# Review article

## Sleep apnea hypopnea syndrome and liver injury

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***Keywords:*** *sleep apnea hypopnea syndrome; intermittent hypoxia; nonalcoholic fatty liver disease; insulin resistance; oxidative stress*

**Objective** A general review was made of studies involving: (1) the relationship between sleep apnea hypopnea syndrome/sleep apnea style intermittent hypoxia and liver injury and (2) the mechanism that causes the liver injury.

**Data sources** The data used in this review were mainly from Medline and PubMed published in English from 1993 to February 2009. The search term was "sleep apnea hypopnea syndrome".

**Study selection** (1) Clinical and laboratory evidence that sleep apnea hypopnea syndrome and sleep apnea style intermittent hypoxia leads to liver injury; (2) the mechanism that causes the liver injury.

**Results** The effect of sleep apnea hypopnea syndrome and sleep apnea style intermittent hypoxia on the liver function is characterized by serum aminotransferase elevation. The liver histological injury includes hepatic steatosis, hepatocyte ballooning, lobular inflammation, lobular necrosis, and liver fibrosis. Sleep apnea hypopnea syndrome and sleep apnea style intermittent hypoxia can cause insulin resistance and oxidative stress.

**Conclusions** Sleep apnea hypopnea syndrome and sleep apnea style intermittent hypoxia can lead to chronic liver injury, which, in most cases, is shown as nonalcoholic fatty liver disease. Insulin resistance and oxidative stress caused by sleep apnea hypopnea syndrome and sleep apnea style intermittent hypoxia play an important role in the mechanism of chronic liver disease development.

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Sleep apnea hypopnea syndrome (SAHS) is a common disease with potential fatality. The prevalence of SAHS is 2% to 4% of the total adults, 20% to 40% of those aged 65 years and older, and more than 50% of the obese individuals. The 5-year case-fatality rate for untreated, severe SAHS patients is as high as 11% to 13%.[1-4] The characteristic of SAHS is that the patients experience apnea repeatedly during sleep, which leads to repetitive cycles of hypoxia and reoxygenation. The frequency of apnea is 5 to 10 instances per hour. Different from any other hypoxia patterns, this hypoxia process is a special feature of SAHS and is referred to as sleep apnea style intermittent hypoxia (SASIH).[5]

SAHS has not been recognized until the late 1980s. Since then, however, it has raised broad and rapidly growing concerns and academic interests within the medical world due to its high morbidity and severe damage to organs. Since its birth, SAHS research has gone through a history that evolved from the very early stage of epidemiological research to the study of onset mechanism of the disease, and finally to the current stage of multi-organ impairment mechanism studies. Researches first showed that SAHS was closely related to cardiovascular and cerebrovascular diseases. It was then established, by both epidemiological and clinical studies, that SAHS was an independent risk factor to diseases such as hypertension, coronary heart disease, heart failure, and stroke.[6-10] Furthermore, damages caused by SAHS were not just limited to cardiovascular and cerebrovascular diseases. It also affected the respiratory, urinogenital or endocrine system. Recent studies have shown that SAHS and SASIH can also lead to chronic liver injury and nonalcoholic fatty liver disease (NAFLD), independent of obesity.[11-15] This review will give a summary of studies on the relationship between SAHS/SASIH and liver disease and its underline mechanisms.

### SAHS, NAFLD AND METABOLIC SYNDROME

NAFLD is a clinicopathological term characterized by triglyceride accumulation in hepatocytes (hepatic steatosis) in the absence of a history of significant alcohol use or other known liver diseases. The disease spectrum of NAFLD ranges from isolated fatty liver, nonalcoholic steatohepatitis and fibrosis to end-stage liver cirrhosis. The prevalence of NAFLD is estimated to range from 10% to 24% in the general population and from 57% to 74% in the obese population. Its predisposing factors, either individual or combined, include obesity, diabetes mellitus, and dyslipidemia. In approximately 42% to 90% of patients whose serum aminotransferase are high but without other liver diseases, the causing factor is NAFLD.[16,17] Metabolic syndrome is a condition where various metabolic disorders coexist in an individual. It is characterized by a constellation of central obesity, glucose intolerance, dyslipidemia, and hypertension.

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Metabolic syndrome accounts for 20% to 30% of the general population,[18] and the percentage in the older population is 2 to 3 times higher than that in the population aged 20–50 years.

