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Retinopathy in Metabolic Dysfunction-associated Steatotic Liver Disease: A Complex Interrelationship

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Introduction

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), formerly known as Non-Alcoholic Fatty Liver Disease (NAFLD), has emerged as a major global health concern due to its strong association with metabolic syndrome, insulin resistance, and systemic inflammation. Characterized by excessive fat accumulation in the liver, MASLD often progresses to more severe conditions such as steatohepatitis, fibrosis, cirrhosis, and even hepatocellular carcinoma. Beyond its hepatic manifestations, MASLD has been increasingly linked to extrahepatic complications, including cardiovascular disease, chronic kidney disease, and neurological disorders. Among these, the relationship between MASLD and retinopathy has gained growing attention, as both conditions share common metabolic risk factors such as hyperglycemia, dyslipidemia, hypertension, and chronic inflammation. Retinopathy, particularly diabetic and hypertensive retinopathy, is a leading cause of vision impairment and blindness, resulting from microvascular damage in the retina. Given the shared pathophysiological pathways, emerging evidence suggests that MASLD may contribute to retinal microvascular dysfunction, exacerbating the risk and severity of retinopathy. This review aims to explore the intricate interplay between MASLD and retinopathy, elucidating the underlying mechanisms, clinical implications, and potential therapeutic strategies to mitigate the ocular complications associated with metabolic liver disease [1].

Description

The liver and the eye are highly vascularized organs that are susceptible to metabolic disturbances, particularly those driven by insulin resistance, dyslipidemia, and chronic low-grade inflammation. The pathogenesis of MASLD and retinopathy is deeply interconnected through systemic metabolic dysfunction, endothelial damage, oxidative stress, and inflammatory mediators. In MASLD, hepatic fat accumulation triggers lipotoxicity, which induces oxidative stress, mitochondrial dysfunction, and the activation of pro-inflammatory cytokines such as Tumor Necrosis Factor-Alpha (TNF-α), Interleukin-6 (IL-6), And C - reactive protein (CRP). These systemic inflammatory signals not only exacerbate liver damage but also contribute to endothelial dysfunction in the retinal vasculature, promoting microvascular injury, increased vascular permeability, and neovascularization hallmarks of retinopathy [2].

Hypertension, another common comorbidity of MASLD, exacerbates retinal micro vascular injury by increasing shear stress on the retinal capillaries, leading to endothelial dysfunction, vascular leakage, and progressive retinal ischemia. The Renin-Angiotensin-Aldosterone System (RAAS), which is often dysregulated in MASLD, plays a significant role in retinal pathophysiology. Angiotensin II promotes vasoconstriction, oxidative stress, and pro-inflammatory cytokine release, contributing to retinal vascular remodeling and neovascularization in hypertensive retinopathyInsulin resistance, a central feature of MASLD, plays a crucial role in retinal vascular dysfunction. Insulin resistance leads to hyperglycemia and compensatory hyperinsulinemia, which disrupts normal retinal endothelial cell function by impairing nitric oxide bioavailability, increasing oxidative stress, and promoting pericyte apoptosis. This endothelial dysfunction results in capillary basement membrane thickening, microaneurysm formation, and retinal ischemia, which are characteristic findings in both diabetic and hypertensive retinopathy. Additionally, MASLD-related dyslipidemia marked by elevated triglycerides and low HDL cholesterol further contributes to retinal vascular damage by increasing lipid deposition in the retinal microvasculature, leading to exudates, hemorrhages, and capillary occlusion [3].

