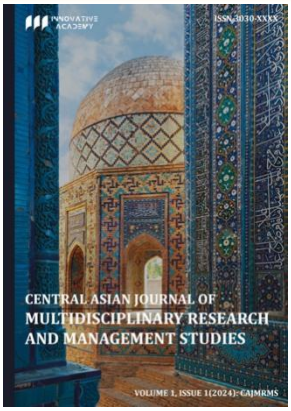

CHARACTERISTICS OF THE CLINICAL COURSE OF RHEUMATOID ARTHRITIS IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Rheumatoid arthritis (RA) and diabetes mellitus (DM), particularly type 2 DM, are chronic inflammatory diseases whose co-occurrence presents a significant clinical challenge. This article reviews the specific characteristics of RA in patients with DM. The comorbidity is relatively common and driven by shared pathophysiological mechanisms, primarily chronic inflammation mediated by pro-inflammatory cytokines such as TNF-α and IL-6, which contribute to both insulin resistance and joint destruction. The clinical course of RA in diabetic patients is characterized by atypical symptom presentation (masked pain due to neuropathy), a complex overlap of arthropathies, and a markedly increased risk for severe complications, including accelerated cardiovascular disease, osteoporosis, infections, renal impairment, and ocular damage. Diagnosis is complicated by the confounding effects of hyperglycemia on inflammatory markers and imaging findings. Effective management requires a multidisciplinary approach prioritizing strict glycemic control, careful selection of antirheumatic drugs with consideration of their metabolic effects, and aggressive prophylaxis against cardiovascular and skeletal complications. Early detection, individualized treatment, and coordinated care among specialists are crucial for improving outcomes and quality of life in this high-risk patient population.

Introduction

Rheumatoid arthritis (RA) and diabetes mellitus (DM), particularly type 2 DM, are chronic diseases that pose a serious threat to public health in both developed and developing countries. When these two diseases occur simultaneously in a single patient, significant changes occur in their clinical course, diagnosis, treatment methods, and prognosis. Today, the pathophysiological mechanisms and clinical significance of this comorbid condition are being widely studied. This article aims to summarize and analyze literature data on the specific characteristics of the clinical course, diagnostic difficulties, treatment strategies, and outcomes of RA in patients with DM.

Main Body

Epidemiological Indicators and Risk Factors. The co-occurrence of diabetes mellitus and rheumatoid arthritis is relatively common. Epidemiological studies indicate that the risk of developing DM in RA patients is 1.5 to 2 times higher. Conversely, the likelihood of developing

RA also increases in individuals with DM. This mutual correlation is explained by inflammation, insulin resistance, genetic predisposition, and lifestyle factors. The comorbidity of type 2 DM and RA is more frequently observed in women, elderly patients, and overweight individuals.

Similarity of Pathogenetic Mechanisms and Mutual Influence. Inflammatory processes play a central role in the pathogenesis of both RA and DM. In RA, infiltration of T-lymphocytes, macrophages, and fibroblasts and the production of cytokines (TNF-α, IL-1, IL-6, IL-17) are observed in the synovial membrane. These pro-inflammatory cytokines lead to systemic inflammation not only in the joints but throughout the entire body.

In DM, especially type 2, insulin resistance of tissues is the main pathological event. Disruption of insulin signaling in adipose tissue, liver, and muscle tissues results in hyperglycemia. However, insulin resistance is also closely linked to active inflammation. Adipokines (leptin, resistin, adiponectin) released from adipose tissue and cytokines (TNF-α, IL-6) produced by macrophages inhibit insulin signaling pathways.

Thus, pro-inflammatory cytokines such as TNF-α and IL-6 occupy a common pathogenetic position in the development of both diseases. When RA becomes active, the plasma levels of these cytokines increase, which enhances insulin resistance and worsens the course of DM. Conversely, in a patient with DM, hyperglycemia and metabolic stress can activate inflammatory processes in cells, thereby exacerbating autoimmune reactions in the joints.

Specific Characteristics of the Clinical Course. RA clinical course in patients with DM is distinguished by a number of specific features:

a) Changes in Pain and Stiffness Symptoms: Diabetic peripheral neuropathy alters the mechanisms of pain perception. As a result, the classic early morning stiffness and joint pain characteristic of RA may not be perceived by the patient in the traditional way. This can lead to the disease not being identified at an early stage. The nature of the pain may have neuropathic features.

b) Addition of Arthropathies: DM can cause its own specific diabetic osteoarthropathy (Charcot foot), which primarily affects the joints of the foot. RA, on the other hand, more commonly damages the small joints of the hands and feet, as well as the elbows, knees, and shoulder joints. When both types of joint damage occur together, the clinical picture becomes very complex and requires differential diagnosis.

c) Increased Risk of Cardiovascular Complications: Both RA and DM are independent risk factors for atherosclerosis. In RA, active inflammation damages the endothelium, disrupts the lipid profile, and alters hemostasis. DM causes damage to the vascular wall through hyperglycemia, dyslipidemia, and hyperinsulinemia. Therefore, when these two diseases co-occur, the risk of myocardial infarction, stroke, peripheral arterial disease, and heart failure sharply increases. Some studies indicate that the risk of cardiovascular events in RA+DM comorbidity is higher than with each disease independently.