Many characteristics are common among SAHS, NAFLD and metabolic syndrome. They are all common and frequently occurring illnesses; they are all closely related to factors such as obesity, aging, glycometabolic disorder, dyslipidemia and hypertension; and they all share the same pathophysiological basis, insulin resistance.[16,19,20] In deed, SAHS, NAFLD and metabolic syndrome are so closely interrelated in a triangle type of relationship (Figure 1) that it is natural for them to coexist in one individual. It has been demonstrated that metabolic syndrome, characterized with obesity, can lead to NAFLD and SAHS[21,22] But at the same time, SAHS can also foster metabolic syndrome components such as hypertension,[23] insulin resistance and dyslipidemia.[19,24,25] Therefore, recent studies on both SAHS and NAFLD have paid more attention to their interaction mechanisms. Increasing evidence indicates that SAHS not only leads to NAFLD, but also may drive the process in which NAFLD progresses from simple hepatic steatosis to the more advanced stages of steatohepatitis and liver fibrosis, independent of obesity.[11,12,15]

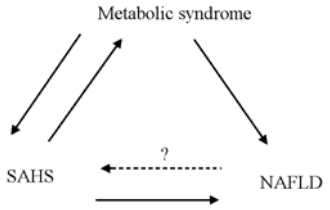


**Figure 1.** Relationship of metabolic syndrome, SAHS and NAFLD.

## EVIDENCES SUPPORTING THAT SAHS LEADS TO LIVER INJURY

### SAHS and abnormal liver enzymes

Chin et al[26] investigated the effects of obstructive sleep apnea hypopnea syndrome (OSAHS) on serum aminotransferase levels in obese patients. They found that 35% of 44 obese OSAHS patients had abnormal aminotransferase levels. But continuous positive airway pressure (CPAP) therapy decreased aminotransferase levels. Jouet et al[27] found that among morbidly obese patients (body mass index (BMI) male ≥40 kg/m$^2$, female ≥35 kg/m$^2$), those who are combined with OSAHS had a significantly higher level of liver enzymes than those without OSAHS. The percentage of patients with elevated liver enzymes tended to increase with more severe OSAHS (25%, 42.9%, 52.8% in patients with no OSAHS, moderate or severe OSAHS, respectively), suggesting that OSAHS is a risk factor for elevated liver enzymes. The study of Kallwitz et al[13] also supports the above conclusion.

However, obesity appears to be an important predisposing factor of NAFLD. In a study, the liver enzymes level was not different between none-obese OSAHS patients and age-, BMI- and gender-matched non-OSAHS patients.[28] More recent studies have revealed that SAHS is a risk factor for elevated liver enzymes and the elevation of liver enzymes is closely associated with the severity of SAHS and nocturnal hypoxemia. It is independent of body weight state.[11,29] Evaluation of OSAHS showed that 20% of 163 patients had elevated level of liver enzymes. Meanwhile, the levels of liver enzymes were elevated in 18% of moderate OSAHS patients, 32% of severe OSAHS patients and 8.6% of the BMI-matched controls. Further study also showed that while the elevation of liver enzymes in OSAHS patients was associated with both BMI and severe OSAHS, the presence of severe OSAHS was a far stronger predictor of elevated liver enzymes (odds ratio (*OR*) 5.9) than elevated BMI (*OR* 1.13).[11] Another study of 109 OSAHS patients (BMI (31.4±5.4) kg/m$^2$) showed that the level of serum aminotransferase was positively correlated with the lowest oxygen saturation level during sleep and the percent of time below 90% saturation, but not correlated with BMI.[15]

The conclusion that SAHS/SASIH can lead to elevated liver enzymes is also supported by animal experiment. Savransky et al[12] studied the effect of chronic intermittent hypoxia on the serum aminotransferase level of lean C57BL/6J mice. In the experiment, 30 lean C57BL/6J mice were divided into 2 groups of 15 each, were fed with a regular chow diet. The mice were subjected either to chronic intermittent hypoxia or intermittent air (control conditions) 12 hours a day for 12 weeks. The starting levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) of both groups were the same. The result showed that chronic intermittent hypoxia resulted in a 2-fold increase in activity of serum ALT, whereas the activity of AST and ALP was unchanged. The experiment was repeated with modified conditions to induce fatty liver on C57BL/6J mice by feeding a high-fat, high-cholesterol diet, and the mice were exposed either to chronic intermittent hypoxia or intermittent air (control conditions) for 6 months. The result of the new experiment showed that the chronic intermittent hypoxia caused a greater than 3-fold increase in serum AST levels and a greater than 4-fold increase in serum ALT levels, while the ALP and total bilirubin levels were unchanged.[29] This indicates that chronic intermittent hypoxia can cause elevated serum aminotransferase on C57BL/6J mice regardless of preconditions of liver diseases.

