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Non-alcoholic fatty liver disease and sleep disorders

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Abstract

Studies have shown that Nonalcoholic fatty liver disease (NAFLD) may be associated with sleep disorders. In order to explore the explicit relationship between the two, we systematically reviewed the effects of sleep disorders, especially obstructive sleep apnea (OSA), on the incidence of NAFLD, and analyzed the possible mechanisms after adjusting for confounding factors. NAFLD is independently associated with sleep disorders. Different sleep disorders may be the cause of the onset and aggravation of NAFLD. An excessive or insufficient sleep duration, poor sleep quality, insomnia, sleep-wake disorders , and OSA may increase the incidence of NAFLD. Despite some researches suggesting a unidirectional causal link between the two, specifically, the onset of NAFLD is identified as a result of changes in sleep characteristics, and the reverse relationship does not hold true. Nevertheless, there is still a lack of specific research explaining why individuals with NAFLD have a higher risk of developing sleep disorders. Further research is needed to establish a clear relationship between NAFLD and sleep disorders. This will lay the groundwork for earlier identification of potential patients, which is crucial for earlier monitoring, diagnosis, effective prevention, and treatment of NAFLD.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases, with an estimated global prevalence of NAFLD at 25% [1]. Its epidemiological and demographic characteristics varies around the world, which is positively correlated with obesity prevalence [2]. In China, due to unhealthy human lifestyle behaviors, the prevalence of NAFLD has risen sharply, with 23.8% in 2001 up to 32.9% in 2018, which is gradually replacing hepatitis B as the main cause of chronic liver disease [3]. NAFLD is a systemic disease characterized by steatosis and abnormal accumulation of fat in hepatic parenchymal cells, metabolically stressed liver damage closely related to insulin resistance (IR), as well as certain genetic factors, possessing complex multifactorial pathogenesis and heterogeneous clinical manifestations [4, 5]. Non-alcoholic steatohepatitis (NASH), a subtype of NAFLD, is a potential progressive liver disease that may lead to cirrhosis, hepatocellular carcinoma, and even death [6]. Various extrahepatic manifestations such as chronic kidney disease, cardiovascular disease and obstructive sleep apnea (OSA), is also associated with NAFLD, imposing a substantial burden and economic impact on patients and society [7].In the past decades, studies have found that sleep disorders might facilitate the development of NAFLD accompanied by obesity, inflammation, IR, as well as glucose or lipid metabolic disorders [8]. The underlying mechanism may be related to the increased secretion of stress hormones (such as cortisol and catecholamines) by activating the hypothalamic-pituitary-adrenal (HPA) axis, thereby increasing the risk of the metabolic syndrome [9]. Nowadays, there is an increasing interest in understanding whether different sleep patterns can serve as causative factors for NAFLD. Current research on sleep stage changes in non-alcoholic fatty liver disease (NAFLD) patients shows inconsistent findings. Some studies indicate a possible decrease in the percentage of REM sleep in NAFLD patients[10]. Additionally, other studies suggest changes in NREM sleep structure, such as a potential decrease in the proportion of slow wave sleep. Further large-scale research is needed to gain a better understanding of these sleep characteristics in NAFLD patients[11]. [LB1] In this mini review, the association between different sleep traits and NAFLD was investigated, the recent advances concerning the

correlations between NAFLD and sleep disorders were summed up, the complicated and interrelated relationship between OSA and NAFLD were elucidated, as well as their identical and different mechanisms and clinical features were discussed. Furthermore, the effect of CPAP treatment on OSA was also summarized, aiming to provide current and future therapeutic implications for NAFLD.

