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Review

Research Progress on the Correlation between Obstructive Sleep Apnea Hypopnea Syndrome and Metabolic Related Fatty Liver Disease

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Abstract: Metabolic dysfunction-associated fatty liver disease (MAFLD), a newly named term for fatty liver disease, offers clearer diagnostic criteria compared to the traditional non-alcoholic fatty liver disease (NAFLD). This helps identify high-risk individuals earlier and improves diagnostic accuracy. The introduction of MAFLD not only reduces the need to rule out other liver diseases but also decreases the social stigma associated with the disease, making it widely accepted by multiple international societies. Obstructive sleep apnea hypopnea syndrome (OSAHS) is significantly linked to MAFLD. Chronic intermittent hypoxia (CIH), caused by OSAHS, promotes the development and progression of MAFLD through mechanisms such as excessive sympathetic nervous system activity, oxidative stress, and insulin resistance. This review aims to summarize and connect existing research findings to deepen the understanding of the relationship, diagnosis, and management of OSAHS and MAFLD patients.

Keywords: MAFLD; NAFLD; obstructive sleep apnea; metabolic disorders; treatment strategies

1. Introduction

1.1. Definitions and Epidemiology of MAFLD

1.1.1. MAFLD and NAFLD

Metabolic dysfunction-associated fatty liver disease (MAFLD) is the most common liver metabolic disease in the world, affecting about a quarter of the global adult population [1-3]. The main pathogenesis of MAFLD involves liver glucose metabolism, lipid metabolism disorder, insulin resistance (Insulin resistance, IR) and other factors [4,5]. With MAFLD as a new disease named in the medical field, it is considered to be an evolution of the spectrum of diseases (Nonalcoholic fatty liver disease, NAFLD), covering nonalcoholic fatty liver, nonalcoholic steatohepatitis, related cirrhosis, liver cancer and other diseases [6-8]. This new name emphasizes the dominant role of metabolic abnormalities in liver disease and establishes these factors as the core of studies on MAFLD and its extrahepatic associations [9].

In the context of overlapping histological features with alcoholic liver disease, how to define the clinical and research position of MAFLD has become the focus of academic attention [10,11]. The new diagnostic framework emphasizes the leading role of metabolic disorders in the pathogenesis of diseases, and includes obesity, type 2 diabetes and other metabolic abnormalities as necessary conditions. It reconstructs the diagnosis of diseases and provides a theoretical basis for systematic study of its extrinsic effects [1-3]. Although some preliminary studies have shown that MAFLD is more sensitive than NAFLD in screening for advanced liver fibrosis and identifying metabolic risk, the evidence on its

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clinical predictive value and long-term prognostic significance is still limited, and there is currently a lack of systematic validation in large-scale prospective cohorts [12]. Since the term was published, a large number of literatures has adopted the expression of MAFLD, and some international guidelines and expert consensus have also incorporated it into the standardized diagnosis and treatment terminology system [13-15]. However, there are still disputes on the uniformity and applicability of naming worldwide, especially in the promotion and practice of cross-regional and cross-population research, which still need to be further explored.

1.1.2. Diagnostic criteria of MAFLD

The diagnosis of MAFLD is based on the confirmation of hepatic fat deposition by imaging, histological evaluation or non-invasive biomarkers, combined with the characteristics associated with metabolic disorders for classification [1]. First, hepatic steatosis should reach at least 5% and other concurrent liver diseases (such as excessive alcohol consumption) should be excluded (Figure 1) [16]. Second, the diagnosis of MAFLD requires that patients have at least one metabolic disorder factor, including type 2 diabetes mellitus (T2DM), overweight or obesity classified by race-specific BMI. Third, it includes other metabolic risk factors associated with hepatic fat accumulation, such as hypertension, elevated blood glucose levels, insulin resistance (IR), high C-reactive protein (CRP), increased waist circumference, and dyslipidemia [17]. For individuals with a healthy weight, at least 2 of the 7 risk factors are required to confirm MAFLD. Liver steatosis can be diagnosed as MAFLD when combined with any of the metabolic risk stratification [1].

Figure 1. Diagnosis of MAFLD.

1.1.3. The difference between clinical diagnosis of NAFLD and MAFLD

The most significant difference between NAFLD and MAFLD is not only the formal recognition of the role of metabolic pathway in disease progression, but also that the diagnosis of MAFLD no longer requires the exclusion of the presence of concomitant liver disease [1,18]. In short, MAFLD primarily highlights the characteristics of the disease itself, rather than what it does not include. The diagnosis of MAFLD is independent of the presence of other types of liver disease. Compared to traditional NAFLD, MAFLD significantly increases the risk of cardiovascular events and is independently associated with occult atherosclerotic diseases. Therefore, diagnosing MAFLD has higher clinical value in indicating the need for cardiovascular assessment and intervention [19,20]. By identifying individual metabolic risk factors, MAFLD showed a significant advantage in controlling the risk of overweight, obesity and T2DM [1,18,21].

1.1.4. The harm and causes of fatty liver

Patients with fatty liver are not only at risk of cirrhosis and liver cancer, but also at risk of type 2 diabetes mellitus (T2DM), cardiovascular disease and kidney disease, which can severely affect the quality of life and health of patients [22,23]. Obesity is a common cause of fatty liver disease [24]. And is closely related to IR [23,25]. The risk of MAFLD in obese individuals is 3.5 times that of individuals with normal body mass index (BMI), and the severity of MAFLD tends to increase in individuals with higher BMI [26]. A growing

body of research suggests that adipose tissue has multiple functions in the body, some of which, such as brown fat, are harmless to the body [27]. In addition, the distribution of adipose tissue is closely related to an individual's health [27]. Therefore, it is not possible to simply judge the health status by the amount of overweight and fat accumulation, because there are different phenotypes such as metabolically healthy obesity and metabolically unhealthy non-obesity [28]. Lipid transport proteins, leptin, and tumor necrosis factor α (TNF-α) secreted by adipocytes [29]. Inflammatory mediators such as lipocalin and leptin can affect the development of MAFLD by regulating liver fat accumulation, IR and liver fibrosis [30].

Visceral o besity i ndex (VAI) was proposed by Amato et al [31]. It is a reliable predictor of visceral obesity, which combines waist circumference (Waist circumference, WC), BMI, waist-to-height ratio (Waist-to-height ratio, WHtR), triglycerides (Triglyceride, TG) and high-density lipoprotein cholesterol. In recent years, the relationship between VAI and metabolic-related diseases has been widely studied [32]. Lipid accumulation products (Lipid Accumulation Products, LAP) is an easily available indicator composed of WC and triglycerides. Compared with simple central obesity, LAP may be more reflective of the degree of lipid accumulation [33,34]. In addition, triglyceride-glucose index (Triglyceride-Glucose Index, TyG) is a reliable alternative index for identifying IR and evaluating the progression of liver fibrosis [35,36]. It has been shown to be associated with cardiovascular disease, diabetes, diabetic nephropathy and a variety of other diseases [37-39].

