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Hypoxia-Induced Oxidative Stress in Fatty Liver Disease: Mechanisms and Therapeutic Perspectives

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Abstract

Fatty liver disease, particularly metabolic dysfunction-associated fatty liver disease (MAFLD), has become one of the most prevalent metabolic disorders worldwide. Hypoxia is widely recognized as a major pathogenic factor that exacerbates hepatic lipid accumulation, inflammation, and oxidative injury. Hepatic hypoxia can arise from obesity-related microvascular dysfunction, excessive adipose tissue accumulation, and conditions such as obstructive sleep apnea, which impede oxygen delivery to hepatocytes. In hypoxic environments, the stabilization of hypoxia-inducible factor-1α (HIF-1α) modifies gene expression associated with lipid metabolism, inflammatory signaling, and redox equilibrium, leading to heightened production of reactive oxygen species (ROS), mitochondrial dysfunction, and diminished antioxidant defenses. These changes exacerbate oxidative stress and harm liver cells. Hypoxia-induced oxidative stress activates lipid metabolic pathways, creating a positive feedback loop that accelerates the advancement of the disease from uncomplicated steatosis to non-alcoholic steatohepatitis (NASH) and fibrosis. Clinical evidence corroborates this correlation, showing that individuals with intermittent or chronic hypoxia exhibit 2-3 times higher levels of liver enzymes, inflammatory mediators, and fibrosis markers compared to controls. We understand more about how oxidative stress and hypoxia affect each other at the molecular level, but there aren't many treatments that directly target these processes. This narrative review consolidates recent findings regarding the role of hypoxia in eliciting oxidative stress in fatty liver disease and emphasizes innovative therapeutic strategies, including antioxidants, mitochondrial-targeted pharmacotherapies, and lifestyle alterations. These techniques hold potential for impeding or halting the advancement of fibrosis; however, more meticulously designed clinical trials are necessary to validate their efficacy.

Kata kunci: Hypoxia, Oxidative Stress, Fatty Liver Disease, MAFLD, Mitochondrial dysfunction.

INTRODUCTION

Fatty liver disease, now commonly referred to as metabolic dysfunction-associated fatty liver disease (MAFLD), has emerged as one of the most prevalent metabolic disorders globally. Its global burden continues to rise in parallel with obesity, insulin resistance, and sedentary lifestyles. MAFLD includes a range of conditions, from simple steatosis to more advanced ones like non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). It is a major cause of chronic liver disease morbidity and mortality (1–3). This progression is caused by mitochondrial dysfunction, oxidative stress, and chronic inflammation, which damage liver cells and disrupt metabolism, as well as lipid buildup (4). Hypoxia has become a key mechanism connecting metabolic dysfunction to liver damage among the many pathological factors. Hepatic and adipose tissue hypoxia frequently results from obesity-related adipose tissue expansion, compromised hepatic microcirculation, and sinusoidal dysfunction.

Extrahepatic conditions, such as obstructive sleep apnea, can cause systemic hypoxia that may be intermittent or persistent (5–7). Stabilization of hypoxia-inducible factors (HIFs) under low oxygen conditions reprograms the transcription of genes implicated in lipid metabolism, angiogenesis, inflammation, and redox regulation (8). This shift caused by hypoxia leads to excessive production of reactive oxygen species (ROS), which makes mitochondrial oxidative phosphorylation less effective and disrupts redox homeostasis. The result increases metabolic stress and speeds up damage to liver cells (4,8).

