International Journal of Cell and Biomedical Science (2026) 5: (13) p463-475
https://doi.org/10.59278/cbs.v5i13.91

REVIEW ARTICLE OPEN ACCESS

From Oxidative Stress to Fibrogenesis: A Comprehensive Review of a Composite Oxidative-Fibrotic Index in Hypoxia-Associated MAFLD

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Submission January 28, 2026
Accepted April 18, 2026
Available online on April 30, 2026

ABSTRACT

Metabolically associated fatty liver disease (MAFLD) is a leading cause of chronic liver disease, with fibrosis representing the strongest predictor of adverse clinical outcomes. Emerging evidence suggests that intermittent hypoxia, commonly associated with obstructive sleep apnea, contributes to fibrosis progression through oxidative stress-mediated mechanisms. This review aims to synthesize current evidence on the role of intermittent hypoxia in driving oxidative stress and hepatic fibrogenesis in MAFLD, and to propose a Composite Oxidative-Fibrotic Index as an integrative biomarker framework. A narrative review was conducted using major biomedical databases to identify experimental and clinical studies evaluating hypoxia-induced oxidative stress, redox-sensitive signaling pathways, and fibrogenic responses in MAFLD. Intermittent hypoxia induces repetitive hypoxia-reoxygenation cycles that promote reactive oxygen species generation, impair antioxidant defenses, and activate redox-sensitive pathways, including HIF-1α, NF-κB, and Nrf2 dysregulation. These mechanisms contribute to hepatic stellate cell activation, extracellular matrix remodeling, and increased liver stiffness. Evidence indicates that individual oxidative and fibrogenic biomarkers are insufficient to capture the dynamic progression of fibrosis. The proposed Composite Oxidative-Fibrotic Index integrates oxidative stress markers, signaling mediators, fibrogenic indicators, and liver stiffness measurement into a unified framework. This approach may improve early detection, risk stratification, and monitoring of fibrosis progression in hypoxia-associated MAFLD, with potential implications for biomarker-guided clinical management and targeted therapeutic strategies.

Keywords: Intermittent hypoxia; MAFLD; Oxidative stress; Hepatic fibrosis; Composite oxidative-fibrotic index.

INTRODUCTION

Metabolically associated fatty liver disease (MAFLD) is a hepatic manifestation of systemic metabolic dysfunction and has emerged as one of the most prevalent chronic liver diseases worldwide. [1,2,3] Its clinical spectrum ranges from simple steatosis to steatohepatitis, progressive fibrosis, cirrhosis, and hepatocellular carcinoma. Among these stages, the degree of hepatic fibrosis is recognized as the most significant predictor of liver-related morbidity and mortality, underscoring the urgent need for early detection of fibrogenic activity and reliable biomarkers to monitor disease progression. [1,4]

In addition to classical metabolic risk factors such as obesity, insulin resistance, and dyslipidemia, disturbances in oxygen homeostasis particularly intermittent hypoxia have emerged as important modifiers of disease progression. [8,34] Intermittent hypoxia, a hallmark of obstructive sleep apnea and a frequent comorbidity in metabolic syndrome, is characterized by repetitive cycles of hypoxia and reoxygenation that resemble ischemia-reperfusion injury at the cellular level. [8,9] These cycles promote excessive mitochondrial and cytosolic generation of reactive oxygen species (ROS), leading to redox imbalance, oxidative damage, inflammatory activation, and microvascular dysfunction within the hepatic sinusoidal environment. [10,12,14]

Oxidative stress represents a central molecular mechanism linking intermittent hypoxia to inflammatory and profibrotic responses.[15,16] Hypoxia-reoxygenation cycles enhance electron leakage from the mitochondrial respiratory chain, accelerate lipid peroxidation, and impair endogenous antioxidant defenses. This imbalance is reflected by increased levels of lipid peroxidation markers such as malondialdehyde (MDA) and 4-hydroxynonenal, along with decreased activity of antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). [11,14-16] At the transcriptional level, redox-sensitive regulators such as hypoxia-inducible factor-1α (HIF-1α) and nuclear factor erythroid 2-related factor 2 (Nrf2) play key roles. [18,21,22] While HIF-1α promotes adaptive responses to hypoxia, its sustained activation during intermittent hypoxia has been associated with increased ROS production, inflammation, and profibrotic signaling. [18-20] In contrast, impaired Nrf2 activity compromises antioxidant defense and exacerbates oxidative damage. [21,22]