1.1.5. Triglyceride glucose index

At present, imaging is still the preferred tool for screening fatty liver [40,41]. In a number of studies, abdominal ultrasound has been recommended as a routine test for the initial assessment of liver fat deposition because of its economy, convenience, non-invasiveness and high clinical feasibility [40,41]. Moreover, Vibration-Controlled Transient Elastography (VCTE) has demonstrated excellent performance in practical applications, capable of simultaneously assessing the degree of liver steatosis and fibrosis levels. In contrast, CT and MRI are more suitable for the diagnosis and quantitative assessment of moderate to severe steatosis [42].

After confirming MAFLD, assessing the degree of fibrosis is crucial for stratifying the condition and predicting outcomes. In recent years, non-invasive indicators have gained significant attention in this field, including a range of serum-based biomarkers and liver stiffness parameters. The 2017-2018 National Health and Nutrition Examination Survey (NHANES) in the United States used VCTE technology to collect liver examination data from a large sample population [43]. The VCTE quantified the degree of steatosis by controlled attenuation parameter (Controlled Attenuation Parameter, CAP), and the grade of fibrosis was reflected by liver stiffness measurement (Liver Stiffness Measurement, LSM) [44,45]. However, there is still a lack of a recognized and universal non-invasive scoring system that can comprehensively and accurately integrate the comprehensive risk assessment of steatosis and fibrosis [46].

The combination of serum markers with other indicators is of great value in disease screening due to its convenience, low cost and high diagnostic accuracy [47,48]. Steady-state model evaluation of insulin resistance (HOMA-IR) has been widely used as an effective IR evaluation index for the diagnosis of IR-related diseases, and has become the diagnostic standard of MAFLD [1]. The relationship between NAFLD and parameters related to the TyG index, HOMA-IR has been explored in previous studies, but further evaluation is needed in a larger sample population [49,50]. Further studies showed that TyG-BMI, TyG-WC and TyG-WHtR were reliable indicators of MAFLD [49,51,52]. In addition, the diagnostic criteria for MAFLD include multiple metabolic indicators, and there is still a gap in the study of the role of these parameters in the evaluation of MAFLD and liver fibrosis. A study evaluated the diagnostic accuracy of HOMA-IR and TyG index related parameters in NAFLD, MAFLD, and liver fibrosis [17]. In conclusion, TyG-WC, TyG-

WHtR and TyG-BMI are effective screening indicators that can predict disease status and contribute to metabolic risk assessment and disease progression monitoring, especially in patients with NAFLD and MAFLD.

1.2. Definitions and Epidemiology of OSAHS

1.2.1. Definition and epidemiology

Obstructive sleep apnea hypopnea syndrome (OSAHS) is a common sleep-related respiratory dysfunction, which is characterized by recurrent hypopnea and apnea [53,54]. This abnormal breathing pattern can induce chronic intermittent hypoxia (CIH), which in turn leads to decreased arterial oxygen saturation, carbon dioxide retention, sleep structure disorder, frequent nighttime arousal, increased respiratory drive, and sustained activation of the sympathetic nervous system [55].

Epidemiological data show that the prevalence of OSAHS is about 24 percent in men and 9 percent in women among adults aged 30 to 60. Recent global data estimates suggest that the disease may affect up to 1 billion people [54,56]. In addition, OSAHS can occur in all age groups, and the risk of onset increases with age. In the elderly population, the frequency of nocturnal apnea events is usually higher than that of middle-aged and young adults, and tends to stabilize around age 65 [54,56]. Sex is also one of the important epidemiological characteristics of OSAHS. A large number of studies have shown that the risk of male patients is significantly higher than that of female patients, and the ratio of male to female patients is about 1.5:1 [57]. Although the exact biological mechanism of this gender difference is not fully understood, it is known that the incidence of OSAHS in postmenopausal women is on the rise, which may be related to a change in the pattern of fat distribution, i.e., fat tends to deposit in the upper body region, thereby increasing the likelihood of upper airway collapse [54]. In addition, the decrease of estrogen and progesterone levels in postmenopausal women is also thought to weaken the protective effect on the respiratory regulation center, further increasing the risk of disease [58].

In addition to gender and age, obesity is considered one of the most important risk factors. In addition, racial differences, family genetic background, and unhealthy lifestyle behaviors (such as alcohol consumption and smoking) are also closely associated with the risk of OSAHS [59]. The body mass index (BMI) is positively correlated with the occurrence of OSAHS. The increase of BMI is often accompanied by the increase of upper airway fat deposition, which leads to the increase of airway stenosis and collapse risk [60]. Obesity can also cause restricted lung ventilation function, reduced lung compliance and imbalance of ventilation/perfusion ratio, which further aggravates the burden of respiratory system [60]. Therefore, the prevalence of OSAHS is also significantly increasing in countries or regions with high obesity rates, indicating that weight gain plays a central role in the pathogenesis of the disease [61].

Clinically, the symptoms of OSAHS are often non-specific, including persistent snoring, sleep interruption, frequent awakening at night and excessive daytime sleepiness [54]. Therefore, it is currently recommended that patients with non-specific symptoms such as abnormal somnolence, increased daytime fatigue, and decreased sleep quality be screened for OSAHS. At the same time, individuals with symptoms such as snoring at night, recurrent awakening, or gastroesophageal reflux should be vigilant and consider further evaluation [62].

1.2.2. Diagnosis of OSAHS

According to current international recommendations, the diagnosis of OSAHS should be established after a sleep examination, polysomnography (PSG) monitoring as a diagnostic method, and the 2017 scoring rules should be applied [63]. These rules define apnea as a reduction in airflow by 90% and lasting at least 10 seconds, and hypoventilation as a decrease in flow of at least 50%, a drop in oxygen saturation of 3%, and a duration of at least 10 seconds. The severity of OSAHS is classified based on the number of apnea-

hypopnea events per hour of sleep and the Apnea-Hypopnea Index (AHI). AHI <5 indicates no OSAHS, AHI 5~15 indicates mild OSAHS, AHI 15~30 indicates moderate OSAHS, and AHI>30 indicates severe OSAHS. Sleep apnea events found in sleep records of individuals without symptoms are not considered OSAHS unless the AHI is greater than 15 [42].

1.3. OSAHS Is Associated with MAFLD

Approximately 21% of the global population is estimated to have OSAHS, and its prevalence increases with obesity, age, male sex, and upper airway abnormalities, and is associated with a variety of metabolic complications such as T2DM and MAFLD [64]. In recent years, MAFLD has become the most common cause of chronic liver disease worldwide and is in sync with the obesity epidemic. About one-third of the global population may have MAFLD, and NASH is expected to become the main indication for liver transplantation in the future [65,66]. A recent meta-analysis of individual data from France showed that the prevalence of fatty liver in patients with severe OSAHS was 85%, and 26% of these patients had signs of liver fibrosis [67]. A meta-analysis by Musso and colleagues found that OSAHS patients are twice as likely to develop fatty liver, steatohepatitis, and liver fibrosis compared to non-obese individuals, and this risk is independent of obesity. In the pediatric population, a link between OSAHS and MAFLD has also been observed, with 44% of non-obese and 68% of obese OSAHS children showing signs of MAFLD [67].

