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NON-ALCOHOLIC FATTY LIVER DISEASE: METABOLIC INTERACTIONS, RENAL IMPLICATIONS, AND MODERN MANAGEMENT STRATEGIES

Abstract. Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent metabolic disorder closely associated with obesity, type 2 diabetes mellitus, and chronic kidney disease. The disease spectrum ranges from simple steatosis to non-alcoholic steatohepatitis, fibrosis, and cirrhosis. Increasing evidence highlights the systemic nature of NAFLD, emphasizing its role in metabolic and cardiovascular complications. This review provides an in-depth analysis of pathogenetic mechanisms, including insulin resistance, lipotoxicity, oxidative stress, and inflammation. Special attention is given to the bidirectional relationship between NAFLD, diabetes mellitus, and renal dysfunction. Modern diagnostic tools and current therapeutic strategies are discussed, with emphasis on personalized and multidisciplinary approaches.

Keywords: NAFLD, insulin resistance, diabetes mellitus, chronic kidney disease, steatohepatitis, fibrosis, metabolic syndrome.

Non-alcoholic fatty liver disease has emerged as one of the most significant global health challenges of the 21st century, reflecting the increasing prevalence of metabolic disorders. The condition affects approximately 25–30% of the adult population and is particularly common among individuals with obesity and type 2 diabetes mellitus [1]. Importantly, NAFLD is no longer considered an isolated liver pathology but rather a systemic disease that interacts closely with endocrine and renal systems.

The pathogenesis of NAFLD is multifactorial and best explained by the “multiple-hit” hypothesis, which integrates metabolic, inflammatory, and genetic factors. Insulin resistance remains the central mechanism underlying disease development. In insulin-resistant states, increased lipolysis in adipose tissue leads to elevated free fatty acid flux to the liver. These fatty acids accumulate in hepatocytes, promoting triglyceride deposition and hepatic steatosis. Simultaneously, insulin resistance enhances hepatic de novo lipogenesis while impairing lipid export, further aggravating fat accumulation [2].

As hepatic steatosis progresses, lipotoxicity becomes a critical factor contributing to hepatocellular injury. Accumulated lipids undergo oxidation, generating reactive oxygen species that damage mitochondrial structures and cellular membranes. This oxidative stress activates inflammatory signaling pathways, resulting in the release of proinflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6. These mediators promote hepatocyte apoptosis and necrosis, driving the transition from simple steatosis to non-alcoholic steatohepatitis [3].

The close relationship between NAFLD and type 2 diabetes mellitus deserves particular attention. These conditions share common pathogenetic mechanisms, primarily insulin resistance and chronic low-grade inflammation. In patients with diabetes, NAFLD tends to progress more rapidly and is associated with a higher risk of fibrosis and cirrhosis. Conversely, the presence of NAFLD exacerbates insulin resistance and worsens glycemic control, creating a vicious cycle that accelerates disease progression [4].

Recent studies have also highlighted a significant association between NAFLD and chronic kidney disease. The mechanisms linking these conditions include systemic inflammation, endothelial dysfunction, and activation of the renin–angiotensin–aldosterone system. Hepatic insulin resistance contributes to altered lipid metabolism and increased production of atherogenic lipoproteins, which may damage renal microvasculature. Additionally, inflammatory mediators released from the liver may directly affect renal function, promoting fibrosis and decline in glomerular filtration rate [5]. Thus, NAFLD should be considered an independent risk factor for kidney disease progression.

The diagnosis of NAFLD remains challenging due to the often asymptomatic course of the disease. Mild elevations in liver enzymes are frequently the first laboratory findings but lack specificity. Imaging techniques, particularly ultrasonography, are widely used for initial detection. However, more advanced modalities such as transient elastography and magnetic resonance imaging provide better assessment of liver fat content and fibrosis. Although liver biopsy remains the gold standard for diagnosis, its invasive nature limits its use to selected cases [6].

From a clinical perspective, NAFLD is associated with significant morbidity and mortality. Cardiovascular disease represents the leading cause of death in these patients, exceeding liver-related complications. Furthermore, the presence of NAFLD increases the risk of developing hepatocellular carcinoma, even in the absence of cirrhosis. These findings underscore the importance of early diagnosis and comprehensive management.

The management of NAFLD is primarily based on modification of lifestyle factors. Weight loss through dietary intervention and increased physical activity remains the most effective strategy. A reduction of body weight by 7–10% has been shown to significantly improve liver histology, including reduction of steatosis and inflammation. Dietary patterns such as the Mediterranean diet have demonstrated beneficial effects on metabolic parameters and liver function.

Pharmacological treatment options are currently limited but continue to evolve. Insulin sensitizers, such as pioglitazone, have shown efficacy in improving liver histology in patients with non-alcoholic steatohepatitis. Antioxidants, including vitamin E, may reduce oxidative stress and inflammation in selected patients. In recent years, novel therapeutic agents targeting specific molecular pathways, including fibrosis and inflammation, have been активно исследованы and show promising results.

An integrated approach is essential in the management of NAFLD, particularly in patients with comorbid diabetes and renal dysfunction. This includes strict glycemic control, management of dyslipidemia, and monitoring of renal function. Multidisciplinary collaboration between endocrinologists, hepatologists, and nephrologists is crucial to achieve optimal outcomes.

Despite advances in understanding NAFLD, several challenges remain. There is a need for reliable non-invasive biomarkers for early diagnosis and disease monitoring. Furthermore, the development of targeted therapies addressing the underlying mechanisms of the disease remains a priority. Future research should focus on personalized medicine approaches, taking into account genetic, metabolic, and environmental factors.

Conclusion

Non-alcoholic fatty liver disease is a complex and multifactorial disorder with significant metabolic, hepatic, and renal implications. Its strong association with diabetes mellitus and chronic kidney disease highlights the need for a comprehensive and interdisciplinary approach to

patient care. Early diagnosis, lifestyle modification, and emerging pharmacological therapies are essential components of effective management. Continued research will play a key role in improving outcomes and reducing the global burden of this disease.

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