The interaction between oxidative stress and inflammatory signaling is critical for the activation of hepatic stellate cells (HSCs), the principal effector cells in liver fibrogenesis. [23,24] Reactive oxygen species and hypoxia-responsive pathways stimulate transforming growth factor-β (TGF-β) signaling and related profibrotic cascades, resulting in increased expression of α-smooth muscle actin (α-SMA), collagen types I and III, and disruption of the matrix metalloproteinase/tissue inhibitor balance (MMP/TIMP). [1-3,6] Both experimental and clinical studies demonstrate that the severity of intermittent hypoxia correlates with increased liver stiffness, higher fibrosis scores, and elevated fibrogenic markers, even after adjusting for conventional metabolic risk factors. [34-36] These findings indicate that intermittent hypoxia acts as an independent driver of fibrosis progression through an oxidative-fibrotic axis.

Despite growing evidence linking oxidative stress and fibrogenesis, most biomarkers are still evaluated in isolation, reflecting either redox imbalance or fibrotic activity. Such single-parameter approaches fail to capture the complex and sequential pathophysiological continuum connecting intermittent hypoxia, oxidative injury, inflammatory activation, and extracellular matrix remodeling. Therefore, an integrative framework that combines oxidative stress markers (e.g., MDA, antioxidant enzyme activity, Nrf2, and HIF-1α signaling) with fibrogenic indicators (e.g., TGF-β1, α-SMA, collagen deposition, and non-invasive liver stiffness measurement) may provide a more sensitive and mechanistically informed assessment of early fibrosis progression. [19,23,24]

In this context, the concept of a Composite Oxidative-Fibrotic Index emerges as a promising approach to integrate molecular redox imbalance with structural fibrogenic responses into a unified diagnostic and prognostic framework. Such an index may facilitate the early detection of hypoxia-driven fibrogenesis, improve risk stratification, and support monitoring of therapeutic interventions targeting oxidative and profibrotic pathways. [2-4,21] Accordingly, this review aims to systematically integrate experimental and clinical evidence linking intermittent hypoxia to oxidative stress and hepatic fibrogenesis in MAFLD, and to propose a Composite Oxidative-Fibrotic Index as a novel framework for biomarker-guided assessment and translational application.

MATERIALS AND METHODS

Literature Search Strategy

A thorough literature review was performed to find experimental and clinical studies that looked at the association between intermittent hypoxia, oxidative stress, and liver fibrogenesis in metabolic dysfunction-associated fatty liver disease (MAFLD). We used the keywords "intermittent hypoxia," "obstructive sleep apnea," "MAFLD/NAFLD," "oxidative stress," "reactive oxygen species," "Nrf2," "HIF-1α," "hepatic stellate cells," "TGF-β," "α-SMA," "collagen," "MMP," "TIMP," and "liver stiffness" to search for articles published between 2000 and 2025 in PubMed, Scopus, Web of Science, and Google Scholar. A total of 186 records were identified through database searches, after removing duplicates, 142 articles remained for title and abstract screening. Of these, 78 articles were assessed for eligibility, and 41 studies fulfilling the inclusion criteria were ultimately included in this review.

Study Selection and Data Extraction

We included original experimental studies, clinical observational studies, and pertinent review articles published in English if they:

1) Examined intermittent hypoxia or hypoxia-related conditions
2) Evaluated oxidative stress biomarkers or hypoxia-responsive signaling
3) Assessed fibrogenic pathways or fibrosis-related indicators in the liver.

Studies concentrating on non-hepatic tissues or devoid of molecular or biomarker data were omitted. We took data on oxidative stress markers (MDA, antioxidant enzymes, Nrf2, HIF-1α), profibrotic mediators (TGF-β1, α-SMA, collagen, MMP/TIMP), and non-invasive fibrosis parameters (liver stiffness measurement) and put them together in a way that supports the idea of a Composite Oxidative-Fibrotic Index.

RESULTS

Integrated Evidence of the Oxidative-Fibrotic Axis in Hypoxia-Associated MAFLD

The literature reviewed consistently demonstrated that intermittent hypoxia causes the liver to make too many reactive oxygen species, damage lipids, and weaken its own antioxidant systems. Elevated malondialdehyde concentrations and diminished activities of superoxide dismutase, catalase, and glutathione peroxidase were noted in both experimental and clinical contexts, signifying a sustained redox imbalance during hypoxia-reoxygenation cycles.[1-3] Transforming growth factor-β1 (TGF-β1) is widely acknowledged as the principal profibrotic cytokine that stimulates HSC activation and ECM production. Hypoxia and oxidative stress augment TGF-β1 transcription and signaling via HIF-1α-dependent and redox-sensitive pathways, resulting in the phosphorylation of SMAD2/3 and the subsequent activation of collagen type I and III genes. Experimental models of intermittent hypoxia coupled with metabolic stress exhibit significant upregulation of hepatic TGF-β1 expression, alongside an increase in α-SMA-positive stellate cells and expedited fibrotic remodeling.[4-6]