CIH and the associated hypoxia-reoxygenation cycle are considered key pathophysiological mechanisms in OSAHS-induced metabolic disorders and the progression of MAFLD. Although the specific molecular pathways by which OSAHS affects liver metabolic function have not been fully elucidated, numerous studies have demonstrated a close relationship between the two. This association may be due to common obesity-related phenotypic features or may arise independently of body weight [68]. Moreover, multiple studies have observed a positive correlation between the severity of nocturnal hypoxemia in OSAHS and the pathological extent of MAFLD, suggesting that hypoxic load may play a central role in promoting liver lipid deposition and inflammatory responses. Additionally, recent research indicates that the MAFLD state, defined by the Fatty Liver Index (FLI), significantly increases the risk of OSAHS, supporting a bidirectional interaction between the two conditions [69,70]. Based on data from representative populations in the United States, further evidence suggests that MAFLD, characterized by elevated liver enzymes, is also closely associated with sleep disorders, reflecting a potential link between liver damage and abnormal sleep structure [71]. Although the above epidemiological and mechanistic studies provide preliminary evidence for the association between the two, there is still a lack of large-scale, prospective randomized controlled trials (RCT) to verify this causal pathway.

2. Research Progress on the Mechanism of OSAHS and MAFLD

2.1. The Effect of Obesity on Obstructive Sleep Apnea and Metabolic Related Fatty Liver Disease

OSAHS induces a variety of metabolic disorders through repeated CIH processes, and its downstream effects include a series of metabolic abnormalities such as excessive activation of the sympathetic nervous system, increased oxidative stress levels, chronic low inflammatory state, abnormal lipid metabolism, and insulin resistance. These changes are considered to be an important pathological basis for the association between OSAHS and MAFLD.

Obesity, especially central obesity, is not only an important risk factor for the occurrence of OSAHS, but also mediates its effects on the metabolic system through a variety of pathways. Traditionally, OSAHS is attributed to the anatomical narrowing of the upper airway caused by obesity, but the latest research shows that its pathogenesis is far more than structural abnormalities [72,73]. Metabolic changes associated with obesity, insulin resistance, glucose regulation imbalance and abnormal increase of inflammatory factors

such as leptin in circulation can all exacerbate the occurrence and development of OSAHS [73]. In addition, obesity may also lead to decreased upper airway muscle tone by activating the sympathetic nervous system and inducing inflammatory pathways associated with chronic low-level muscle activity, which can lead to airway collapse during sleep and increase the risk of central or obstructive apnea [72]. A recent systematic review and meta-analysis showed that about 50% of MAFLD patients were obese, and the prevalence of obesity was as high as 80% in patients who progressed to NASH [73]. The above data further emphasize the bridging role of obesity in the pathogenesis of OSAHS and MAFLD, suggesting that it may be an important mediator between the two.

2.2. Pathophysiology

There is currently no human study confirming the tissue-specific effects of CIH. Several studies using experimental mouse models have provided insights into the potential impact of CIH on the pathogenesis of MAFLD. Initially, a double hit mechanism was proposed, where (1) liver fat accumulation and IR occur, followed by (2) inflammatory damage caused by oxidative stress, leading to steatohepatitis and liver fibrosis [74]. Recently, a process called "multiple parallel strikes" has been proposed, which is thought to work through multiple mechanisms [74]. Insulin resistance and metabolic health, oxidative stress, intestinal microecological imbalance and molecular changes caused by CIH are thought to be involved in the pathogenesis of MAFLD.

2.3. Chronic Intermittent Hypoxia, Insulin Resistance and Metabolic Health

CIH plays a mediating role in the development of IR, T2DM, and glucose metabolism disorders, and this mechanism does not depend on obesity. CIH can induce systemic inflammation, primarily through the activation of the nuclear factor kappaB (NF-κB) signaling pathway. The activation of this transcription factor leads to the upregulation of various pro-inflammatory factors, contributing to cardiovascular and metabolic damage [74].

In addition, the persistent hypoxia and associated hypercapnia in CIH can stimulate peripheral chemoreceptors, which in turn induces autonomic dysfunction, manifested by increased sympathetic nervous system activity [75]. This abnormal neural regulation is closely linked to the imbalance in liver lipid metabolism. The underlying mechanisms include: the excessive activity of the sympathetic nervous system leading to elevated levels of catecholamines and cortisol. These hormonal changes not only reduce insulin sensitivity but also impair glucose uptake by peripheral tissues and enhance hepatic gluconeogenesis, thereby increasing the metabolic burden [76]. At the same time, CIH is accompanied by a large amount of reactive oxygen species (Reactive Oxygen Species, ROS), which can activate liver macrophages (Kupffer cells) and promote the aggregation of inflammatory cells, forming a local inflammatory microenvironment, thus further aggravating hepatic steatosis [77]. On the other hand, under hypoxic conditions, adipose tissue exhibits functional disorders, including enhanced proliferation of fat cells, increased lipolysis, and higher levels of inflammatory factor release. This process leads to a significant rise in the concentration of free fatty acids (FFAs) in the plasma. FFAs act as signaling mediators, further promoting liver lipid accumulation and gluconeogenesis, thus creating a vicious cycle that ultimately triggers and exacerbates IR [74].

IR promotes the increased expression of the SREBP-1c gene through the aforementioned mechanisms. The specific mechanisms include: (1) the downregulation of Insulin receptor substrate 2 (IRS-2), (2) the inhibition of FFA β-oxidation, (3) the inhibition of lipolysis, and (4) the activation of Phosphatidylinositol-3 kinase (PI3K) [78]. The increase of SREBP-1c promotes the generation of new fat, which eventually leads to the occurrence of fatty liver. The increase of insulin level also directly activates PI3K, leading to hepatocyte apoptosis and inflammation, and then causes steatohepatitis [78].

2.4. Hypoxia-Inducible Factor Activates the Relevant Signaling Pathway of MAFLD

Hypoxia-inducible factors (HIFs) induce the accumulation of lipids in hepatocytes, which leads to the development of MAFLD and further progresses to steatohepatitis and liver fibrosis [79]. The cellular mechanism of the human body is highly dependent on oxygen, and even a slight reduction in oxygen can trigger a rapid adaptive oxygen response, and the activation of HIF and NF-κB pathway is of great significance for the development of MAFLD [77]. Sleep fragmentation / CIH exposure activates the inflammatory cascade by upregulating the expression of HIF1a complex, inducing the expression of target genes, and inducing downstream effects on glucose and lipid metabolism, angiogenesis, and epithelial-mesenchymal transformation, thereby interacting with hypoxia response elements [77]. Recent studies have shown that CIH leads to an imbalance between Treg/Th17 cells (regulatory T cells/T helper cell 17) through the expression of the HIF1a subunit and subsequent activation of the mTOR-HIF1a-TLR4-IL-6 (mammalian rapamycin target protein-HIF1a-steroid receptor 4-interleukin 6) inflammatory pathway [80]. This process exacerbates oxidative stress and hypoxia, accelerating the progression of steatohepatitis and liver fibrosis.