Recent studies have demonstrated a strong epidemiological link between MASLD and the prevalence of retinopathy. Individuals with MASLD exhibit a higher risk of developing diabetic retinopathy, independent of traditional diabetes risk factors. Moreover, the severity of hepatic steatosis and fibrosis in MASLD has been correlated with worsening retinal microvascular abnormalities, suggesting a dose-dependent relationship between liver disease progression and ocular complications. The mechanistic connection between liver fibrosis and retinal vascular dysfunction may be mediated through systemic endothelial dysfunction, altered lipid metabolism, and chronic low-grade inflammation Beyond diabetic and hypertensive retinopathy, MASLD may also contribute to Age-Related Macular Degeneration (AMD) and other retinal degenerative disorders. The systemic pro-inflammatory state induced by MASLD accelerates Retinal Pigment Epithelium (RPE) dysfunction, oxidative damage, and neovascularization, all of which are implicated in the pathogenesis of AMD. Additionally, altered gut microbiota composition in MASLD has been proposed as a potential mediator linking liver disease to retinal disorders through the gut-liver-retina axis. Gut dysbiosis promotes increased intestinal permeability, systemic endotoxemia, and inflammation, which may further exacerbate retinal vascular dysfunction [4].

Given the growing evidence linking MASLD to retinopathy, early screening and comprehensive management strategies are essential to prevent vision-threatening complications in individuals with metabolic liver disease. Integrating retinal imaging modalities such as Optical Coherence Tomography (OCT) and fundus photography into routine metabolic syndrome assessments may facilitate early detection of subclinical retinal microvascular changes in MASLD patients. Additionally, biomarkers of liver fibrosis, including Fibrosis-4 (FIB-4) index and non-invasive imaging techniques like transient elastography, may help stratify the risk of retinopathy in individuals with MASLD.

From a therapeutic perspective, addressing MASLD-related metabolic dysfunction may have beneficial effects on retinal health. Lifestyle interventions, including dietary modifications, weight loss, and physical activity, remain the cornerstone of MASLD and retinopathy management, as they improve insulin sensitivity, reduce systemic inflammation, and mitigate endothelial dysfunction. Pharmacological interventions targeting metabolic pathways, such as GLP-1 receptor agonists and SGLT2 inhibitors, have demonstrated promising effects in improving both hepatic and retinal outcomes. Emerging therapies targeting hepatic fibrosis, including FXR agonists and anti-inflammatory agents, may also hold potential in preventing retinal vascular complications. Despite advancements in understanding the MASLD-retinopathy connection, several challenges remain. The heterogeneity of MASLD phenotypes, variations in retinopathy progression, and the influence of genetic and environmental factors complicate the establishment of causative links between liver disease and retinal dysfunction. Future research should focus on elucidating the

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molecular mechanisms underlying MASLD-related retinal vascular pathology, exploring the role of gut microbiota in the gut-liver-retina axis, and investigating novel therapeutic strategies targeting shared metabolic pathways. Longitudinal studies assessing the impact of MASLD treatment on retinopathy progression will be crucial in defining optimal management approaches for at-risk individuals. Additionally, the role of lipid-lowering agents, such as statins and PCSK9 inhibitors, in reducing retinopathy risk warrants further investigation, given their ability to modulate lipid metabolism and endothelial function [5].

Conclusion

In conclusion, MASLD is not merely a hepatic disorder but a systemic metabolic disease with far-reaching implications, including an increased risk of retinopathy. The shared pathophysiological mechanisms between MASLD and retinopathy encompassing insulin resistance, endothelial dysfunction, chronic inflammation, and dyslipidemia underscore the need for a multidisciplinary approach to patient management. Early identification and intervention strategies aimed at controlling metabolic dysfunction, improving hepatic health, and preserving retinal vascular integrity are essential to reducing the burden of vision impairment in MASLD patients. Integrating retinal screening into MASLD care protocols, leveraging novel biomarkers, and exploring targeted therapies may pave the way for improved clinical outcomes. As research continues to unravel the intricate liver-retina connection, a deeper understanding of the interplay between MASLD and retinopathy will enhance preventive and therapeutic strategies, ultimately improving the quality of life for individuals affected by metabolic dysfunction-associated liver and eye diseases.

Acknowledgement

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Conflict of Interest

None.

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