Hypoxia-induced ROS production directly affects lipid metabolism pathways, creating a self-reinforcing cycle in which oxidative stress worsens steatosis, inflammation, and fibrosis, which are all important factors in the progression to NASH (4,9). Hypoxia-induced ROS generation directly interacts with lipid metabolic pathways, creating a self-perpetuating cycle where oxidative stress exacerbates steatosis, inflammation, and fibrosis, which are critical factors in the progression to NASH (2,9). Clinical studies provide additional evidence for the mechanistic role of hypoxia in the pathogenesis of MAFLD. People with oxygen desaturation, especially those with obstructive sleep apnea, have higher levels of liver enzymes, more oxidative stress markers, and more advanced fibrosis than people who are metabolically similar but don't have hypoxia (10–12). While several therapeutic strategies, such as antioxidants, mitochondrial-targeted agents, and lifestyle modifications, have demonstrated promise, targeted therapies that specifically disrupt the hypoxia–oxidative stress axis are still scarce (2,13).

This narrative review aims to synthesize current evidence on the mechanisms through which hypoxia induces oxidative stress in fatty liver disease, clarify the interactions between hypoxia, reactive oxygen species (ROS), and lipid metabolism, and explore innovative therapeutic strategies targeting these pathways. A deeper understanding of this mechanistic axis may enhance the development of more precise and effective therapies for managing MAFLD.

LITERATURE SEARCH STRATEGY

This narrative review was constructed from an extensive examination of pertinent literature published predominantly in the past ten years. We found articles by searching PubMed, Scopus, and Google Scholar with different combinations of the following keywords: hypoxia, oxidative stress, fatty liver disease, MAFLD, NASH, mitochondrial dysfunction, and HIF-1α. The literature examined in this review encompasses publications from 2015 to 2025, thereby incorporating both seminal studies and the latest scientific developments. Additional references were included by manually reviewing the bibliographies of important publications to make sure that new ideas and mechanistic insights were well covered. Only peer-reviewed articles composed in English were deemed acceptable. This work is a narrative review, so there were no set rules for which studies to include or leave out. Instead, studies were chosen based on how well they explained the links between hypoxia and oxidative stress in fatty liver disease.

Crosstalk Between Hypoxia, Oxidative Stress, and Lipid Metabolism

The relationship between hypoxia, oxidative stress, and lipid metabolism is a key factor in the development of fatty liver disease. Hypoxia alters hepatic lipid metabolism by stabilizing hypoxia-inducible factor-1α (HIF-1α), which enhances the transcriptional upregulation of lipogenic mediators, including sterol regulatory element-binding protein-1c (SREBP-1c) and fatty acid synthase (FASN), while simultaneously inhibiting peroxisome proliferator-activated receptor-α (PPAR-α), a crucial regulator of mitochondrial β-oxidation (2,14). The simultaneous increase in

lipogenesis and decrease in lipid catabolism leads to excessive triglyceride accumulation, rendering hepatocytes more vulnerable to oxidative stress. Hypoxia increases fatty acid intake by upregulating transporters such as CD36 and FATP, exacerbating lipid accumulation in the steatotic liver (15). The simultaneous increase in lipogenesis and decrease in lipid catabolism leads to excessive triglyceride buildup, rendering hepatocytes more vulnerable to oxidative stress. Hypoxia increases fatty acid uptake by upregulating transporters such as CD36 and FATP, thereby exacerbating lipid buildup in the steatotic liver (16). Reactive oxygen species (ROS) induce lipotoxicity, impair mitochondrial DNA, disrupt oxidative phosphorylation, and facilitate the opening of the mitochondrial permeability transition pore (mPTP). In parallel, hypoxia induces transcriptional activation of NADPH oxidases, particularly NOX2 and NOX4, generating additional ROS from non-mitochondrial sources and amplifying oxidative injury (17).