There is growing evidence that, in addition to the activation of HIF1a, hypoxia-induced activation of HIF2a can also lead to upregulation of genes associated with free fatty acid (FFA) uptake and hepatic cell fat accumulation, while inhibiting fat synthesis and β-oxidation [40]. The study also showed that in hypoxic HepG2 cells, the increase of HIF2a could promote the expression of adipogenesis-related proteins, which further increased FFA uptake and lipofuscinosis [81]. The upregulation of HIF2a can also activate the NF-κB pathway, further exacerbating steatohepatitis [82].

2.5. Oxidative Stress and Chronic Inflammation Induced by Chronic Intermittent Hypoxia

Under hypoxic conditions, NF-κB activates Kupffer cells and generates ROS [40]. The increase in ROS interacts with FFAs, leading to lipid peroxidation, mitochondrial dysfunction and subsequent liver damage [83]. Repetitive sleep fragmentation and wakefulness may also trigger endothelial dysfunction and increase the recruitment of inflammatory cytokines (such as IL-6) [84]. In addition, Kupffer cells release inflammatory cytokines (e.g., IL-6, TNF-α), which are thought to promote the development of MAFLD and drive its progression to NASH [77]. A recent study on a mouse model explored how CIH regulates the development and progression of MAFLD through the NF-κB signaling pathway associated with nuclear factor erythropoietin-related factor 2 (NFR2) and receptor-interacting serine/threonine protein kinase 3 (RIPK3)-dependent necrotic apoptosis [85]. When RIPK3 is downregulated, hepatocyte necrotic apoptosis and the ensuing inflammation and oxidative stress are relieved. This finding opens a new research direction for exploring the therapeutic strategies of OSAHS-induced MAFLD.

2.6. Chronic Intermittent Hypoxia and Changes in Intestinal Flora

CIH induced by OSAHS can affect liver function by affecting the composition of intestinal microecology, which has been preliminarily verified in children. In animal experiments, mice exposed to CIH showed obvious damage to intestinal mucosal barrier function, increased intestinal permeability, and significantly increased levels of LPS and endotoxins [86]. This process is believed to trigger a low-level chronic inflammatory state and accelerate liver cell damage and dysfunction by activating the innate immune pathway of the liver, particularly through the upregulation of Toll-like receptor 4 (TLR4). These changes form one of the core mechanisms of the gut-liver axis dysregulation. In the context of OSAHS, this pathway may drive the onset and progression of MAFLD through the continuous activation of intestinal inflammatory signals.

3. Management Strategy

3.1. Principle of Integrated Management

There is currently a lack of unified management guidelines for patients with OSAHS and MAFLD. In clinical practice, the primary goal of interventions should be to identify and assess metabolic risks early, thereby reducing the incidence of cardiovascular complications and slowing disease progression. The basic treatment strategy primarily involves behavioral interventions and comprehensive lifestyle optimization, with a particular emphasis on non-pharmacological measures such as weight control, nutritional regulation, and exercise.

3.2. Behavioral/Lifestyle Changes

A large number of evidence-based studies have confirmed that weight loss through systematic dietary management and regular exercise can significantly improve the histopathological characteristics of MAFLD and the degree of respiratory abnormalities of OSAHS [40]. Vilare-Gomez et al. showed that when weight loss reached 7% to 10%, the inflammatory activity of the liver was significantly relieved, and some individuals could even reverse fatty hepatitis [40]. In addition, the apnea-hypopnea index (AHI) of OSAHS patients who lost more than 10 kg of body weight decreased by more than 9 times per hour [87].

In addition, independent of weight changes, physical exercise was associated with a reduction in the severity of OSAHS, a reduction in liver triglyceride accumulation, an improvement in fatty degeneration, and a decrease in liver stiffness of about 20% [40,88]. However, maintaining effective weight management over the long term remains challenging, and therefore a multidisciplinary integrated intervention strategy combining nutrition, sports medicine, psychological support and behavioral therapy is recommended to improve compliance and persistence of interventions.

3.3. Pharmacological Management

In recent years, a variety of metabolic modulatory drugs have been explored to improve the pathological state of both OSAHS and MAFLD [89]. Some antidiabetic drugs, especially glucagon-like peptide-1 (GLP-1) receptor agonists, have shown positive effects in improving AHI, reducing body weight and regulating liver enzyme levels [89]. For example, liraglutide showed good safety in randomized controlled studies and was effective in reducing the frequency of sleep-related breathing events and liver function abnormalities [90].

In addition, some antioxidants such as vitamin E have been reported to have potential in the treatment of MAFLD, although the evidence is not yet sufficient [40]. Currently, the US Food and Drug Administration (FDA) has not approved any specific drug for the treatment of MAFLD, but several new candidates such as obeticholic acid, elafibranor and selonsertib have entered phase III clinical trials and have shown initial improvement in liver inflammation and fibrosis [90]. Further validation of these drugs is expected to provide new treatment options for patients with MAFLD and OSAHS.

3.4. Continuous Airway Positive Pressure

Continuous positive airway pressure (CPAP) is the gold standard treatment for OSAHS. Although studies have shown an association between OSAHS and MAFLD, large-scale RCTs have not shown significant benefits of CPAP on blood glucose, IR, or inflammatory markers, except for improvements in blood pressure [90]. The lack of evidence may be due to the limited number of CPAP trials, poor compliance, or the fact that CPAP targets only CIH and does not include obesity in the multiple pathogenic mechanisms of MAFLD. Moreover, most existing studies have focused on short-term effects, and longer-term studies are needed to assess the true impact of CPAP on MAFLD.

4. Conclusions

Obstructive sleep apnea hypopnea syndrome (OSAHS) and metabolic fatty liver disease (MAFLD) are closely linked, showing significant interactions in epidemiology, pathogenesis, and clinical management. MAFLD is primarily diagnosed based on metabolic disorders, emphasizing factors such as obesity and type 2 diabetes more than traditional non-alcoholic fatty liver disease (NAFLD). Chronic intermittent hypoxia (CIH) caused by OSAHS, through mechanisms like excessive sympathetic nervous system activation, oxidative stress, insulin resistance, activation of the hypoxia-inducible factor (HIF) pathway, and dysregulation of the gut-liver axis, along with obesity (such as fat deposition in the upper airway and release of free fatty acids), promotes the development of MAFLD. Clinical management focuses on behavioral interventions; a weight loss of 7% to 10% can alleviate liver inflammation, regular exercise can improve liver fibrosis, and continuous positive airway pressure (CPAP) and GLP-1 receptor agonists have shown some effectiveness but limited evidence. Current research needs to verify the cross-population applicability of MAFLD diagnostic criteria, clarify the specific damage mechanisms of CIH to hepatocytes, and evaluate the long-term efficacy of interventions through long-term randomized controlled trials, providing more precise evidence-based support for the coordinated prevention and control of these two conditions.