Annotation 1

NON-ALCOHOLIC FATTY LIVER DISEASE AND SLEEP DISORDERS

Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases, with an estimated global prevalence of NAFLD at 25% [1 .[Its epidemiological and demographic characteristics varies around the world, which is positively correlated with obesity prevalence [2] .In China, due to unhealthy human lifestyle behaviors, the prevalence of NAFLD has risen sharply, with 23.8% in 2001 up to 32.9% in 2018, which is gradually replacing hepatitis B as the main cause of chronic liver disease [3]. NAFLD is a systemic disease characterized by steatosis and abnormal accumulation of fat in hepatic parenchymal cells, metabolically stressed liver damage closely related to insulin resistance) IR ,(as well as certain genetic factors, possessing complex multifactorial pathogenesis and heterogeneous clinical manifestations [4, 5 .[Non-alcoholic steatohepatitis (NASH), a subtype of NAFLD, is a potential progressive liver disease that may lead to cirrhosis, hepatocellular carcinoma, and even death [6 .[Various extrahepatic manifestations such as chronic kidney disease, cardiovascular disease and obstructive sleep apnea (OSA), is also associated with NAFLD, imposing a substantial burden and economic impact on patients and society [7].In the past decades, studies have found that sleep disorders might facilitate the development of NAFLD accompanied by obesity, inflammation, IR, as well as glucose or lipid metabolic disorders [8]. The underlying mechanism may be related to the increased secretion of stress hormones (such as cortisol and catecholamines) by activating the hypothalamic-pituitary-adrenal (HPA) axis, thereby increasing the risk of the metabolic syndrome [9].

Nowadays, there is an increasing interest in understanding whether different sleep patterns can serve as causative factors for NAFLD. Current research on sleep stage changes in non-alcoholic fatty liver disease (NAFLD) patients shows inconsistent findings .Some studies indicate a possible decrease in the percentage of REM sleep in NAFLD patients[10]. Additionally, other studies suggest changes in NREM sleep structure, such as a potential decrease in the proportion of slow wave sleep. Further large-scale research is needed to gain a better understanding of these sleep characteristics in NAFLD patients[11 .[[LB1 [In this mini review, the association between different sleep traits and NAFLD was investigated, the recent advances concerning the correlations between NAFLD and sleep disorders were summed up, the complicated and interrelated relationship between OSA and NAFLD were elucidated, as well as their identical and different mechanisms and clinical features were discussed. Furthermore, the effect of CPAP treatment on OSA was also summarized, aiming to provide current and future therapeutic implications for NAFLD.

Annotation 1

PATHOGENESIS OF NAFLD

The pathogenesis of NAFLD is complex and multi-factorial. Previous studies have confirmed its positive correlations with metabolic diseases such as obesity, IR, metabolic syndrome, and type 2 diabetes. Pathogenesis has been frequently probed and two hypotheses were successively proposed, namely the early proposed "two-hit" model and the current "multiple-hit theory". The "two-hit" model believes that IR and abnormal hepatic lipid accumulation is the first hit, while the oxidative stress and inflammation is the second one [12]; however, because other alternative factors including glucose and lipid metabolism disorders, intestinal flora disorder and epigenetic regulation were confirmed to be involved in the NAFLD development, the "multiple-hit theory" has been widely accepted nowadays [13]. In addition, a dysregulated circadian rhythm due to sleep modes changes has been implicated in the pathogenesis of NAFLD [14, 15]. As one of the most reliable markers of circadian rhythm, melatonin (MT) is also

involved in the NAFLD pathogenesis. It is known that MT promotes sleep, circadian rhythms, and neuroendocrine processes. Current evidence suggests that MT protects against liver damage by inhibiting oxidation, inflammation, hepatic stellate cell (HSC) proliferation, and hepatocyte apoptosis, thus inhibiting the progression of NAFLD[16]. [LB1] Ren, J. *et al* observed that melatonin could ameliorate FD (high-fat diet)/CIH (chronic intermittent hypoxia)-induced hepatocellular damage by activating SIRT1-mediated autophagy signaling [17].