Altered extracellular matrix turnover is marked by an increased expression of tissue inhibitors of metalloproteinases and disrupted ratios of matrix metalloproteinases (MMPs) to tissue inhibitors of metalloproteinases (TIMPs), which further contributes to net matrix accumulation. [6-8] In clinical settings, patients experiencing intermittent hypoxia or obstructive sleep apnea have demonstrated elevated liver stiffness measurements and fibrosis scores. These metrics correlate with the severity

of nocturnal oxygen desaturation and the levels of circulating profibrotic mediators. The mechanistic interplay between intermittent hypoxia, oxidative stress, and fibrogenesis is summarized in figure 1.

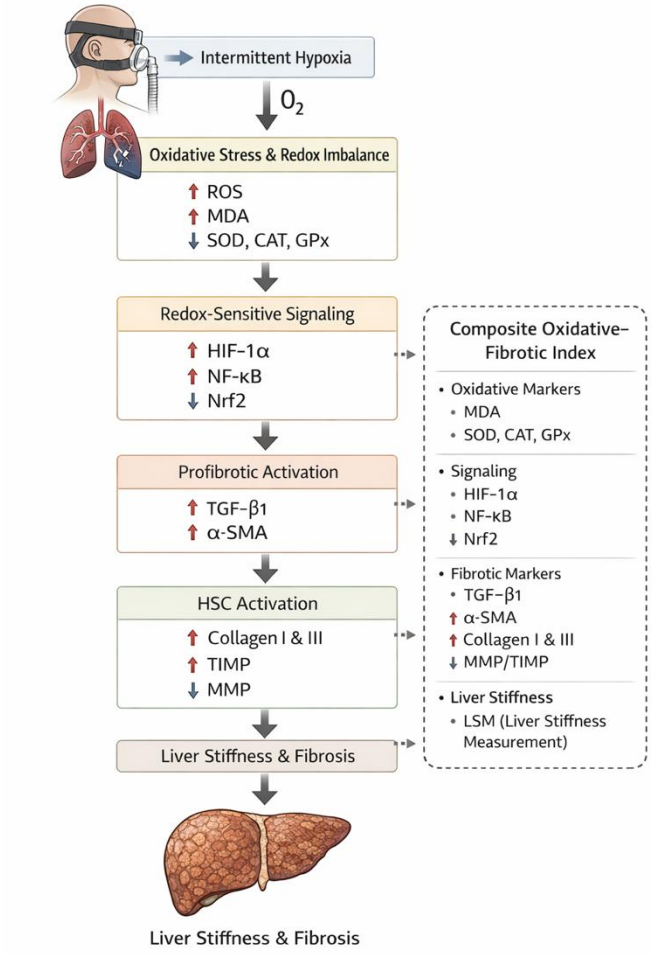

Figure 1. Mechanistic pathway linking intermittent hypoxia to liver fibrosis and the proposed composite oxidative-fibrotic index.

Intermittent hypoxia induces repetitive hypoxia-reoxygenation cycles, leading to excessive reactive oxygen species (ROS) generation and redox imbalance, characterized by increased malondialdehyde (MDA) levels and reduced antioxidant enzyme activity (SOD, CAT, and GPx). [8-10, 12,14-16]. This oxidative environment activates redox-sensitive signaling pathways, including hypoxia-inducible HIF-1α and NF-κB, along with impaired nuclear factor erythroid 2-related factor 2 (Nrf2). [18-22,28] These pathways promote profibrotic signaling, particularly transforming TGF-β1 and α-SMA, leading to HSC activation. [4,6,23,24,26] Activated HSCs enhance ECM remodeling, characterized by increased collagen deposition and imbalance between metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), ultimately resulting in increased liver stiffness and fibrosis. [1-3,6-8,34-36] The proposed composite oxidative-fibrotic index integrates oxidative stress markers, signaling mediators, fibrogenic markers, and liver stiffness measurement (LSM) into a unified framework for early detection and monitoring of fibrosis progression in hypoxia-associated MAFLD. [19,23-24,39] The studies we looked at demonstrateed that oxidative stress markers, hypoxia-

responsive transcription factors, fibrogenic cytokines, cellular activation markers, and biomechanical indicators of fibrosis all worked together to create a pathophysiological continuum