References

1. M. Eslam, P. N. Newsome, S. K. Sarin, Q. M. Anstee, G. Targher, M. Romero-Gomez, et al., "A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement," *J. Hepatol.*, vol. 73, no. 1, pp. 202–209, 2020, doi: 10.1016/j.jhep.2020.03.039.
2. M. Eslam, A. J. Sanyal, and J. George, "Toward more accurate nomenclature for fatty liver diseases," *Gastroenterology*, vol. 157, no. 3, pp. 590–593, 2019, doi: 10.1053/j.gastro.2019.05.064.
3. M. Eslam, A. J. Sanyal, J. George, A. Sanyal, B. Neuschwander-Tetri, C. Tiribelli, et al., "MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease," *Gastroenterology*, vol. 158, no. 7, pp. 1999–2014, 2020, doi: 10.1053/j.gastro.2019.11.312.
4. R. Loomba, S. L. Friedman, and G. I. Shulman, "Mechanisms and disease consequences of nonalcoholic fatty liver disease," *Cell*, vol. 184, no. 10, pp. 2537–2564, 2021, doi: 10.1016/j.cell.2021.04.015.
5. G. I. Smith, M. Shankaran, M. Yoshino, G. G. Schweitzer, M. Chondronikola, J. W. Beals, et al., "Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease," *J. Clin. Invest.*, vol. 130, no. 3, pp. 1453–1460, 2020, doi: 10.1172/JCI134165.
6. A. Geier, M. E. Rinella, M. M. Balp, S. J. McKenna, C. A. Brass, R. Przybysz, et al., "Real-world burden of nonalcoholic steatohepatitis," *Clin. Gastroenterol. Hepatol.*, vol. 19, no. 5, pp. 1020–1029, 2021, doi: 10.1016/j.cgh.2020.06.064.
7. Q. M. Anstee, H. L. Reeves, E. Kotsiliti, et al., "From NASH to HCC: current concepts and future challenges," *Nat. Rev. Gastroenterol. Hepatol.*, vol. 16, pp. 411–428, 2019, doi: 10.1038/s41575-019-0145-7.
8. R. S. Taylor, R. J. Taylor, S. Bayliss, H. Hagström, P. Nasr, J. M. Schattenberg, et al., "Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis," *Gastroenterology*, vol. 158, no. 6, pp. 1611–1625, 2020, doi: 10.1053/j.gastro.2020.01.043.
9. H. Peng, L. Pan, S. Ran, M. Wang, S. Huang, M. Zhao, Z. Cao, Z. Yao, L. Xu, Q. Yang, and W. Lv, "Prediction of MAFLD and NAFLD using different screening indexes: A cross-sectional study in U.S. adults," *Front. Endocrinol.*, vol. 14, p. 1083032, 2023, doi: 10.3389/fendo.2023.1083032.
10. C. Gofton, Y. Upendran, M. H. Zheng, and J. George, "MAFLD: How is it different from NAFLD?" *Clin. Mol. Hepatol.*, vol. 29, Suppl., pp. S17–S31, Feb. 2023, doi: 10.3350/cmh.2022.0367.
11. C. O. Demirtas and Y. Yilmaz, "Metabolic-associated fatty liver disease: Time to integrate ground-breaking new terminology to our clinical practice?" *Hepatol. Forum*, vol. 1, no. 3, pp. 79–81, Sep. 2020, doi: 10.14744/hf.2020.2020.0024.
12. S. U. Lin, J. Huang, M. Wang, R. Kumar, Y. Liu, S. Liu, et al., "Comparison of MAFLD and NAFLD diagnostic criteria in real world," *Liver Int.*, vol. 40, no. 9, pp. 2082–2089, 2020, doi: 10.1111/liv.14548.
13. M. El-Shabrawi, I. Memon, D. Attia, and N. M. El-Koofy, "The International Society of Tropical Paediatrics (ISTP) endorses the redefinition of fatty liver disease," *J. Hepatol.*, vol. 76, no. 3, pp. 738–739, 2022, doi: 10.1016/j.jhep.2021.11.016.
14. M. Eslam, S. K. Sarin, V. W. S. Wong, et al., "The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease," *Hepatol. Int.*, vol. 14, pp. 889–919, 2020, doi: 10.1007/s12072-020-10094-2.
15. N. Mendez-Sanchez, M. Arrese, A. Gadano, C. P. Oliveira, E. Fassio, J. P. Arab, et al., "The Latin American Association for the Study of the Liver (ALEH) position statement on the redefinition of fatty liver disease," *Lancet Gastroenterol. Hepatol.*, vol. 6, no. 1, pp. 65–72, 2021, doi: 10.1016/S2468-1253(20)30340-X.