CORRELATIONS BETWEEN SLEEP AND NAFLD

In this review, we see sleep duration, daytime napping, daytime sleepiness, sleep quality and sleep habits as sleep-related traits (Table 1). A randomized controlled trial indicates a causal relationship between sleep characteristics and NAFLD. The onset of NAFLD is the result of changes in sleep patterns, whereas alterations in sleep characteristics are not the cause of NAFLD. The causal relationship between the two is unidirectional[18].[LB2] Recent studies concerning the relationship between sleep duration and NAFLD suggest that short sleep duration and long daytime naps are the risk factors for NAFLD [19-21]. A cohort study has shown that in young adults, short sleep duration is independently associated with an increased risk of incident nonalcoholic fatty liver disease, regardless of the presence of intermediate/high fibrosis scores[22]. [LB3] Furthermore, a cross-sectional study found a decreasing trend in the proportion of NAFLD in pace with increased sleep duration in men, whereas in women, the proportion of NAFLD displayed a U-shaped distribution, with the lowest in the group (6-7 h of sleep) and the highest in the group (≤ 6 h or ≥ 8 h of sleep) [23]. Similarly, Meta-analysis relating to the relationship between sleep duration (or quality) and NAFLD incidence manifested that both short sleep duration (≤ 6 h) and long sleep duration (≥ 8 h) may increase the risk of NAFLD, and the incidence of NAFLD increases as the sleep duration decreased[24][LB4] [25]. Accordingly, a case-control study on NAFLD demonstrated that optimal sleep duration (7-9 h/d) is negatively associated with IR and liver stiffness in patients with NAFLD [26]. Taken together, both too short or too long sleep duration may increase the risk of NAFLD in both men and women.

In addition, there were differences in the association between sleep duration and NAFLD in different populations: 1) Taking gender into account, a community-based longitudinal cohort study concluded that short sleep duration reduced the risk of NAFLD in men but had no risk in women [27]While Liu *et al* found that sleep duration is an independent influencing factor for male NAFLD. The risk of NAFLD decreases with an increase in sleep duration in males, but there is also no significant correlation observed in females[28].[LB5] A cross-sectional survey involving 4828 participants suggested that sleep quality was associated with NAFLD, and there were also gender differences [29]. 2) Taking age into account, excessive nighttime sleep duration was associated with a moderately increased risk of NAFLD in a retrospective study targeted at the middle-aged or elderly men in China [30]. Besides, in another cohort study of middle-aged or elderly people in South Korea, a positive correlation was also found between excessive sleep duration and elevated NAFLD scores [31].

SLEEP DISORDERS AFFECT NAFLD

A population-based study showed that NAFLD is independently associated with sleep disorders after the adjustment of age, gender, and ethnicity [32]. Sleep disorders are present in NAFLD regardless of underlying cirrhosis[33]. [LB6] he prevalence of sleep disorders was significantly higher in individuals with NAFLD compared to controls; while the prevalence of NAFLD was higher in individuals with sleep disorders compared to those good sleepers [34]. Common sleep disorders associated with NAFLD include insomnia, daytime sleepiness, sleep-wake disorders and sleep-disordered breathing such as OSA（Table 2）.

Insomnia and daytime sleepiness

A Meta-analysis of seven studies showed that people with insomnia or excessive daytime sleepiness have an increased risk of NAFLD [35]. Patients with NAFLD may have more severe daytime sleepiness and shorter sleep duration[36]. And a mendelian randomization analyzed that trouble getting up in the morning and insomnia were associated with an increased risk of NAFLD[37]. [LB7] Similarly, a case-control study found that nearly 30% of patients with biopsy-proven NAFLD confirmed insomnia, and

the prevalence of NAFLD in insomnia patients was significantly higher than that in non-insomnia patients [38]. Furthermore, daytime sleepiness is significantly linked to the biochemical and histologic surrogates of NAFLD severity, not only positively correlated with liver enzymes and IR independent of cirrhosis, but also positively correlated with the degree of fibrosis [39].