DISCUSSION

Intermittent Hypoxia and Oxidative Stress Biomarkers

Intermittent hypoxia is characterized by repeated cycles of reduced oxygen tension followed by rapid reoxygenation, a pattern that closely mimics ischemia-reperfusion injury at both cellular and subcellular levels. This oscillating oxygen profile leads to significant mitochondrial dysfunction and the excessive production of reactive oxygen species (ROS), primarily superoxide anions, hydrogen peroxide, and hydroxyl radicals. During the reoxygenation phase, there is a marked increase in electron leakage from complexes I and III of the mitochondrial respiratory chain. This phenomenon triggers an oxidative burst, leading to damage to lipids, proteins, and DNA. The resulting redox imbalance in the liver disrupts the equilibrium of hepatocytes, alters the function of sinusoidal endothelial cells, and creates a pro-oxidant microenvironment that promotes signaling pathways associated with inflammation and fibrosis. [8-10] Lipid peroxidation products are widely recognized as key quantitative indicators of oxidative stress in liver damage related to low oxygen levels. Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) result from the peroxidation of polyunsaturated fatty acids and serve as markers for the degree of oxidative damage to cellular membranes. Experimental models of intermittent hypoxia and MAFLD associated with hypoxia exhibit consistent and significant increases in both hepatic and circulating levels of MDA, which correlate with the severity of steatosis, inflammatory infiltration, and early stages of fibrotic remodeling. [5,11,12] These aldehydic by-products serve as biomarkers and bioactive mediators, worsening cellular injury by forming adducts with proteins and nucleic acids and perpetuating oxidative and inflammatory cascades. [13] Endogenous antioxidant defense systems serve as the primary counter-regulatory mechanism against the accumulation of reactive oxygen species (ROS) induced by hypoxia. Superoxide dismutase (SOD) catalyzes the conversion of superoxide into hydrogen peroxide, which is then transformed into water and oxygen by catalase (CAT) and glutathione peroxidase (GPx). In situations of sustained or repeated hypoxic exposure, the activity of these enzymes often decreases, indicating a potential exhaustion or downregulation of antioxidant capacity. Research has demonstrated reduced activities of SOD, CAT, and GPx in experimental models of intermittent hypoxia, as well as in patients suffering from hypoxia-associated metabolic liver disease, suggesting a disruption between ROS production and detoxification processes. [14-16]

The ratio of lipid peroxidation products to antioxidant enzyme activity serves as a functional index of redox status and has been suggested as a sensitive marker for early oxidative damage preceding overt histological fibrosis. [17] Redox-sensitive signaling pathways, particularly hypoxia-inducible factor-1α (HIF-1α) and nuclear factor erythroid 2-related factor 2 (Nrf2), play a crucial role in regulating oxidative stress at the transcriptional level. The stabilization of HIF-1α in low oxygen conditions increases the expression of genes involved in glycolytic metabolism, angiogenesis, and cell survival. However, persistent or cyclical activation of HIF-1α has been demonstrated to worsen the production of mitochondrial reactive oxygen species (ROS) and to interact with profibrotic mediators, such as transforming growth factor-β. [18-20]

Nrf2 operates as the master regulator of antioxidant gene expression, overseeing the transcription of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase-1 through antioxidant response elements. When Nrf2 activation is impaired, or the

Nrf2-Keap1 axis is disrupted under conditions of chronic intermittent hypoxia, there is inadequate induction of cytoprotective enzymes, leading to an accumulation of oxidative damage. [11,21,22] The rise in lipid peroxidation markers, the inhibition of enzymatic antioxidant defenses, and the dysregulation of HIF-1α and Nrf2 signaling collectively form a cohesive set of oxidative stress biomarkers indicative of the redox effects of intermittent hypoxia in MAFLD. These parameters signify oxidative injury and elucidate the upstream mechanisms that initiate inflammatory activation and subsequent fibrogenesis driven by hepatic stellate cells. [23-25] As a result, they make up the oxidative part of the proposed Composite Oxidative-Fibrotic Index and are the molecular basis for connecting hypoxic stress to progressive liver fibrosis.