d) Increased Susceptibility to Infections: Medications used to treat RA, such as methotrexate, biological agents, and concomitant steroids, weaken the immune system. DM, in turn, impairs the function of neutrophils, macrophages, and T-lymphocytes, and also worsens microcirculation. As a result, patients become more prone to acute and chronic infections (pneumonia, urinary tract infections, purulent inflammations of the skin and soft tissues). This complicates RA treatment because immunosuppressive therapy can provoke infections.

e) Accelerated Development of Osteoporosis: In RA, active inflammation increases osteoclast activity (via the RANKL/RANK/OPG system) and long-term use of corticosteroids disrupts bone metabolism. In DM, hyperglycemia inhibits osteoblast function, and secondary hyperparathyroidism and vitamin D deficiency resulting from diabetic nephropathy accelerate bone resorption. Therefore, when both diseases are present, the risk of osteoporosis and pathological fractures, especially vertebral compression fractures, increases sharply.

f) Impairment of Renal Function: RA can damage the kidneys due to its specific vasculitis or amyloidosis. In DM, diabetic nephropathy is one of the most common complications. Some drugs used for RA (e.g., nonsteroidal anti-inflammatory drugs - NSAIDs) can have nephrotoxic effects. In

comorbid conditions, the risk of developing renal failure is high, which significantly limits the excretion of a number of antirheumatic drugs (e.g., methotrexate).

g) Ocular Complications: In RA, keratoconjunctivitis sicca (related or unrelated to Sjögren's syndrome) and scleritis may be observed. In DM, diabetic retinopathy, cataracts, and glaucoma develop. When these complications occur together, they can seriously impair vision.

4. Diagnostic Difficulties. Laboratory Tests: In patients with DM, against the background of hyperglycemia and insulin resistance, inflammatory markers (CRP, erythrocyte sedimentation rate - ESR) may be chronically elevated. This makes it difficult to accurately assess the activity level of RA. Furthermore, reactive hyperfibrinogenemia in DM can cause an increase in ESR.

Serological Indicators: Anti-CCP (anti-cyclic citrullinated peptide antibodies) and rheumatoid factor (RF) are specific serological markers for RA. However, according to some sources, quantitative indicators of these markers may also increase in DM, although this issue is debatable. Therefore, clinical presentation and instrumental methods become crucial in diagnosis.

Radiological Examination: Periarticular osteopenia, bone erosions, and joint space narrowing characteristic of RA may be masked or mixed with changes from diabetic osteoarthropathy against the background of DM. MRI and ultrasound help identify changes in soft tissues (synovitis, tenosynovitis), but muscle atrophy and neuropathy that develop in DM can also affect these findings.

Treatment Strategies and Approach.

A multidisciplinary approach is necessary for treating this comorbid condition:

a) Priority of Metabolic Control: Strict compensation of DM is necessary not only in itself but also to reduce the inflammatory process in RA. When hyperglycemia decreases, the levels of inflammatory cytokines also drop. There is evidence that RA activity is lower in compensated DM.

b) Pharmacotherapy of Rheumatoid Arthritis: Methotrexate: Considered the "gold standard" for RA. Some data suggest it may slightly improve insulin resistance, but its use requires careful monitoring of liver and kidney function, especially if DM complications are present.

Hydroxychloroquine: Its activity is lower than methotrexate, but it has a beneficial effect in reducing cardiovascular risk. There is information that it may increase insulin sensitivity in DM.

Biological and Synthetic Targeted Drugs (bDMARDs and tsDMARDs): TNF-α inhibitors (infliximab, adalimumab, etanercept) have a strong anti-inflammatory effect. However, they can increase susceptibility to infections, so they should be used with caution if DM is uncompensated or if there are infectious foci. There is evidence of a positive effect of TNF-α inhibitors on glucose metabolism and insulin sensitivity.

JAK-2 Inhibitors (Tofacitinib, Baricitinib): Small molecule drugs. Their use in DM may worsen hyperglycemia, so regular monitoring of glucose levels is necessary.

Glucocorticoids (GC): In low doses (prednisone 5-10 mg/day), they quickly bring clinical improvement, but in DM they can significantly worsen glycemia, cause weight gain, hypertension, and osteoporosis. They should be used temporarily and at the lowest effective doses.

c) Reducing Cardiovascular Risk (Cardioprotection): Statins, strict control of hypertension and hyperglycemia, and aspirin prophylaxis (as prescribed by a doctor) are necessary.

d) Osteoporosis Prophylaxis: Calcium and vitamin D supplementation, and the use of bisphosphonates, teriparatide, or denosumab for osteoporosis treatment may be indicated.

e) Diet and Physical Activity: Maintaining normal weight, limiting salt and simple carbohydrates, and following an anti-inflammatory diet (high in omega-3 fatty acids, antioxidants). Physical exercise increases insulin sensitivity, maintains joint mobility, and increases muscle strength.

f) Multidisciplinary Team: An endocrinologist, rheumatologist, cardiologist, nephrologist, ophthalmologist, physiotherapist, dietitian, and podiatrist should be involved.

Conclusion

The combination of diabetes mellitus and rheumatoid arthritis creates a complex situation in clinical practice. In this condition, not only the specific signs of each disease but also complications arising from their mutually reinforcing effects (cardiovascular, infectious, osteoporosis, nephropathy) prevail. Diagnostically, interpreting inflammation markers is difficult, and in treatment, drugs used

for one disease may worsen the other. Therefore, early detection, an individual approach, strict control of metabolic status, and teamwork among various specialists are of decisive importance for improving the patient's quality of life, reducing disability, and lowering mortality. In the future, deeper pathogenetic and clinical research in this direction is necessary.

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