### SAHS leads to NAFLD

Current evidences show that, from a histopathological perspective, SAHS liver injury is mainly characterized by NAFLD. Its pathological changes include simple fatty liver (hepatic steatosis), steatohepatitis (hepatocyte ballooning, lobular inflammation and lobular necrosis based on hepatic steatosis, with or without fibrosis) and

liver fibrosis.

Some researchers studied the histological changes of liver tissue of patients with severe obesity, especially of those who are combined with SAHS, by studying samples of liver tissue obtained by bariatric surgery.[13,14,30] In 85 patients undergoing bariatric surgery, Kallwitz et al[13] found that 51% of obesity patients were also combined with OSAHS. Within this part of the population, both the trend toward histologic evidence of progressive liver disease and the proportion with lobular inflammation and liver fibrosis are significantly higher than those of the rest of the population and those with simple obesity. Another larger scale study showed that, among 101 obesity patients undergoing bariatric surgery, 81.2% combined with OSAHS. From a histological perspective, severe OSAHS patients bear more significant risk of both steatohepatitis and liver fibrosis. Meanwhile, nocturnal hypoxemia is more serious in patients with steatohepatitis or liver fibrosis.[14]

Tanne et al[11] investigated liver injury in 163 consecutive nondrinking patients with OSAHS. They found that patients with severe OSAHS had a higher percentage of carrying steatohepatitis than those with moderate or none OSAHS. Multivariate analysis indicated that in OSAHS patients hepatic steatosis and lobular necrosis are correlated with apnea hypopnea index (AHI), but independent of age and BMI. Tatsumi et al[28] examined whether non-obese patients with OSAHS were prone to develop hepatic steatosis and whether repeated hypoxemia contributed to the progression of steatohepatitis. They measured liver/spleen ratio through abdominal computerized tomography. Hepatic steatosis was defined by a liver/spleen ratio <0.9. Developing steatohepatitis was evaluated by serum levels of type III procollagen (P-III-P), and P-III-P >0.8 U/ml was chosen as the diagnostic indicator for liver fibrosis. This study included 83 non-obese (BMI $\leq$30 kg/m$^2$) patients with OSAHS and 41 age-, BMI- and gender-matched patients without OSAHS. Although the result suggested that the frequency of hepatic steatosis from the two groups showed no statistical difference, the serum levels of P-III-P in OSAHS patients correlated negatively with the average oxygen saturation during sleep, and positively with AHI. Multiple regression analysis showed that the average oxygen saturation was the only explanatory variable for P-III-P values. It was concluded that the average oxygen desaturation during sleep was a risk factor for developing steatohepatitis, and that the severity of OSAHS contributed to the pathogenesis of liver fibrosis. Meanwhile, researchers also acknowledged that even though P-III-P is a potent indicator of liver fibrosis, liver biopsy is the most reliable diagnostic indicator of steatohepatitis.

The finding of liver injury in non-obese patients with OSAHS was also confirmed by animal experiment.[12,29] Exposed to chronic intermittent hypoxia for 12 weeks, lean C57BL/6J mice on regular chow diet did not show any histological evidence of hepatic steatosis.[12] Researchers of the experiment divided the lean C57BL/6J mice into two groups: one fed with a high-fat, high-cholesterol diet plus chronic intermittent hypoxia, and the other fed with a high-fat, high-cholesterol diet plus intermittent air. After exposure for 6 months, the mice fed with a high-fat, high-cholesterol diet and chronic intermittent hypoxia showed various NAFLD histological changes such as hepatic steatosis, lobular inflammation and liver fibrosis. The mice fed with a high-fat, high-cholesterol diet plus intermittent air, however, showed only hepatic steatosis but no histological evidence of steatohepatitis.[29] It is clear that chronic intermittent hypoxia is the factor for hepatic steatosis to progress toward steatohepatitis.