16. N. Chalasani, Z. Younossi, J. E. Lavine, M. Charlton, K. Cusi, M. Rinella, et al., "The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases," *Hepatology*, vol. 67, no. 1, pp. 328–357, 2018, doi: 10.1002/hep.29367.
17. Y. Xue, J. Xu, M. Li, and Y. Gao, "Potential screening indicators for early diagnosis of NAFLD/MAFLD and liver fibrosis: Triglyceride glucose index–related parameters," *Front. Endocrinol.*, vol. 13, Art. no. 951689, 2022, doi: 10.3389/fendo.2022.951689.
18. T. Kawaguchi, T. Tsutsumi, D. Nakano, M. Eslam, J. George, and T. Torimura, "MAFLD enhances clinical practice for liver disease in the Asia-Pacific region," *Clin. Mol. Hepatol.*, vol. 28, no. 2, pp. 150–163, Apr. 2022, doi: 10.3350/cmh.2021.0310.
19. M. A. Niriella, D. S. Ediriweera, A. Kasturiratne, S. T. De Silva, A. S. Dassanayaka, A. P. De Silva, et al., "Outcomes of NAFLD and MAFLD: results from a community-based, prospective cohort study," *PLoS One*, vol. 16, no. 2, Art. no. e0245762, 2021, doi: 10.1371/journal.pone.0245762.
20. G. T. S. Guerreiro, L. Longo, M. A. Fonseca, et al., "Does the risk of cardiovascular events differ between biopsy-proven NAFLD and MAFLD?," *Hepatol. Int.*, vol. 15, pp. 380–391, 2021, doi: 10.1007/s12072-021-10157-y.
21. T. Miyake, B. Matsuura, S. Furukawa, T. Ishihara, O. Yoshida, M. Miyazaki, et al., "Fatty liver with metabolic disorder, such as metabolic dysfunction-associated fatty liver disease, indicates high risk for developing diabetes mellitus," *J. Diabetes Investig.*, vol. 13, no. 7, pp. 1245–1252, 2022, doi: 10.1111/jdi.13772.
22. G. Targher, H. Tilg, and C. D. Byrne, "Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach," *Lancet Gastroenterol. Hepatol.*, vol. 6, no. 7, pp. 578–588, 2021, doi: 10.1016/S2468-1253(21)00020-0.
23. M. E. Khamseh, M. Malek, S. Jahangiri, et al., "Insulin resistance/sensitivity measures as screening indicators of metabolic-associated fatty liver disease and liver fibrosis," *Dig. Dis. Sci.*, vol. 69, pp. 1430–1443, 2024, doi: 10.1007/s10620-024-08309-9.
24. K. Trochimczyk, M. Flisiak-Jackiewicz, A. Bobrus-Chociej, A. Lebensztejn, M. Wojtkowska, J. Jamiołkowski, and D. M. Lebensztejn, "Biochemical and anthropometric indices of insulin resistance in obese and overweight children with metabolic dysfunction-associated fatty liver disease," *Med. Sci. Monit.*, vol. 30, p. e943375, Jul. 3, 2024, doi: 10.12659/MSM.943375.
25. S. Suwała and R. Junik, "Metabolic-associated fatty liver disease and the role of hormones in its aetiopathogenesis," *Endokrynol. Pol.*, vol. 75, no. 3, pp. 237–252, 2024, doi: 10.5603/ep.99689.
26. M. V. Machado and H. Cortez-Pinto, "NAFLD, MAFLD and obesity: brothers in arms?," *Nat. Rev. Gastroenterol. Hepatol.*, vol. 20, pp. 67–68, 2023, doi: 10.1038/s41575-022-00717-4.
27. Q. Yu, S. Huang, T. T. Xu, Y. C. Wang and S. Ju, "Measuring brown fat using MRI and implications in the metabolic syndrome," *J. Magn. Reson. Imaging*, vol. 54, no. 5, pp. 1377–1392, 2021, doi: 10.1002/jmri.27340.
28. M. Blüher, "Metabolically Healthy Obesity," *Endocr. Rev.*, vol. 41, no. 3, bnaa004, Jun. 2020, doi: 10.1210/endrev/bnaa004.
29. Y. Sakurai, N. Kubota, T. Yamauchi and T. Kadowaki, "Role of Insulin Resistance in MAFLD," *Int. J. Mol. Sci.*, vol. 22, no. 8, p. 4156, 2021, doi: 10.3390/ijms22084156.
30. C. Boutari and C. S. Mantzoros, "Adiponectin and leptin in the diagnosis and therapy of NAFLD," *Metabolism*, vol. 103, 154028, 2020, doi: 10.1016/j.metabol.2019.154028.
31. M. Tang, X.-H. Wei, H. Cao, Q. Zhen, F. Liu, Y.-F. Wang, N.-G. Fan and Y.-D. Peng, "Association between Chinese visceral adiposity index and metabolic-associated fatty liver disease in Chinese adults with type 2 diabetes mellitus," *Front. Endocrinol.*, vol. 13, 935980, 2022, doi: 10.3389/fendo.2022.935980.
32. Z. Niu, J. Chen, H. Wang, R. Wang, H. Peng, S. Duan and S. Yao, "Predictive Value of the Chinese Visceral Adiposity Index for Metabolic Dysfunction-Associated Fatty Liver Disease and Elevated Alanine Aminotransferase Levels in Nonobese Chinese Adults: A Cross-Sectional Study," *J. Inflamm. Res.*, vol. 17, pp. 3893–3913, 2024, doi: 10.2147/JIR.S468093.
33. H. Li, Y. Zhang, H. Luo and R. Lin, "The lipid accumulation product is a powerful tool to diagnose metabolic dysfunction-associated fatty liver disease in the United States adults," *Front. Endocrinol.*, vol. 13, 977625, 2022, doi: 10.3389/fendo.2022.977625.
34. S. A. Hosseini, M. Alipour, S. Sarvandian et al., "Assessment of the appropriate cutoff points for anthropometric indices and their relationship with cardio-metabolic indices to predict the risk of metabolic associated fatty liver disease," *BMC Endocr. Disord.*, vol. 24, p. 79, 2024, doi: 10.1186/s12902-024-01615-3.
35. S. Zhang, T. Du, J. Zhang et al., "The triglyceride and glucose index (TyG) is an effective biomarker to identify nonalcoholic fatty liver disease," *Lipids Health Dis.*, vol. 16, p. 15, 2017, doi: 10.1186/s12944-017-0409-6.
36. H. Tutunchi, F. Naeini, M. Mobasseri and A. Ostadrahimi, "Triglyceride glucose (TyG) index and the progression of liver fibrosis: A cross-sectional study," *Clin. Nutr. ESPEN*, vol. 44, pp. 483–487, 2021, doi: 10.1016/j.clnesp.2021.04.025.
37. J. Alizargar, C.-H. Bai, N.-C. Hsieh et al., "Use of the triglyceride-glucose index (TyG) in cardiovascular disease patients," *Cardiovasc. Diabetol.*, vol. 19, p. 8, 2020, doi: 10.1186/s12933-019-0982-2.
38. L. Wang, H.-L. Cong, J.-X. Zhang et al., "Triglyceride-glucose index predicts adverse cardiovascular events in patients with diabetes and acute coronary syndrome," *Cardiovasc. Diabetol.*, vol. 19, p. 80, 2020, doi: 10.1186/s12933-020-01054-z.
39. L. Lv, Y. Zhou, X. Chen, L. Gong, J. Wu and W. Luo, "Relationship Between the TyG Index and Diabetic Kidney Disease in Patients with Type-2 Diabetes Mellitus," *Diabetes Metab. Syndr. Obes.*, vol. 14, pp. 3299–3306, 2021, doi: 10.2147/DMSO.S318255.
40. A. Preshy and J. Brown, "A bidirectional association between obstructive sleep apnea and metabolic-associated fatty liver disease," *Endocrinol. Metab. Clin. North Am.*, vol. 52, no. 3, pp. 509–520, 2023, doi: 10.1016/j.ecl.2023.01.006.