Sleep-wake disorders

Sleep-wake disorder, also known as non-24-hour sleep-wake rhythm disorder (N24SWD), is a circadian rhythm sleep-wake disorder characterized by an inability to entrain to the 24-hour environment. Sleep-wake disorders may increase the risk of NAFLD in patients suffered from obesity, IR, inflammation, and disorders in glucose or lipid metabolism, resulting in weight gain by increasing the food-sensitive dopaminergic activity [40] and the circulation concentration of growth hormone-releasing peptide [41]. It is well-known that IR played a central role in the progression of hepatic steatosis and fibrosis. Therefore, IR may be a major intersection between sleep-wake disorders and NAFLD [42]. In addition, sleep-wake disorders can also facilitate glycometabolism, promote lipid mobilization in adipose tissue by increasing cortisol hormone concentrations and weakening the tissue response to insulin, and accelerate the transport of free fatty acids to the liver [43]. Increased sympathetic nervous system and adrenal cortical activity may lead to the adverse metabolic effects of sleep-wake disorders. In a comparative study, the sleep of healthy volunteers was experimentally fragmented at all stages using auditory and mechanical stimuli. After two nights of sleep fragmentation, the results indicated that insulin sensitivity and glucose effectiveness, i.e., the ability of glucose to mobilize itself was independent of the insulin response, were both decreased. And morning cortisol levels were elevated, the sympathetic nervous system was excited [44]. Sleep-wake disorders are also associated with elevated pro-inflammatory factors such as interleukin IL-1β, which are involved in the development of liver inflammation promoting NAFLD [45].

Sleep-disordered breathing

OSA is the most common sleep breathing disorder. A general population-based polysomnography study showed that the incidence of mild OSA was estimated to be 59% in men but 33% in women, while the incidence of moderate to severe OSA was estimated to be 30% in men but 13% in women [46]. It is characterized by episodes of apnea, hypopnea and sleep fragmentation (SF) due to restricted airflow in the collapsed upper airway during sleep [47]. It has been shown that SF-induced intermittent hypoxia (IH) and sleep deprivation are associated with IR and metabolic dysfunction, as well as adipose tissue dysfunction are thought to play key roles in the metabolic abnormalities of OSA [48, 49]. Snoring is the direct consequence of airway collapse in OSA patients, which is independently and positively associated with a higher incidence of NAFLD [50]. There is growing evidence that OSA is involved in the development of NAFLD with IH act as the most important connecting factor [51, 52]. The IH of OSA may also be involved in the progression of NAFLD by affecting the level of liver enzymes. It increased hepatic production of lysyl oxidase (LOX), an enzyme that cross-links collagen, may serve as a biomarker of liver fibrosis in patients with severe obesity and NAFLD [53]. In animal models, IH can directly induce hepatic steatosis by repeating brief hypoxia and reoxygenation simulating OSA [54]. Fu Y *et al* found that IH caused by OSA may aggravate NAFLD and lead to a higher risk of NASH in patients with obesity [55].

OSA affects NAFLD

There are many studies on the aspects of OSA affects NAFLD. Severe OSA is more likely to be associated with significant liver disease, one possible reason being its independent correlation with increased liver stiffness[56]. [LB8] A systematic review and meta-analysis demonstrated that OSA is associated with an increased risk of NAFLD, NASH and fibrosis [57]. Jin S et al. found significant correlations between OSA and NAFLD in terms of hepatic steatosis, lobular inflammation and fibrosis, suggesting that OSA may be involved in the progression of NAFLD through elevated liver enzyme levels and hepatic histological changes [58]. In the presence of obesity, patients with OSA may potentially contribute to liver injury in NAFLD through insulin resistance and systemic inflammation[59]. [LB9] And another case-control study showed that in the

absence of considering obesity and metabolic syndrome, patients with OSA have a significantly high incidence of NAFLD and exhibit notable hepatic fibrosis[60]. After excluding the confounding factor of obesity, the severity of OSA emerges as an independent risk factor for both NAFLD and liver fibrosis[61]. [LB10] Krolow GK *et al* found that patients with moderate to severe OSA had an increased risk of hepatic fibrosis after adjusting for obesity level [62]. Kim *et al* demonstrated that the severity of OSA increased with the prevalence of NAFLD regardless of the gender. And compared to non-obese OSA patients, obese patients with OSA were more prone to developing NAFLD. In addition, regarding hepatic steatosis, there was no association between liver fibrosis and the severity of OSA[63]. And a retrospective analysis suggested that it is age and obesity that predicted high liver fibrosis risk as assessed by noninvasive scoring systems, but not OSA severity[64]. [LB11] While in a cross-sectional study with human subjects, the risk of hepatic steatosis increased along with the severity of OSA and sleep-related hypoxemia after the adjustment of confounding factors including centripetal obesity [65].