Hypoxia-Responsive and Inflammatory Signaling: A Connection between Oxidative Stress and Fibrogenesis

Intermittent hypoxia not only causes oxidative stress, but it also turns on a complicated network of signaling pathways that respond to hypoxia and inflammation. These pathways act as a molecular bridge between redox imbalance and liver fibrogenesis. Hypoxia-inducible factor-1α (HIF-1α) is a key part of this response. During hypoxic phases, prolyl hydroxylase activity is stopped, which keeps HIF-1α stable and lets it escape proteasomal degradation. Cyclic stabilization of HIF-1α during intermittent hypoxia leads to the recurrent transcriptional activation of genes associated with glycolytic metabolism, angiogenesis, and cell survival. However, ongoing or repeated activation of HIF-1α has also been associated to increased production of mitochondrial reactive oxygen species (ROS), endothelial dysfunction, and the initiation of profibrotic signaling in the liver. [14,19] HIF-1α regulates fibrogenic pathways both directly and indirectly through its interactions with transforming growth factor-β (TGF-β), platelet-derived growth factor, and vascular endothelial growth factor. This regulation facilitates the proliferation, migration, and trans differentiation of hepatic stellate cells (HSCs) into collagen-producing myofibroblasts. Research conducted in models of intermittent hypoxia and metabolic dysfunction-associated fatty liver disease (MAFLD) demonstrates that activating HIF-1α in liver and stellate cells increases levels of α-smooth muscle actin (α-SMA), collagen type I, and connective tissue growth factor. This indicates a direct connection between the detection of low oxygen levels and alterations in the structure of the extracellular matrix.[24,26] The oxidative stress generated during cycles of hypoxia and reoxygenation activates redox-sensitive inflammatory pathways, particularly the nuclear factor-κB (NF-κB) pathway. Reactive oxygen species (ROS) lead to the degradation of IκB, allowing NF-κB to translocate to the nucleus, where it initiates the production of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and monocyte chemoattractant protein-1. These cytokines promote the activation of Kupffer cells and the recruitment of macrophages, resulting in a chronic inflammatory microenvironment. This environment works in tandem with hypoxia-driven signaling to further enhance the activation of hepatic stellate cells (HSC) and the process of fibrogenesis. [4,6,14]

Crosstalk between HIF-1α and NF-κB further strengthens this process. NF-κB can transcriptionally upregulate HIF-1α, and HIF-1α can increase the expression of inflammatory genes. This creates a positive feedback loop that keeps both hypoxic adaptation and inflammatory amplification going when there is intermittent hypoxia. This interaction is especially important in MAFLD, where metabolic stress, lipotoxicity, and hypoxia come together to keep the body in a state of low-grade chronic inflammation and constant profibrotic signaling.[4,6] Nuclear factor erythroid 2-related factor 2 (Nrf2) serves as a key regulator of antioxidant and anti-inflammatory responses, counteracting various pathological pathways. Under normal physiological conditions, the activation of Nrf2 triggers the expression of cytoprotective and antioxidant genes while simultaneously inhibiting NF-κB-dependent transcription. However, chronic intermittent hypoxia and persistent

metabolic stress can impair Nrf2's responsiveness. This impairment may lead to insufficient antioxidant defense and a loss of inhibitory control over inflammatory and fibrogenic pathways. [27-29] Lowering Nrf2 activity has been associated to stronger TGF-β signaling, increased levels of α-SMA, and faster collagen deposition. This phenomenon facilitate early detection hepatic stellate cells to become active and liver fibrosis to get worse. [30]

HIF-1α-mediated hypoxia sensing, NF-κB-driven inflammatory activation, and Nrf2-regulated antioxidant defense form a cohesive signaling axis that converts transient hypoxic stress into prolonged profibrotic activation. Dysregulation of this axis leads to ongoing oxidative damage, heightened inflammation, and the transdifferentiation of stellate cells, establishing a mechanistic continuum that connects redox imbalance to structural liver remodeling in hypoxia-associated MAFLD. [11,32] These pathways constitute the signaling core of the proposed Composite Oxidative-Fibrotic Index, enhancing biochemical oxidative markers and structural fibrosis indicators within a cohesive framework for the early detection and risk stratification of fibrosis progression.