Lipid peroxidation products such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) accumulate during this process, forming adducts with cellular proteins and exacerbating hepatocyte dysfunction (18). Hypoxia-induced ROS further interacts with endoplasmic reticulum (ER) stress, creating a self-perpetuating cycle of oxidative injury. Excessive lipid accumulation disrupts the equilibrium of the endoplasmic reticulum (ER), initiating the unfolded protein response (UPR). In the absence of sufficient oxygen, this imbalance exacerbates due to inadequate ATP for proper protein folding. The accumulation of ROS under ER stress exacerbates redox imbalance in cells (19). Reactive oxygen species (ROS) activate redox-sensitive transcription factors such as NF-κB, leading to the secretion of inflammatory cytokines (including TNF-α and IL-6) and the activation of Kupffer cells. This exacerbates oxygen deprivation and diminishes hepatic microvascular perfusion (11). Clinical and experimental models of intermittent hypoxia, exemplified by obstructive sleep apnea, exhibit exacerbated oxidative stress, steatosis, and fibrosis resulting from recurrent cycles of hypoxia and reoxygenation, underscoring the dynamic influence of variable oxygen tension on hepatic redox pathways (20).

Taken together, these interactions form a vicious cycle: hypoxia enhances lipogenesis and suppresses β-oxidation; lipid accumulation amplifies mitochondrial overload and ROS production; ROS intensifies ER stress and inflammation; and inflammation worsens hepatic microcirculation, deepening hypoxia. This interconnected pathophysiology hastens the progression from uncomplicated steatosis to non-alcoholic steatohepatitis (NASH) and fibrosis.

Therapeutic Implications: Inhibiting key components of this cycle, such as HIF-1α, using pharmacological agents, may disrupt hypoxia-induced lipogenesis and ROS amplification, thereby decelerating the progression to NASH (21). Furthermore, antioxidant treatments or PPAR-α modulators may mitigate oxidative stress and fat buildup, offering possible intervention options linked to broader inflammatory pathways discussed in subsequent sections.

Hypoxia-Associated Inflammation and Fibrosis

Hypoxia significantly contributes to liver inflammation and fibrosis. It operates via numerous interconnected molecular pathways that exacerbate liver damage in fatty liver disease. In conditions of insufficient oxygen, hepatocytes and non-parenchymal cells undergo transcriptional reprogramming regulated by HIF-1α and HIF-2α. This increases the likelihood of producing pro-inflammatory and pro-fibrogenic mediators such as TNF-α, IL-1β, IL-6, and chemokines like MCP-1 (22,23). Cytokines recruit monocytes and activate Kupffer cells, the resident macrophages of the liver. This induces an inflammatory microenvironment characterized by an oxidative burst, activation of NADPH oxidase, and increased production of reactive oxygen

species (ROS) (24). Cytokines recruit monocytes and activate Kupffer cells, the resident macrophages of the liver. This induces an inflammatory microenvironment characterized by an oxidative burst, activation of NADPH oxidase, and increased production of reactive oxygen species (ROS) (25). Hypoxia increases the levels of matrix metalloproteinases (MMP-2 and MMP-9) and tissue inhibitors of metalloproteinases (TIMPs), disrupting the turnover of the extracellular matrix (ECM) and accelerating scar formation (26).

The oxidative environment enhances the fibrotic response. Reactive oxygen species (ROS) activate hematopoietic stem cells (HSCs) via redox-sensitive pathways, including JNK, p38 MAPK, and NF-κB, thereby establishing a direct link between oxidative stress and extracellular matrix (ECM) remodeling (27). Furthermore, recurrent episodes of hypoxia and reoxygenation, particularly in conditions such as obstructive sleep apnea (OSA), exacerbate liver inflammation in a manner analogous to ischemia-reperfusion injury. Rapid fluctuations in oxygen levels lead to excessive production of mitochondrial reactive oxygen species (ROS), activation of the inflammasome, and a transition of macrophages to a pro-inflammatory M1 phenotype (28). Furthermore, recurrent episodes of hypoxia and reoxygenation, particularly in conditions such as obstructive sleep apnea (OSA), exacerbate liver inflammation in a manner analogous to ischemia-reperfusion injury. Rapid fluctuations in oxygen levels lead to excessive production of mitochondrial reactive oxygen species (ROS), activation of the inflammasome, and a transition of macrophages to a pro-inflammatory M1 phenotype (29). Recurrent episodes of hypoxia and reoxygenation, especially in conditions like obstructive sleep apnea (OSA), intensify liver inflammation similarly to ischemia-reperfusion injury. Rapid changes in oxygen levels result in increased production of mitochondrial reactive oxygen species (ROS), activation of the inflammasome, and a shift of macrophages to a pro-inflammatory M1 phenotype (11). Hypoxia promotes the translocation of endotoxins from the gut, thereby enhancing the activation of Kupffer cells via TLR4 signaling and intensifying inflammatory cascades (30).