### SAHS and hypoxic hepatitis

Histological evidence that SAHS leads to liver injury concentrates on NAFLD. But there are also a few cases suggest that severe SAHS leads to histological changes of hypoxic hepatitis.[31,32] Hypoxic hepatitis, also known as ischemic hepatitis or shock liver, is a condition of acute liver cell degeneration, necrosis and liver functional damage caused by acute failure of hepatic blood perfusion. It is mainly caused by congestive cardiac failure, respiratory failure, toxic/septic shock, etc. It is histologically characterized as various degrees of centrilobular liver cell necrosis.[33] In a prospective study of 142 patients with hypoxic hepatitis collected during a 10-year period, the researchers encountered two patients who suffered from morbid obesity combined with severe OSAHS.[31] Oxygen arterial saturation was very low, less than 35% in both patients and there was no clinical evidence of circulatory failure and shock. This finding was also reported by Mathurin et al[32] that one patient with obesity and OSAHS developed hypoxic hepatitis. Currently, there is no clear evidence supporting that SAHS is correlated with hypoxic hepatitis.

## THE MECHANISM THAT SAHS AND SASIH LEAD TO LIVER INJURY

### SAHS and insulin resistance

The term insulin resistance refers to an impaired biological response to insulin and hence a reduced insulin-mediated glucose disposal by surrounding tissues, especially muscle and fatty tissue.[34] Insulin resistance is the pathophysiologic basis of many metabolism related diseases, including NAFLD.[16] Insulin resistance, on one hand, results in increased release of free fatty acids (FFAs) from adipocytes, which leads to a large amount of FFAs released into blood circulation and, therefore, greater FFAs uptake by the liver; on the other hand, it decreases the liver's ability to oxidize and resolve FFAs, since FFAs esterify into triglycerides, and disturb triglyceride export into the circulation as very low density lipoprotein. It finally causes the accumulation of excessive triglycerides in the liver and thereby forms hepatic steatosis and fatty

liver.[35,36]

SAHS is independently associated with insulin resistance. Ip et al[19] suggested that, after controlling for obesity and other important confounding factors of insulin resistance, the sleep disorder parameter (AHI and minimum oxygen saturation) of SAHS patients were significantly associated with insulin resistance parameter (fasting serum insulin level and insulin resistance index). For every unit increases in AHI, the level of insulin resistance rises by about 0.5% and the same correlation also exits in non-obese patients with SAHS. Currently, the mechanism that SAHS leads to insulin resistance is not yet completely understood. It is surmised that the mechanism might be related to various factors, such as central obesity, oxidative stress induced by intermittent hypoxia, sleep deprivation, participation of inflammatory cytokine, fat factor, etc.[37,38] It is accepted that the insulin resistance caused by SAHS is the fundamental mechanism for the formation of fatty liver.[13-15]

**SAHS and oxidative stress**

Clinical practice and laboratory experiments indicated that SAHS is an oxidative stress disease.[39-42] Oxidative stress results from an imbalance between pro-oxidant and antioxidant chemical species that leads to oxidative damage of cellular macromolecules. Under SAHS, the process of repetitive hypoxia and reoxygenation, which is similar to the ischemia-reperfusion injury, can produce a large amount of reactive oxygen species (ROS) and thereby leads to an oxidative stress status.[39-42] Some evidence indicates that the oxidative stress induced by intermittent hypoxia directly participates in the process in which NAFLD progresses from hepatic steatosis to steatohepatitis.[29]

ROS may induce lipid peroxidation, particularly for unsaturated fatty acids in cell membranes. The impact of such aggression is manifold. First, it modifies physicochemical properties of cell membrane. By impacting membrane receptor and enzyme activity, antigen expression, intercellular interactions, and membrane permeability, it causes liver cell degeneration and necrosis. Second, liver stellate cells become activated, change their morphology and function, synthesize the various components of extracellular matrix, increase collagen deposit, and form liver fibrosis. Third, it activates nuclear factor kappa B (NF-κB) and thereby induces the expression of genes for numerous proinflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukins 2, 6, intercellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein (MCP-1). As a result, it leads to inflammatory response to the liver. Finally, several pathways and factors may lead to the apoptosis of hepatocytes, including oxidative stress itself, TNF-α, and FFAs.[36] These can lead directly to changes such as hepatocyte degeneration and necrosis, inflammation and liver fibrosis, which are the histological characteristics of steatohepatitis. Therefore, if insulin resistance is the foundation for the formation of fatty liver, oxidative stress and the lipid peroxidation it induced is the core factor that makes hepatic steatosis progress to steatohepatitis.[36]