41. L. Castera, M. Friedrich-Rust and R. Loomba, "Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease," *Gastroenterology*, vol. 156, no. 5, pp. 1264–1281, 2019, doi: 10.1053/j.gastro.2018.12.036.
42. J. A. Douglas, C. L. Chai-Coetzer, D. McEvoy et al., "Guidelines for sleep studies in adults—a position statement of the Australasian Sleep Association," *Sleep Med.*, vol. 36, Suppl. 1, pp. S2–S22, 2017, doi: 10.1016/j.sleep.2017.03.019.
43. E. Vilar-Gomez, R. Vuppalanchi, A. Mladenovic et al., "Prevalence of high-risk nonalcoholic steatohepatitis (NASH) in the United States: results from NHANES 2017–2018," *Clin. Gastroenterol. Hepatol.*, vol. 21, no. 1, pp. 115–124, 2023, doi: 10.1016/j.cgh.2021.12.029.
44. M. S. Siddiqui, R. Vuppalanchi, M. L. Van Natta et al., "Vibration-controlled transient elastography to assess fibrosis and steatosis in patients with nonalcoholic fatty liver disease," *Clin. Gastroenterol. Hepatol.*, vol. 17, no. 1, pp. 156–163, 2019, doi: 10.1016/j.cgh.2018.04.043.
45. P. J. Eddowes, M. Sasso, M. Allison et al., "Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease," *Gastroenterology*, vol. 156, no. 6, pp. 1717–1730, 2019, doi: 10.1053/j.gastro.2019.01.042.
46. Y. L. Wu, R. Kumar, M. F. Wang, M. Singh, J. F. Huang, Y. Y. Zhu and S. Lin, "Validation of conventional non-invasive fibrosis scoring systems in patients with metabolic associated fatty liver disease," *World J. Gastroenterol.*, vol. 27, no. 34, pp. 5753–5763, Sep. 2021, doi: 10.3748/wjg.v27.i34.5753.
47. R. Loomba and L. A. Adams, "Advances in non-invasive assessment of hepatic fibrosis," *Gut*, vol. 69, no. 7, pp. 1343–1352, 2020, doi: 10.1136/gutjnl-2018-317593.
48. V. W. S. Wong, L. A. Adams, V. de Lédinghen et al., "Noninvasive biomarkers in NAFLD and NASH—current progress and future promise," *Nat. Rev. Gastroenterol. Hepatol.*, vol. 15, pp. 461–478, 2018, doi: 10.1038/s41575-018-0014-9.
49. G. Sheng, S. Lu, Q. Xie et al., "The usefulness of obesity and lipid-related indices to predict the presence of non-alcoholic fatty liver disease," *Lipids Health Dis.*, vol. 20, p. 134, 2021, doi: 10.1186/s12944-021-01561-2.
50. M. Shimada, H. Kawahara, K. Ozaki et al., "Usefulness of a combined evaluation of the serum adiponectin level, HOMA-IR, and serum type IV collagen 7S level to predict the early stage of nonalcoholic steatohepatitis," *Am. J. Gastroenterol.*, vol. 102, no. 9, pp. 1931–1938, 2007, doi: 10.1111/j.1572-0241.2007.01322.x.
51. M. Malek, M. E. Khamseh, H. Chehrehgosha et al., "Triglyceride glucose-waist to height ratio: a novel and effective marker for identifying hepatic steatosis in individuals with type 2 diabetes mellitus," *Endocrine*, vol. 74, pp. 538–545, 2021, doi: 10.1007/s12020-021-02815-w.
52. H. Peng, J. Xiang, L. Pan et al., "METS-IR/HOMA-IR and MAFLD in U.S. adults: dose–response correlation and the effect mediated by physical activity," *BMC Endocr. Disord.*, vol. 24, p. 132, 2024, doi: 10.1186/s12902-024-01646-w.
53. M. M. Lyons, N. Y. Bhatt, A. I. Pack and U. J. Magalang, "Global burden of sleep-disordered breathing and its implications," *Respirology*, vol. 25, no. 7, pp. 690–702, 2020, doi: 10.1111/resp.13838.
54. R. Lv, X. Liu, Y. Zhang et al., "Pathophysiological mechanisms and therapeutic approaches in obstructive sleep apnea syndrome," *Sig. Transduct. Target. Ther.*, vol. 8, p. 218, 2023, doi: 10.1038/s41392-023-01496-3.
55. M. F. Pengo, S. Bonafini, C. Fava and J. Steier, "Cardiorespiratory interaction with continuous positive airway pressure," *J. Thorac. Dis.*, vol. 10, Suppl. 1, pp. S57–S70, Jan. 2018, doi: 10.21037/jtd.2018.01.39.
56. G. Salzano, F. Maglitto, A. Bisogno et al., "Obstructive sleep apnoea/hypopnoea syndrome: relationship with obesity and management in obese patients," *Acta Otorhinolaryngol. Ital.*, vol. 41, no. 2, pp. 120–130, Apr. 2021, doi: 10.14639/0392-100X-N1100.
57. J. Theorell-Haglöw, C. B. Miller, D. J. Bartlett, B. J. Yee, H. D. Openshaw and R. R. Grunstein, "Gender differences in obstructive sleep apnoea, insomnia and restless legs syndrome in adults–What do we know? A clinical update," *Sleep Med. Rev.*, vol. 38, pp. 28–38, 2018, doi: 10.1016/j.smrv.2017.03.003.
58. S. Laouafa, A. Ribon-Demars, F. Marcouiller et al., "Estradiol protects against cardiorespiratory dysfunctions and oxidative stress in intermittent hypoxia," *Sleep*, vol. 40, no. 8, zsx104, Aug. 2017, doi: 10.1093/sleep/zsx104.
59. X. Chen, R. Wang, P. Zee et al., "Racial/ethnic differences in sleep disturbances: the Multi-Ethnic Study of Atherosclerosis (MESA)," *Sleep*, vol. 38, no. 6, pp. 877–888, Jun. 2015, doi: 10.5665/sleep.4732.
60. S. C. Veasey and I. M. Rosen, "Obstructive sleep apnea in adults," *N. Engl. J. Med.*, vol. 380, no. 15, pp. 1442–1449, 2019, doi: 10.1056/NEJMcp1816152.
61. A. S. Gami, S. M. Caples and V. K. Somers, "Obesity and obstructive sleep apnea," *Endocrinol. Metab. Clin. North Am.*, vol. 32, no. 4, pp. 869–894, 2003, doi: 10.1016/S0889-8529(03)00069-0.
62. D. J. Gottlieb and N. M. Punjabi, "Diagnosis and management of obstructive sleep apnea: a review," *JAMA*, vol. 323, no. 14, pp. 1389–1400, 2020, doi: 10.1001/jama.2020.3514.
63. V. K. Kapur, D. H. Auckley, S. Chowdhuri et al., "Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline," *J. Clin. Sleep Med.*, vol. 13, no. 3, pp. 479–504, 2017, doi: 10.5664/jcsm.6506.
64. A. V. Benjafield, N. T. Ayas, P. R. Eastwood et al., "Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis," *Lancet Respir. Med.*, vol. 7, no. 8, pp. 687–698, 2019, doi: 10.1016/S2213-2600(19)30198-5.