Hypoxia-induced inflammation and fibrosis are critical determinants of disease progression in MAFLD. Hypoxia acts as a key amplifier by integrating metabolic stress, immune activation, and extracellular matrix remodeling, thereby promoting the transition from simple steatosis to non-alcoholic steatohepatitis (NASH) and connecting oxidative injury to structural liver damage. The mechanistic insights highlight hypoxia-associated pathways, particularly HIF signaling, ROS generation, and HSC activation, as potential therapeutic targets for reducing inflammation and preventing fibrotic remodeling in fatty liver disease.

Clinical Evidence Linking Hypoxia and Fatty Liver Disease

Clinical and epidemiological studies consistently demonstrate a significant association between hypoxia, both chronic and acute, and the severity of fatty liver disease. Individuals with obstructive sleep apnea (OSA), characterized by intermittent hypoxia (IH), demonstrate markedly higher rates of hepatic steatosis, inflammation, and fibrosis compared to those with similar metabolic risk profiles without hypoxia (11). Intermittent hypoxia (IH) induces recurrent episodes of oxygen desaturation and reoxygenation, resembling ischemia-reperfusion injury. This process elevates systemic oxidative stress, activates inflammatory pathways, and impedes hepatic blood flow. Clinical cohorts demonstrate a positive correlation between the severity of nocturnal oxygen desaturation and levels of ALT, AST, γ-GT, liver stiffness, and histological NASH scores (7). IH induces recurrent cycles of oxygen desaturation and reoxygenation, resembling ischemia-reperfusion injury, which elevates oxidative stress, activates inflammatory pathways, and impairs hepatic blood flow. Clinical cohorts indicate a positive correlation between the severity of

nocturnal oxygen desaturation and levels of ALT, AST, γ-GT, liver stiffness, and histological NASH scores (31). Imaging studies utilizing oxygen-sensitive MRI have confirmed the presence of hepatic tissue hypoxia in patients with MAFLD, demonstrating greater hypoxia in individuals with advanced fibrosis and increased hepatic fat fraction. Imaging studies utilizing oxygen-sensitive MRI have confirmed the presence of hepatic tissue hypoxia in patients with MAFLD, demonstrating greater hypoxia in individuals with advanced fibrosis and increased hepatic fat fraction (32). Liver biopsies from patients with MAFLD/NASH show increased expression of HIF-1α, NOX isoforms, and lipid peroxidation markers, including MDA and 4-HNE, suggesting a mechanistic link between hypoxia and oxidative damage at the tissue level (33).

Clinical intervention studies provide strong evidence that the treatment of obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) improves liver enzymes, decreases inflammatory markers, and lowers hepatic fat accumulation, suggesting a causal relationship between hypoxia and the advancement of non-alcoholic fatty liver disease (NAFLD) (12,34). Clinical intervention studies provide strong evidence that the treatment of obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) improves liver enzymes, decreases inflammatory markers, and lowers hepatic fat accumulation, suggesting a causal relationship between hypoxia and the advancement of non-alcoholic fatty liver disease (NAFLD) (35,36). Additionally, population-based cohort studies show that low resting oxygen saturation and higher haematocrits are surrogate markers of chronic hypoxic stress and are independently associated with greater MAFLD prevalence and fibrosis scores (37). The clinical findings indicate that hypoxia significantly exacerbates liver injury, interacting with metabolic risk factors to accelerate the progression from simple steatosis to NASH and fibrosis.

