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METABOLICALLY ASSOCIATED FATTY LIVER DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS: CURRENT UNDERSTANDING AND RESEARCH PERSPECTIVES

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Abstract: Metabolically associated fatty liver disease (MAFLD) is a prevalent liver disorder strongly linked to metabolic dysfunction. Rheumatoid arthritis (RA), a chronic autoimmune disease, is increasingly recognized for its association with metabolic disturbances and hepatic involvement.
Objective: This review explores the pathophysiological interactions between MAFLD and RA, emphasizing shared inflammatory and metabolic mechanisms.
Methods: A narrative literature review was conducted using recent clinical and experimental studies to elucidate common pathways, particularly the role of fibroblast growth factor 21 (FGF21).
Results: Both diseases share key mechanisms including insulin resistance, chronic inflammation, and cytokine-mediated tissue damage. FGF21 emerges as a potential integrative biomarker and therapeutic target due to its dual involvement in metabolic regulation and inflammation.
Conclusion: Recognizing and addressing the bidirectional relationship between MAFLD and RA is essential for effective disease management. Monitoring FGF21 levels may improve risk stratification and guide individualized therapy.

Keywords: Metabolically associated fatty liver disease (MAFLD), rheumatoid arthritis (RA), chronic inflammation, fibroblast growth factor 21 (FGF21), insulin resistance, steatohepatitis, diagnosis, liver fibrosis, anti-inflammatory therapy.

Introduction

Metabolically associated fatty liver disease (MAFLD) is one of the most common chronic liver conditions, closely related to metabolic disorders such as insulin resistance, obesity, and dyslipidemia. In recent years, there has been growing interest in exploring the relationship between MAFLD and systemic inflammatory diseases such as rheumatoid arthritis (RA). RA is a chronic autoimmune disease accompanied by systemic inflammation and joint damage, which significantly affects the body's metabolic processes. Studying the mechanisms of interaction between MAFLD and RA, as well as identifying factors influencing their combined course, is of great importance for both clinical practice and the development of personalized therapeutic strategies.

Pathogenesis of MAFLD

MAFLD encompasses a spectrum of pathological liver changes, ranging from simple steatosis to steatohepatitis, fibrosis, and cirrhosis. Current concepts of pathogenesis are based on the “multiple-hit” hypothesis, which includes metabolic, inflammatory, and genetic factors (Buzzetti et al., 2020). Key mechanisms include:
- Insulin resistance, which leads to an excessive influx of free fatty acids into the liver and

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enhanced lipogenesis;
- Oxidative stress, causing hepatocyte injury and triggering apoptotic cascades;
- Chronic inflammation, associated with the activation of proinflammatory cytokines such as TNF-α and IL-6, which also play a key role in the pathogenesis of RA (Vasiliev et al., 2022).
Thus, the pathogenesis of MAFLD is multifactorial and demonstrates significant overlap with immunoinflammatory processes underlying rheumatoid arthritis.

MAFLD and Rheumatoid Arthritis

Rheumatoid arthritis (RA) is accompanied by systemic inflammation, which significantly affects metabolic processes and hepatic homeostasis. According to Klymas (2025), the presence of MAFLD in patients with RA is associated with thickening of the carotid intima-media complex, confirming a higher cardiometabolic risk in this group.

Chronic inflammation in RA is driven by excessive production of cytokines, including TNF-α, IL-6, and IL-17A, which are involved in the pathogenesis of both joint and liver damage (Dollinger et al., 2025). These mediators contribute to the development of insulin resistance, lipotoxicity, and activation of hepatic stellate cells, accelerating the progression of fibrosis. Therefore, the pathogenesis of MAFLD and RA shares significant common pathways, explaining the high frequency of their comorbidity.

FGF21 as an Integrative Marker

Fibroblast growth factor 21 (FGF21) is an endocrine regulator synthesized in the liver and adipose tissue, playing a key role in energy and lipid metabolism. In MAFLD, FGF21 levels are significantly elevated, which is considered a compensatory response of the body to metabolic and inflammatory stress (Jin Leigang et al., 2022). However, in the chronic course of the disease, a phenomenon known as FGF21 resistance may develop, where elevated levels no longer produce adequate metabolic effects.

Under RA conditions, FGF21 secretion is enhanced by pro-inflammatory cytokines such as TNF-α and IL-6. A study by Hulejová et al. (2012) showed that FGF21 levels in RA patients are higher than in the control group and correlate with disease activity. This makes FGF21 an integrative marker reflecting both metabolic dysfunction and systemic inflammation. Furthermore, experimental data suggest that recombinant analogs of FGF21 can reduce hepatic steatosis and cytokine production, opening new perspectives for its use as a therapeutic target (Hu et al., 2025).

Impact of RA Therapy on the Course of MAFLD

Pharmacotherapy for rheumatoid arthritis has a significant impact on the metabolic profile and liver function. Glucocorticoids exacerbate insulin resistance and contribute to the development of hepatic steatosis (Wu et al., 2024). Methotrexate, a cornerstone disease-modifying agent, has been associated with hepatotoxicity in some cases. However, recent data suggest that metabolic factors, rather than methotrexate itself, play a decisive role in the development of liver fibrosis (Kharouf et al., 2025).

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Biologic agents (inhibitors of TNF-α, IL-6) have the potential to reduce systemic inflammation and improve metabolic status, which may positively influence the course of MAFLD. Nevertheless, the data remain controversial, and further research is needed (Liu et al., 2025).

Conclusion

MAFLD and RA are diseases pathophysiologically connected through shared metabolic and immunological mechanisms. Chronic inflammation and metabolic dysfunction mutually reinforce each other, promoting the progression of both joint pathology and liver damage. A central component in these interactions is FGF21, whose levels are elevated in both conditions and reflect the severity of systemic inflammation and metabolic disturbances. Studying the dynamics of FGF21 under RA therapy may hold promise for predicting the course of MAFLD and for selecting individualized therapeutic strategies.

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