

What Non-Alcoholic Fatty Liver Disease Has Got to Do with Obstructive Sleep Apnoea Syndrome and viceversa?

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) and obstructive sleep apnoea syndrome (OSAS) are common conditions, frequently encountered in patients with obesity and/or metabolic syndrome. NAFLD and OSAS are complex diseases that involve an interaction of several intertwined factors. Several lines of evidence lend credence to an immune system derangement in these patients, i.e. the low grade chronic inflammation status, reckoned to be the most important factor in causing and maintaining these two illnesses. Furthermore, it is emphasized the main role of spleen involvement, as a novel mechanism. In this review the contribution of the visceral adiposity in both NAFLD and OSAS is stressed as well as the role of intermittent hypoxia. Finally, a post on the prevention of systemic inflammation is made.

Key words: non-alcoholic fatty liver disease (NAFLD) – obstructive sleep apnoea syndrome (OSAS) – body mass index (BMI).

Abbreviations: ALT: alanine aminotransferase; BMI: body mass index; CCR2: chemokine (C-C motif) receptor 2; CRP: C-reactive protein; CPAP: continuous positive airway pressure; FFA: free fatty acid; IGF-I: insulin-like growth factor; IR: insulin resistance; IL-6: interleukin-6; IH: intermittent hypoxia; IKK- β : I κ B kinase β ; LPS: lipopolysaccharide; MCP-1: monocyte chemoattractant protein-1; NAFLD: non-alcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; NEFA: non-esterified fatty acid; NF- κ B: nuclear factor- κ B; OSAS: obstructive sleep apnoea syndrome; PAI-1: plasminogen activator inhibitor-1; ROS: reactive oxygen species; TNF- α : tumor necrosis factor- α ; T2D: type 2 diabetes.

INTRODUCTION

The rising incidence of obesity in recent environment is associated with many obesity-related health complications, including cardiovascular disease, type 2 diabetes (T2D), hyperlipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD). It is estimated that about 70% of those with obstructive sleep apnoea syndrome (OSAS) are obese and that the prevalence of OSA in obese men and women is about 40% [1]. The cluster of insulin resistance (IR), hyperlipidemia, hypertension, and visceral obesity is also labeled as the metabolic syndrome. Non-

alcoholic fatty liver disease, a further expression of the metabolic syndrome, is defined as the accumulation of lipids, primarily in the form of triacylglycerols in individuals not consuming significant amounts of alcohol (<20 g ethanol/d) and in whom other known causes of steatosis, such as certain drugs and toxins, have been excluded. Non-alcoholic fatty liver disease includes simple fatty liver, non-alcoholic steatohepatitis (NASH), cirrhosis postNASH, hepatocellular carcinoma. The “two-hit or multiple hits” hypothesis of NASH states that the accumulation of lipids in the liver is followed by a cascade of prooxidative, hepatotoxic events [2]. Insulin resistance is an almost permanent characteristic of patients suffering from NAFLD/NASH, being a significant predictor of its severity, surprisingly even in those who are not overweight [3].

The OSAS is characterized by repetitive apnoea/hypopnoea episodes during sleep, which are associated with oxygen desaturation and sleep disruption. It has been estimated that between 2% and 4% of the adults in western countries suffer from clinically significant OSAS, and it is becoming more prevalent as the average body weight increases in these populations [4].

Obstructive sleep apnoea syndrome has been associated with features of the metabolic syndrome, including obesity [5], hypertension [6], dyslipidaemia [7] and insulin resistance (IR) [8], some of which are thought to similarly contribute to the pathogenesis of NAFLD [9]. Norman et al have shown that repetitive episodes of hypoxia occurring during sleep in patients with OSAS are an additional causal factor in the development of NAFLD, which is independent from obesity and the metabolic syndrome [10]. Furthermore, uncontrolled treatment studies of adults and children with OSAS with continuous positive airway pressure (CPAP) and tonsillectomy were associated with a lowering of liver enzyme levels, suggesting that CPAP might improve NAFLD in patients with OSAS [11].

These findings, together with the overlap of metabolic syndrome with NAFLD, has recently prompted an evaluation of the epidemiologic and pathophysiologic links between NAFLD and OSAS [12], and of potential therapeutic implications of early OSAS identification and treatment for the treatment of obesity and fatty liver.