Fibrogenic Biomarkers and the Activation of Hepatic Stellate Cells

The activation of hepatic stellate cells (HSCs) is a crucial cellular event in the development of liver fibrosis. This activation represents the final step in a process where oxidative stress, hypoxia-responsive signaling, and chronic inflammation contribute to the accumulation of extracellular matrix (ECM). In a healthy liver, HSCs remain in a dormant state and store vitamin A. However, under conditions of intermittent hypoxia and persistent redox imbalance, HSCs undergo transdifferentiation into proliferative, contractile, and collagen-secreting myofibroblasts. This change is characterized by the de novo expression of α-smooth muscle actin (α-SMA) and an excessive accumulation of fibrillar collagens. [23,24,26] Transforming growth factor-β1 (TGF-β1) is recognized as the primary profibrotic cytokine that activates hepatic stellate cells (HSC) and promotes extracellular matrix (ECM) production. Hypoxia and oxidative stress enhance the transcription and signaling of TGF-β1 through both HIF-1α-dependent and redox-sensitive pathways. This leads to the phosphorylation of SMAD2/3, which subsequently activates the genes responsible for collagen types I and III. Experimental models that simulate intermittent hypoxia combined with metabolic stress demonstrate a significant increase in hepatic TGF-β1 expression, along with a rise in α-SMA-positive stellate cells and accelerated fibrotic remodeling. [4,8,33] Consequently, circulating and tissue levels of TGF-β1 serve as reliable molecular biomarkers that reflect the extent of hypoxia-induced fibrogenic signaling. Circulating and tissue levels of TGF-β1 thus function as reliable molecular biomarkers indicative of the magnitude of hypoxia-induced fibrogenic signaling. α-SMA is the most common cellular marker for activated HSCs, and it is a direct histological and molecular sign of fibrogenic transformation. Elevated α-SMA expression has been consistently documented in animal models subjected to intermittent hypoxia and in patients with hypoxia-related MAFLD, where it correlates with collagen deposition, sinusoidal capillarization, and the deterioration of hepatic microcirculation. [19,23,26] The joint evaluation of TGF-β1 and α-SMA signifies both upstream profibrotic signaling and downstream cellular effector activation in the fibrotic cascade.

The excessive accumulation of extracellular matrix components, notably collagen types I and III, signifies the structural characteristic of progressive fibrosis. Hypoxia-induced activation of HSCs results in increased transcription of the COL1A1 and COL3A1 genes, whereas oxidative stress inhibits matrix degradation by modifying the equilibrium between matrix metalloproteinases (MMPs) and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs). An elevated TIMP-1/MMP-1 or TIMP-2/MMP-2 ratio promotes net matrix accumulation and has been correlated with both experimental and clinical phases of MAFLD-related fibrosis. [1-3] Intermittent

hypoxia exacerbates this imbalance by enhancing HIF-1α-dependent TIMP expression and sustaining inflammatory cytokine production, which collectively impede collagen turnover and facilitate scar formation.

Table 1. Key oxidative, signaling, and fibrogenic biomarkers in hypoxia-associated MAFLD

Domain	Biomarker	Biological Role	Relevance in hypoxia-associated MAFLD
Oxidative stress	Malondialdehyde (MDA)	End-product of lipid peroxidation	Reflects oxidative damage induced by hypoxia–reoxygenation cycles
Antioxidant defense	Superoxide dismutase (SOD)	Converts superoxide into hydrogen peroxide	Decreased activity indicates impaired ROS detoxification
	Catalase (CAT)	Decomposes hydrogen peroxide into water and oxygen	Reduced levels reflect diminished antioxidant capacity
	Glutathione peroxidase (GPx)	Reduces hydrogen peroxide and lipid peroxides	Depletion suggests oxidative stress imbalance
Hypoxia-responsive signaling	Hypoxia-inducible factor-1α (HIF-1α)	Regulates cellular adaptation to hypoxia	Promotes ROS production and profibrotic signaling under intermittent hypoxia
Inflammatory signaling	Nuclear factor erythroid 2-related factor 2 (Nrf2)	Master regulator of antioxidant gene expression	Impaired activation leads to insufficient antioxidant defense
Fibrogenic mediators	Transforming growth factor-β1 (TGF-β1)	Controls transcription of pro-inflammatory cytokines	Enhances chronic inflammation and fibrogenic activation
Celluler activation marker	α-smooth muscle actin (α-SMA)	Marker of activated hepatic stellate cells	Indicates transdifferentiation into fibrogenic myofibroblasts
Extracellular matrix (ECM)	Collagen type I and III	Major structural components of fibrotic tissue	Reflect accumulation of extracellular matrix
Matrix remodeling	Matrix metalloproteinases (MMPs)	Degrade extracellular matrix	Reduced activity contributes to fibrosis progression
	Tissue inhibitors of metalloproteinases (TIMPs)	Inhibit MMP activity	Increased levels promote ECM accumulation
Clinical/structural marker	Liver stiffness measurement (LSM)	Non-invasive assessment of liver elasticity	Reflects fibrosis severity and disease progression