**SAHS and "two-hit" theory for the development of NAFLD**

The pathogenesis and progression of NAFLD can be explained by the so-called "two-hit" theory. Day et al[43,44] initially proposed that the development of NAFLD is the result of "two-hit". Insulin resistance induced by various possible factors such as obesity, diabetes and hyperlipidemia can lead to the deposition of triglycerides in the cytoplasm of hepatocyte, hepatic steatosis and finally, simple fatty liver. This process constitutes the "first hit". Although it is easer in general for the liver with hepatic steatosis to progress to steatohepatitis, in some individuals, steatosis, whatever its etiology, never progresses to steatohepatitis. Thus it is not necessarily true that hepatic steatosis always progresses to steatohepatitis. The deciding factor for the progression is the existence of the "second hit", of which the source is the increase of ROS caused by any etiology. The oxidative stress induced by ROS is capable of initiating enough lipid peroxidation to overcome the normal cellular defense mechanisms, initiating lipid peroxidation process, producing necroinflammation and forming steatohepatitis. Factors such as hepatitis virus, alcohol, some drugs and toxins can all lead to liver oxidative stress through various pathways.

As it turns out, the relationship between SAHS and liver injury is consistent with the "two-hit" theory proposed to explain the pathogenesis and progression of NAFLD.[13-15,28,29] Insulin resistance induced by factors such as obesity, dyslipidemia and intermittent hypoxia in SAHS patients causes hepatic triglyceride accumulation and thereby leads to hepatic steatosis. The "second hit", formed by oxidative stress induced by SASIH, drives the simple fatty liver to progress to steatohepatitis and liver fibrosis (Figure 2). The existence of hepatic steatosis is necessary for the inflammation process to progress. Animal experiment shows, without hepatic steatosis, chronic intermittent hypoxia only causes minor liver injury with no significant inflammation. On the other hand, for hepatic steatosis induced by high fat diet, chronic intermittent hypoxia can clearly lead to a tendency of steatohepatitis.[12,29]

## SUMMARY

Accumulating evidence from both animal and human data shows that SAHS and SASIH can cause chronic liver injury, which is mainly characterized by NAFLD. There is a causal relationship between SAHS and NAFLD. The insulin resistance and oxidative stress induced by SAHS and SASIH play an important role in the mechanism of chronic liver injury process.

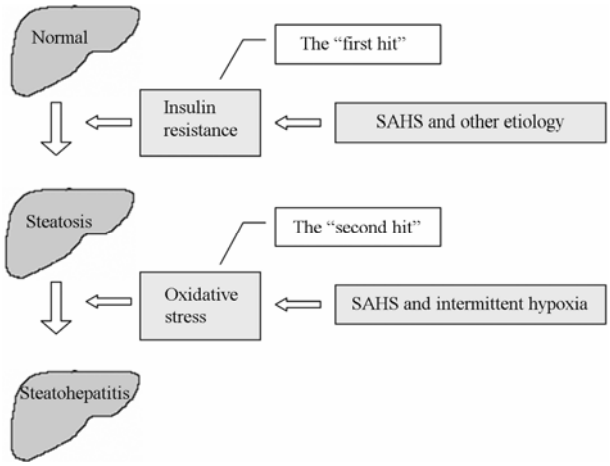


**Figure 2.** The pathogenesis of liver injury for SAHS.

Studies on the relationship between SAHS and NAFLD are just getting started. Many challenges need to be tackled such as lack of large-scale survey on the prevalence of NAFLD in SAHS patients, the precise mechanism of liver injury, and whether NAFLD can be reversed by the treatment of SAHS, etc. Since research efforts worldwide are being directed to the multi-system impairment caused by SAHS, it is hopeful that the key elements in preventing and treating SAHS target organ injury will be discovered and new efficient treatments will be invented.

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