Recent studies have been devoted to figuring out the influence of IH and OSA-related parameters on NAFLD severity. A multivariate analysis showed that AHI, oxygen desaturation index (ODI), lowest desaturation values, and percentage of sleep duration with mean nocturnal oxygen saturation (SpO2) were independent predictors of NAFLD after adjustment for BMI, weight, and IR (the most correlated parameter for the severity of NAFLD was the duration of IH during sleep) [66]. Furthermore, decreasing SpO2 during sleep was also associated independently with a higher risk of liver cytolysis [65]. Benotti, P. *et al* found that OSA severity (as measured by the apnea-hypopnea index (AHI)) and hypoxia parameters were positively correlated with NAFLD severity in subjects without metabolic syndrome [67]. Cakmak E et al. reported that AHI and ODI values were significantly higher in the moderate and severe NAFLD groups compared to the counterparts in the non-NAFLD group; SpO2 and lowest O2 saturation (LaSO2) were significantly lower in the mild and severe NAFLD groups. These results revealed that the parameters AHI, ODI, LaSO2, and SpO2 Levels play pivotal roles in the

association between NAFLD and OSA [68]. The severity of OSA was also associated with a decrease in high-density lipoprotein-cholesterol (HDL) and an increase in BMI, triglycerides (TG), homeostasis model assessment IR index (HOMA), transaminases and FIB-4 index (a noninvasive score for liver fibrosis) [69]. Human subjects with OSA had significantly higher levels of ALT and AST than those without OSA [70]. A single-center, cross-sectional study indicated that OSA may be an independent risk factor for dyslipidemia, and that OSA and obesity have a synergistic effect on ALT elevation[71]. And a cross-sectional study showed that the risk of developing NAFLD increases in older patients with OSA, the high TG is an important factor leading to the development of liver injury[72]. [LB12] Given that the pathological mechanism of OSA promotes the development of NAFLD, there are three aspects included, as shown in Figure 1.

Figure 1. the pathological mechanism of OSA promotes the development of NAFLD. OSA cause glucose and lipid metabolism disorders, intestinal flora disorder and hepatic inflammation through the sympathetic nervous system, endotoxemia and hepatic TLR-4.[LB13]

(1)Metabolism disorders in glucose and lipid

OSA is independently associated with metabolic dysfunction, including dyslipidemia and IR. Yokoe, T. *et al* found that IH impaired glucose homeostasis and stimulated pancreatic β-cell replication only during periods of hypoxic exposure, but the presence of hyperglycaemia may increase the hypoxic susceptibility of β-cells [73]. The mechanism of systemic glucoregulation by glucose-sensing neurons in the ventromedial hypothalamic Nucleus (VMH) also involved in the process of IH inducing the occurrence of IR by up-regulating the sympathetic nervous system, increasing circulating free fatty acids (FFAs) and hepatic glycogenolysis[74].[LB14] In addition, IH induces the occurrence of hyperlipidemia by inhibiting the clearance of triglyceride rich lipoproteins (TRLP). Drager, L. F. *et al* observed that, in the male C57BL/6J mice on

high-cholesterol diet under exposure to IH air for 4 wk, the clearance of lipoprotein lipase (LpL), a key enzyme for lipoprotein clearance, was inhibited; but a significant increase in total cholesterol and triglyceride levels [75]. IH-induced hyperlipidemia is also associated with up-regulation of sterol regulatory element binding protein-1 (SREBP-1) and over-expression of stearoyl coenzyme A desaturase 1 (SCD-1) [76, 77]. In conclusion, the mechanism by which OSA promotes the development of NAFLD may be IH-reduced utilization of FFAs by limiting the β-oxidation in mitochondria, and the excessive FFAs are diverted to the synthesis of TG and cholesterol to trigger hyperlipidemia, which ultimately leads to the development of NAFLD.