65. M. H. Le, Y. H. Yeo, X. Li et al., "2019 global NAFLD prevalence: a systematic review and meta-analysis," *Clin. Gastroenterol. Hepatol.*, vol. 20, no. 12, pp. 2809–2817, 2022, doi: 10.1016/j.cgh.2021.12.002.
66. P. Sangro, M. de la Torre Aláez, B. Sangro et al., "Metabolic dysfunction–associated fatty liver disease (MAFLD): an update of the recent advances in pharmacological treatment," *J. Physiol. Biochem.*, vol. 79, pp. 869–879, 2023, doi: 10.1007/s13105-023-00954-4.
67. G. Musso, M. Cassader, C. Olivetti, F. Rosina, G. Carbone and R. Gambino, "Association of obstructive sleep apnoea with the presence and severity of non-alcoholic fatty liver disease: A systematic review and meta-analysis," *Obes. Rev.*, vol. 14, no. 5, pp. 417–431, 2013, doi: 10.1111/obr.12020.
68. O. A. Mesarwi, R. Loomba and A. Malhotra, "Obstructive sleep apnea, hypoxia, and nonalcoholic fatty liver disease," *Am. J. Respir. Crit. Care Med.*, vol. 199, no. 7, pp. 830–841, 2019, doi: 10.1164/rccm.201806-1109TR.
69. N. Kim, J.-H. Roh, H. Lee, D. Kim and S. J. Heo, "The impact of non-alcoholic fatty liver disease on sleep apnea in healthy adults: A nationwide study of Korea," *PLoS ONE*, vol. 17, no. 7, e0271021, 2022, doi: 10.1371/journal.pone.0271021.
70. G. E. Chung, E. J. Cho, J. J. Yoo et al., "Nonalcoholic fatty liver disease is associated with the development of obstructive sleep apnea," *Sci. Rep.*, vol. 11, 13473, 2021, doi: 10.1038/s41598-021-92703-0.
71. H. M. Mir, M. Stepanova, H. Afendy, R. Cable and Z. M. Younossi, "Association of sleep disorders with nonalcoholic fatty liver disease (NAFLD): a population-based study," *J. Clin. Exp. Hepatol.*, vol. 3, no. 3, pp. 181–185, 2013, doi: 10.1016/j.jceh.2013.06.004.
72. C. Arnaud, T. Bochaton, J. L. Pépin and E. Belaidi, "Obstructive sleep apnoea and cardiovascular consequences: pathophysiological mechanisms," *Arch. Cardiovasc. Dis.*, vol. 113, no. 5, pp. 350–358, 2020, doi: 10.1016/j.acvd.2020.01.003.
73. Z. M. Younossi, A. B. Koenig, D. Abdelatif, Y. Fazel, L. Henry and M. Wymer, "Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes," *Hepatology*, vol. 64, no. 1, pp. 73–84, 2016, doi: 10.1002/hep.28431.
74. E. Buzzetti, M. Pinzani and E. A. Tsochatzis, "The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD)," *Metabolism*, vol. 65, no. 8, pp. 1038–1048, 2016, doi: 10.1016/j.metabol.2015.12.012.
75. R. Iturriaga, J. Alcayaga, M. W. Chapleau and V. K. Somers, "Carotid body chemoreceptors: physiology, pathology, and implications for health and disease," *Physiol. Rev.*, vol. 101, no. 3, pp. 1177–1235, 2021, doi: 10.1152/physrev.00039.2019.
76. S. Khurana, N. Soda, M. J. A. Shiddiky, R. Nayak and S. Bose, "Current and future strategies for diagnostic and management of obstructive sleep apnea," *Expert Rev. Mol. Diagn.*, vol. 21, no. 12, pp. 1287–1301, 2021, doi: 10.1080/14737159.2021.2002686.
77. J. Cai, M. Hu, Z. Chen et al., "The roles and mechanisms of hypoxia in liver fibrosis," *J. Transl. Med.*, vol. 19, 186, 2021, doi: 10.1186/s12967-021-02854-x.
78. S. C. Pal, M. Eslam and N. Mendez-Sanchez, "Detangling the interrelations between MAFLD, insulin resistance, and key hormones," *Hormones*, vol. 21, pp. 573–589, 2022, doi: 10.1007/s42000-022-00391-w.
79. L. A. Barnes, Y. Xu, A. Sanchez-Azofra, E. A. Moya, M. P. Zhang, L. E. Crotty Alexander, A. Malhotra and O. Mesarwi, "Duration of intermittent hypoxia impacts metabolic outcomes and severity of murine NAFLD," *Front. Sleep*, vol. 2, 1215944, 2023, doi: 10.3389/frsle.2023.1215944.
80. J. Liu, W. Li, W. Zhu, W. He, H. Zhao, Y. Xiang et al., "Chronic intermittent hypoxia promotes the development of experimental non-alcoholic steatohepatitis by modulating Treg/Th17 differentiation," *Acta Biochim. Biophys. Sin.*, vol. 50, no. 12, pp. 1200–1210, 2018, doi: 10.1093/abbs/gmy131.
81. R. Cao, X. Zhao, S. Li, H. Zhou, W. Chen, L. Ren et al., "Hypoxia induces dysregulation of lipid metabolism in HepG2 cells via activation of HIF-2α," *Cell. Physiol. Biochem.*, vol. 34, no. 5, pp. 1427–1441, 2014, doi: 10.1159/000366348.
82. H. Cai, Z. Bai and R. L. Ge, "Hypoxia-inducible factor-2 promotes liver fibrosis in non-alcoholic steatohepatitis liver disease via the NF-κB signalling pathway," *Biochem. Biophys. Res. Commun.*, vol. 540, pp. 67–74, 2021, doi: 10.1016/j.bbrc.2021.01.002.
83. S.-J. Park, J. Garcia Diaz, E. Um and Y. S. Hahn, "Major roles of kupffer cells and macrophages in NAFLD development," *Front. Endocrinol.*, vol. 14, 1150118, 2023, doi: 10.3389/fendo.2023.1150118.
84. Y. Ji, Y. Liang, J. C. Mak and M. S. Ip, "Obstructive sleep apnea, intermittent hypoxia and non-alcoholic fatty liver disease," *Sleep Med.*, vol. 95, pp. 16–28, 2022, doi: 10.1016/j.sleep.2022.04.006.
85. H. Zhang, L. Zhou, Y. Zhou, L. Wang, W. Jiang, L. Liu, and H. Liu, "Intermittent hypoxia aggravates non-alcoholic fatty liver disease via RIPK3-dependent necroptosis-modulated Nrf2/NFκB signaling pathway," *Life Sci.*, vol. 285, p. 119963, Sep. 2021, doi: 10.1016/j.lfs.2021.119963.
86. X.-Z. Li, Z.-C. Xiong, S.-L. Zhang, Q.-Y. Hao, M. Gao, J.-F. Wang, J.-W. Gao, and P.-M. Liu, "Potential ferroptosis key genes in calcific aortic valve disease," *Front. Cardiovasc. Med.*, vol. 9, p. 916841, Jul. 2022, doi: 10.3389/fcvm.2022.916841.
87. C. Antza, G. Kostopoulos, S. Mostafa, K. Nirantharakumar, and A. Tahrani, "The links between sleep duration, obesity and type 2 diabetes mellitus," *J. Endocrinol.*, vol. 252, no. 2, pp. 125–141, Feb. 2022, doi: 10.1530/JOE-21-0155.
88. M. Mendelson, O. D. Lyons, A. Yadollahi, T. Inami, P. Oh, and T. D. Bradley, "Effects of exercise training on sleep apnoea in patients with coronary artery disease: a randomised trial," *Eur. Respir. J.*, vol. 48, no. 1, pp. 142–150, Jul. 2016, doi: 10.1183/13993003.01897-2015.

89. J. Iqbal, H. X. Wu, N. Hu, Y. H. Zhou, L. Li, F. Xiao, and H. D. Zhou, "Effect of glucagon-like peptide-1 receptor agonists on body weight in adults with obesity without diabetes mellitus—a systematic review and meta-analysis of randomized control trials," *Obes. Rev.*, vol. 23, no. 6, p. e13435, Jun. 2022, doi: 10.1111/obr.13435.
90. J. Khoo, J. Hsiang, R. Taneja, N. M. Law, and T. L. Ang, "Comparative effects of liraglutide 3 mg vs structured lifestyle modification on body weight, liver fat and liver function in obese patients with non-alcoholic fatty liver disease: a pilot randomized trial," *Diabetes Obes. Metab.*, vol. 19, no. 12, pp. 1814–1817, Dec. 2017, doi: 10.1111/dom.13007.