Beyond tissue-based markers, non-invasive fibrosis assessment has become an essential component of translational and clinical evaluation. Liver stiffness measurement (LSM), obtained by transient elastography or shear wave elastography, reflects the mechanical consequences of collagen deposition and architectural distortion. Clinical studies in patients with obstructive sleep apnea and MAFLD demonstrate that the severity of nocturnal oxygen desaturation is independently associated with increased LSM values, enhanced fibrosis stages, and elevated circulating profibrotic mediators, including TGF-β1 and TIMP-1.[34-36] These observations offer robust translational evidence for the role of intermittent hypoxia as an autonomous contributor to fibrotic burden and confirm LSM as a functional biomarker that incorporates both molecular and structural aspects of fibrosis.

TGF-β1, α-SMA, collagen content, MMP/TIMP imbalance, and liver stiffness together make up a consistent set of fibrogenic biomarkers that demonstrate different parts of hypoxia-induced fibrotic remodeling, from signaling activation and cellular transdifferentiation to extracellular matrix accumulation and changes in tissue mechanics. When combined with markers that respond to oxidative stress and low oxygen levels, these factors make up the fibrotic part of the proposed Composite Oxidative-Fibrotic Index. This gives a mechanistically sound way to find fibrosis early, assess disease severity, and keep track of how it is getting worse in MAFLD, which is associate to low oxygen levels.[32,37,38] The key oxidative, signaling, and fibrogenic biomarkers involved in hypoxia-associated MAFLD are summarized in Table 1. [1-3,4,6,8,18-24,34-36]

The idea of a Composite Oxidative-Fibrotic Index

The progression of fibrosis in hypoxia-related MAFLD is a dynamic, multi-step process marked by the sequential and overlapping activation of oxidative stress, hypoxia-responsive signaling, inflammation, and extracellular matrix remodeling. Although numerous biomarkers that reflect these processes have been identified, their clinical and experimental applications often rely on single-parameter assessments. This approach fails to capture the interconnected pathophysiological continuum that associates redox imbalance to fibrogenic activation and tissue rigidity. Developing an integrative framework that combines oxidative and fibrotic parameters into a unified index could provide a more sensitive and mechanistically sound tool for the early detection and risk stratification of fibrosis progression.[23,24] An integrative framework that amalgamates oxidative and fibrotic parameters into a cohesive index may yield a more sensitive and mechanistically robust instrument for the early detection and risk stratification of fibrosis progression in MAFLD.[19,39]

When integrated with oxidative stress indicators and hypoxia-responsive signaling pathways, these components form the basis of the proposed Composite Oxidative-Fibrotic Index. This framework captures both upstream molecular drivers—such as reactive oxygen species, impaired antioxidant defenses, HIF-1α, and Nrf2 signaling—and downstream structural outcomes, including collagen deposition and tissue stiffening. Such integration enables a more comprehensive assessment of fibrosis progression and facilitates the identification of early, potentially reversible stages of disease. [2-4,21] Experimental and clinical studies consistently demonstrate that intermittent hypoxia exacerbates oxidative stress, inflammatory signaling, and profibrotic gene expression, thereby reinforcing the oxidative-fibrotic axis.[1,6]

In parallel, the severity of nocturnal hypoxemia has been associated with increased liver stiffness and elevated fibrogenic markers, independent of traditional metabolic risk factors.[6,34,38] From a translational perspective, this index may be operationalized by integrating circulating oxidative stress markers (e.g., malondialdehyde and antioxidant enzyme activity), profibrotic mediators (e.g., TGF-β1 and TIMP-1), and imaging-derived parameters such as liver stiffness measurement into a weighted composite score. This approach provides a unified framework for early detection, risk stratification, and monitoring of fibrosis progression in hypoxia-associated MAFLD.

Nutritional and Phytochemical Regulation of the Oxidative-Fibrotic Axis

Oxidative stress and hypoxia-responsive signaling play a key role in activating hepatic stellate cells and causing fibrosis. As a result, nutritional and phytochemical interventions that target redox imbalance and profibrotic pathways have become promising ways to stop or slow down the progression of fibrosis in people with MAFLD. Natural antioxidants, especially polyphenol-rich plant products, can affect many interconnected molecular pathways, such as Nrf2-mediated antioxidant defense, HIF-1α stabilization, NF-κB-dependent inflammation, and transforming growth

factor-β (TGF-β) signaling. This means that they can have many different effects on the oxidative-fibrotic axis. [23,24] At the same time, Nrf2 activation stops NF-κB-driven inflammatory signaling and indirectly stops profibrotic transcription that depends on TGF-β/SMAD. This limits the activation of hepatic stellate cells and the production of collagen.[2,40]