(2)Inflammation

The roles of IH in the progression of NAFLD are related to inflammation [78]. IH in OSA patients affects liver histology and inflammatory cell activation in NAFLD regardless of obesity or IR [79]. In NAFLD animal models, IH has been shown to modulate inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) to produce pro-inflammatory effects [80, 81]. Savransky, V. *et al* found that the levels of IL-1β, IL-6 and TNF-α were elevated in the mice following exposure to IH, lobular inflammation and fibrosis were documented in the liver [82]. Similarly, comparable results were observed in humans. Schaefer, E. *et al* used *in vitro* models of NASH to study the impacts of IH on the liver, they found that IH contributed to a significant induction of IL-6 expression in both hepatocytes and macrophages [83]. Furthermore, *in vitro* and *in vivo* models of NAFLD, IH promotes the production of inflammatory signals by activating inflammatory bodies or caspase-1 in fat-laden hepatocytes, as well as promoting crosstalk between hepatocytes and Kupffer cells (KCs) by releasing extracellular vehicles (EVs) to induce hepatocellular damage. This is followed by increased cell mortality through a variety of mechanisms, including apoptosis and pyrozoisis [84]. Notably, Taylor, C. T. *et al* discovered that human adipocytes are highly sensitive to IH, which enhances inflammatory gene expression in adipose tissue and the release of inflammatory cytokines involved in the development of NAFLD [85].

(3)Intestinal flora disorder

There is a wide range of microorganisms in human intestine, in which various microorganisms interact with each other to form a dynamic ecosystem called the gut microbial ecology. It has been shown that IH of OSA may affect the ecology of the gut microbiota and mediate a variety of cardiovascular diseases that coexist with OSA [86]. OSA is a risk factor for intestinal injury. No matter what the metabolic status is, intestinal permeability may be a possible factor leading to the susceptibility of OSA patients to NAFLD[87].[LB15] For example, Nobili, V. *et al* found a novel correlation exists between OSA and NAFLD, namely that IH may disrupt the intestinal-liver axis in pediatric NAFLD by increasing the number of gram-negative bacteria in the intestine and intestinal permeability, with increased endotoxemia coupled with toll-like receptor-4 (TLR-4) up-regulation in hepatocytes, Kupffer cells and hepatic stellate cells [88, 89]. In addition, one of the characteristic manifestations of OSA-SF, induces metabolic alterations in the organism that may be mediated in part by concurrent changes in gut microbiota, which was confirmed using SF-derived microbiota routinized in germ-free mice [90]. Chronic SF-induced reversible gut microbiota changes led to systemic and visceral white adipose tissue inflammation in addition to altered insulin sensitivity in mice, most likely *via* enhanced colonic epithelium barrier disruption.

CPAP treatment on OSA and NAFLD

Currently, continuous positive airway pressure (CPAP) is the globally accepted gold standard for the treatment of OSA. It can keep the airway open and reduce daytime sleepiness, improving cognition and sleep quality in OSA patients [91]. There have been many studies performed to explore the effects of CPAP therapy on the OSA patients suffered from NAFLD, but the results obtained were varied. Some observational data suggested that CPAP treatment improves hepatic biochemistry of NAFLD in OSA patients; and that CPAP treatment is statistically significantly associated with improvement of hepatic injury in OSA patients, but a sufficiently long duration of treatment (greater than or equal to 3 months) may be required to achieve a positive effect. Chen, L. D. *et al* enrolled 160 patients with OSA and measured serum transaminases before and after CPAP treatment. After 3 months of treatment, both ALT

and AST levels were decreased significantly [92]. A recent Meta-analysis also showed that, compared to controls, ALT and AST levels were significantly lower in OSA patients after CPAP treatment, and it was more effective in OSA patients treated with CPAP for more than 3 months [93]. Hirono, H. *et al* found a significant reduction in AST and ALT levels and significant improvement in liver injury after 6 months of CPAP treatment in 50 patients with OSA suffered from NAFLD [94]. In addition, the effect of CPAP treatment on NAFLD in OSA patients was also related to the OSA patients' adherence. The patients with good adherence to CPAP showed a significant decreased levels in AST and ALT than those with poor adherence [95]. Sundaram, S. S. *et al* also found that treatment of OSA with CPAP may reverse liver injury parameters and reduce oxidative stress, indicating that CPAP can be a new therapy applied to prevent NAFLD progression in obese children with OSA [96].