Therapeutic Perspectives Targeting Hypoxia and Oxidative Stress in Fatty Liver Disease

Hypoxia and oxidative stress play a critical role in the progression of MAFLD, prompting the development of novel treatments aimed at enhancing mitochondrial function, reducing ROS production, restoring redox balance, and modulating HIF signaling. Antioxidant treatments such as vitamin E, N-acetylcysteine (NAC), curcumin, resveratrol, and quercetin have demonstrated potential in reducing oxidative stress and enhancing liver histology by eliminating free radicals, inhibiting lipid peroxidation, and reinstating the body's antioxidant production capacity (38,39). N-acetylcysteine (NAC), a glutathione precursor, has demonstrated notable efficacy in lowering alanine aminotransferase (ALT) levels, improving hepatic oxidative stress biomarkers, and protecting mitochondrial function in both human and animal studies (38). Targeted treatments increasingly emphasize mitochondria, the primary source of reactive oxygen species (ROS) under hypoxic conditions. MitoQ, SS-31 peptide (elamipretide), and melatonin are compounds that enhance mitochondrial electron transport efficiency, inhibit mPTP opening, and reduce oxidative damage. These pharmaceuticals represent potential options for the treatment of NASH (13,40). Targeted treatments increasingly emphasize mitochondria, the primary source of reactive oxygen species (ROS) under hypoxic conditions. MitoQ, SS-31 peptide (elamipretide), and melatonin are compounds that enhance mitochondrial electron transport efficiency, inhibit mPTP opening, and reduce oxidative damage. Those drugs may be utilized for the treatment of NASH (41,42). The objective of these medications is to regulate oxygen delivery to the liver, inhibit HIF-mediated lipogenesis, and reduce inflammatory signaling.

Lifestyle modifications remain a crucial component of therapeutic interventions. Weight loss, exercise, and intermittent fasting improve hepatic oxygenation, increase mitochondrial biogenesis, and decrease oxidative stress, with clinical trials demonstrating significant reductions

in liver fat content and inflammation (43,44). In patients with OSA-related MAFLD, CPAP therapy reduces the burden of intermittent hypoxia, improves liver enzyme levels, and decreases systemic inflammation, highlighting the importance of addressing extrahepatic sources of hypoxic stress (12,34). Therapeutic strategies aimed at addressing hypoxia and oxidative stress are a significant and growing area of focus in the management of MAFLD. The integration of antioxidant, mitochondrial, hypoxia-modifying, and lifestyle-based strategies may represent the most effective approach to preventing disease progression and liver fibrosis.

CONCLUSIONS

Hypoxia and oxidative stress are critical factors that interact to induce metabolic dysfunction and hepatocyte injury in metabolic dysfunction-associated fatty liver disease (MAFLD). Hypoxia exacerbates lipid accumulation, inflammation, and fibrosis through HIF-mediated transcriptional reprogramming, increased mitochondrial ROS production, and activation of NOX. This establishes a cycle that accelerates the transition from simple steatosis to NASH. Imaging studies, biomarker analyses, and OSA cohorts provide consistent clinical evidence that hypoxia serves as a modifiable risk factor and a mechanistic enhancer of liver injury. Therapeutic strategies targeting oxidative stress, mitochondrial dysfunction, hypoxia signaling, and microvascular impairment demonstrate potential; however, their implementation in effective clinical interventions remains limited. A comprehensive approach that integrates lifestyle modifications, antioxidant therapy, and hypoxia-targeting medications may be the most effective method for decelerating disease progression. Further investigation is required to enhance molecular targets, identify dependable biomarkers, and develop precision therapies tailored to individual hypoxia-redox profiles. Comprehending these pathways is essential for improving clinical outcomes and preventing the long-term complications of MAFLD, thus promoting better global health management.

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