Ficus carica has garnered significant attention as a nutraceutical exhibiting potent antioxidant and cytoprotective attributes in organ injury associated with hypoxia. Experimental studies in intermittent hypoxia and metabolic liver disease models have demonstrated that dietary supplementation or extract administration of *Ficus carica* significantly lowers malondialdehyde levels, restores antioxidant enzyme activity, and improves Nrf2 signaling. [3,6,24,34] Additionally, Ficus carica's modulation of redox balance has been connect to the downregulation of HIF-1α expression, the suppression of pro-inflammatory cytokines, and the reduction of TGF-β1 and α-smooth muscle actin (α-SMA) expression, suggesting the inhibition of hepatic stellate cell transdifferentiation and fibrogenic activation.

In addition to redox regulation, numerous phytochemicals have been demonstrated to disrupt profibrotic signaling pathways directly. Polyphenols like resveratrol, quercetin, and catechins stop the TGF-β/SMAD and platelet-derived growth factor pathways, lower the production of collagen types I and III, and bring the matrix metalloproteinase/tissue inhibitor of metalloproteinase (MMP/TIMP) balance back to normal. This speeds up the breakdown of the extracellular matrix and stops scar tissue from building up.[8,15] These multitarget effects are especially important in intermittent hypoxia, where oxidative stress, hypoxia signaling, and inflammation work together to keep fibrogenesis going. From the standpoint of the proposed Composite Oxidative-Fibrotic Index, nutritional and phytochemical interventions present a distinctive opportunity to influence both upstream oxidative initiators and downstream fibrotic mediators. Reducing lipid peroxidation (such as lowering MDA), restoring antioxidant capacity (including SOD, CAT, GPx, and Nrf2), and inhibiting profibrotic mediators (such as TGF-β1, α-SMA, collagen, and TIMP-1) may result in a quantifiable enhancement of the composite score, accompanied by stabilization or reduction in liver stiffness.[4,6,11] Consequently, nutraceuticals like *Ficus carica* and other antioxidant-rich botanical products may function not only as adjunctive therapeutic agents but also as biological probes that confirm the mechanistic relationship between redox modulation and fibrogenic attenuation in hypoxia-related MAFLD. Their ability to simultaneously target oxidative stress, hypoxia-responsive transcription factors, inflammatory mediators, and extracellular matrix remodeling highlights the rationale for integrating nutritional strategies into a comprehensive management framework and biomarker-guided monitoring of fibrosis progression.

CONCLUSION

In conclusion, intermittent hypoxia is a significant and autonomous factor in the advancement of fibrosis in metabolic dysfunction-associated fatty liver disease (MAFLD) via prolonged oxidative stress, disruption of hypoxia-responsive signaling pathways, and stimulation of hepatic stellate cells. A persistent redox imbalance and pathways mediated by HIF-1α and TGF-β lead to the accumulation of extracellular matrix and increased liver stiffness, even when metabolic risk factors are similar. This review suggests a Composite Oxidative–Fibrotic Index that combines important oxidative stress markers (like malondialdehyde, antioxidant enzyme activity, Nrf2, and HIF-1α signaling) with important fibrogenic markers (like TGF-β1, α-smooth muscle actin, collagen deposition, MMP/TIMP imbalance, and liver stiffness). This integrative framework may enhance the early detection and risk stratification of hypoxia-driven fibrosis in MAFLD by consolidating upstream molecular drivers and downstream structural outcomes. The Composite Oxidative–Fibrotic Index offers a mechanistic

framework for forthcoming biomarker validation and therapeutic oversight, especially for interventions aimed at hypoxia, oxidative stress, and profibrotic signaling pathways.

Acknowledgements

We would like to thank the our colleagues for their encouragement and help during the preparation of this project.

Authors' contributions

All authors participated in the formulation and design of the review. The literature search, data collection, and analysis of oxidative stress, hypoxia-responsive signaling, and fibrogenic pathways were conducted collaboratively. The integration of molecular mechanisms and biomarkers, along with the creation of the composite oxidative-fibrotic index framework, was a collaborative effort. All authors contributed to the drafting and critical revision of the manuscript for significant intellectual content, approved the final version, and consented to be responsible for all facets of the work.

Funding

None.

Conflict of interest

The authors declare that they have no conflict of interest.

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