However, some randomized controlled trials did not show a benefit of CPAP treatment on liver injury in OSA patients. For instance, Jullian-Desayes, I. *et al* detected that six to twelve weeks of effective CPAP did not demonstrate any impact on reducing steatosis, NASH or liver fibrosis even after adjustment for gender, BMI, baseline apnoea/hypopnoea index and severity of liver injury [97]. Also, in the randomized controlled trial by Kohler, M. *et al*, 94 patients with moderate to severe OSAS were randomized to therapeutic or subtherapeutic CPAP treatment. Plasma ALT and AST levels were measured before and after treatment. The results showed that 4 wk of active CPAP treatment showed no beneficial effect on transaminase levels compared to subtherapeutic CPAP in patients with OSAS [98]. Ng, S. *et al* showed that 6 months of CPAP treatment did not improve hepatic steatosis and liver fibrosis, despite a significant correlation between hepatic steatosis and markers of OSA severity [99]. Labarca, G. *et al* performed a systematic evaluation and Meta-analysis in 5 randomized controlled trials involving patients with OSA and NASH under treatment with CPAP, but they did not find obvious changes in hepatic steatosis, liver fibrosis and transaminase levels (ALT and AST) in OSA patients [100]. Above all, differences regarding the effect of CPAP treatment in OSA patients on NAFLD may be related to

the duration of CPAP treatment, compliance of OSA patients and the degree of NAFLD progression.

NAFLD AFFECTS SLEEP DISORDERS

The effects of NAFLD on sleep can be observed from some observational studies, though there are no animal experiments to explain the specific mechanism by which NAFLD affects sleep. NAFLD patients have altered sleep status, namely in NAFLD, sleep duration was shortened, sleep onset was delayed and sleep quality poor [39, 101]. Moreover, NAFLD may increase the risk of developing OSA. A study showed that OSA is common in adults with biopsy-proven NAFLD [102]. Likewise, in a 6-month prospective study, Romdhane, H. *et al* found that the incidence of OSA is relatively higher in patients with NAFLD in comparison with controls [103]. In a nationwide population-based study, Chung, G. E. *et al* found that NAFLD was significantly associated with an increased risk of OSA after adjustment of multiple metabolic variables. Specifically, in younger, men or obese patients with NAFLD, there is a higher risk of OSA than that in older, women or non-obese patients [51].

The mechanism by which NAFLD affects OSA may be related to melatonin metabolism disorder. It's known to us all that sleep is closely related to the metabolism of melatonin, which is metabolized by the liver. Liver metabolic dysfunction in NAFLD patients as disease progresses. What can be found at present is that key factors in NAFLD-induced sleep disorders include hepatic encephalopathy (HE) and circadian rhythm imbalance due to altered melatonin metabolism. Moreover, as the last progression of NAFLD, cirrhosis has an effect on circadian sleep regulation by a delay in the 24-hour melatonin rhythm, which is likely to be related to reduced sensitivity to light signals [104]. The core feature of NAFLD is the discoordination between central and peripheral circadian rhythms [105]. This similar phenomenon also appeared in db/db (hereditary obesity) mice [106], and the main circadian rhythm defect lies in the peripheral liver oscillator rather than the behavioral rhythm or master clock, but as for

the mechanism of how peripheral circadian rhythm disorder affect the central circadian rhythm remains to be explored.

CONCLUSION

This paper provides some significant insights into the correlations between sleep disorders and the occurrence or development of NAFLD. Overlong or short sleep duration and poor sleep quality may increase the risk of NAFLD. Similarly, insomnia, daytime sleepiness, sleep-wake disorders and OSA have promoted the development of NAFLD to some extent. NAFLD is also a risk factor for OSA, it is necessary to screen and monitor the occurrence and development of NAFLD in OSA patients, and CPAP treatment can stabilize and slow down the progression of NAFLD under certain circumstances. Sleep factors can be added to the list of changeable lifestyle behaviors to reduce the risk of NAFLD by way of maintaining proper sleep duration and good sleep quality, as well as improving sleep disorder status.

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