OBESITY, INSULIN RESISTANCE AND OSAS

Patients with obesity are additionally prone to lung diseases compared to their lean counterparts, including decreased lung volumes, decreased exercise capacity, hypoxia and hypoventilation [13]. Obstructive sleep apnoea syndrome is characterized by the recurrent collapse of the upper airway during sleep, resulting in an obstacle to the airflow with subsequent oxygen desaturation, which causes arousal from sleep. The result is sleep fragmentation and daytime somnolence [14]. Central obesity is an unrelated risk factor for OSAS perhaps because of the deposition of fat around the neck and sub-mental region inducing the upper airway

to collapse on supine [15]. Upper body obesity consistently decreases lung volumes [16].

Obesity-hypoventilation syndrome is the predominantly severe form of sleep-disordered breathing with frank respiratory failure. Apnoea is defined as interruption of airflow (through the nose/upper airway) for more than 5 seconds [17]. Obstructive sleep apnoea syndrome is associated with notable non-respiratory morbidity, including an elevated prevalence of metabolic syndrome [18], hypertension, IR and T2D [19] (Fig. 1) and cardiovascular illnesses, such as transient ischemic attacks, stroke, cardiac arrhythmias, myocardial infarction and pulmonary hypertension [17].

As clearly evidenced, hypertension is an important component of the metabolic syndrome. Sufficient correlations exist between free fatty acid (FFA) levels, upper body obesity, T2D and blood pressure [20]. Obstructive sleep apnoea syndrome is also associated with hypertension [18].

Determinants of blood pressure comprehend blood volume, arterial vasoconstriction/relaxation and cardiac output. Several studies have also shown that elevated FFA levels increase vascular sensitivity (in both magnitude and duration) to $\alpha 1$ adrenergic stimuli [21]. The result is increased cardiac output and vasoconstriction, which raises blood pressure. Insulin secretion increases the endogenous release of the potent vasodilator nitric oxide from the endothelium [22]. Furthermore, evidence is increasing that insulin-resistant muscle is characterized by a lowered ability to oxidize fatty acids. An imbalance between fatty acid uptake and FFA oxidation may in turn be a factor promoting accumulation of lipid intermediates and triacylglycerols within skeletal muscle, which is strongly associated with skeletal muscle IR [20]. Elevated FFA reduces nitric oxide synthase activity and thus interferes with nitric oxide-mediated vasorelaxation.

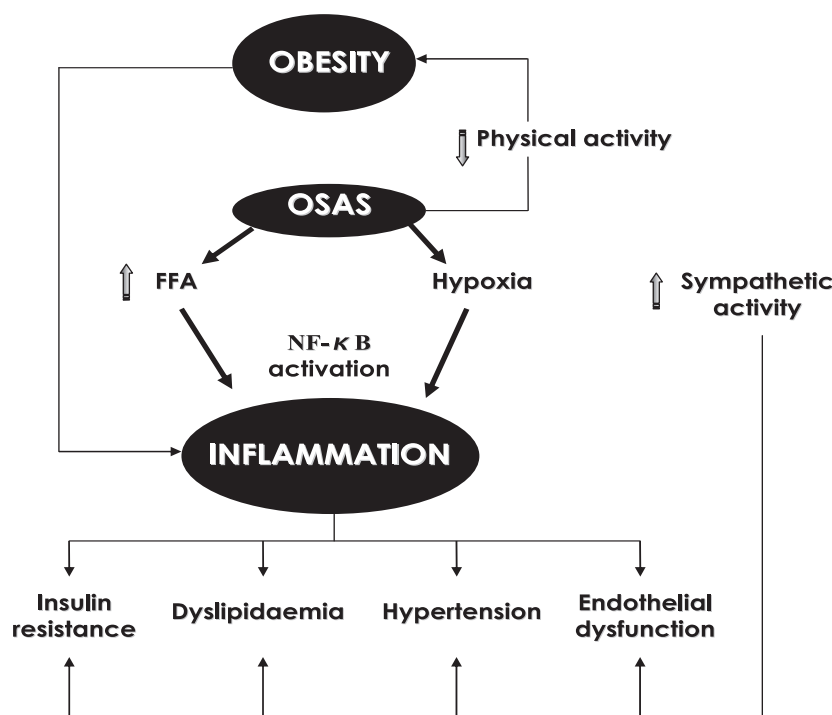


Fig. 1. Correlation between obesity, obstructive sleep apnea syndrome (OSAS), inflammation and metabolic syndrome. FFA, free fatty acid; NFκB, nuclear factor kappa B.

It has been demonstrated that non-esterified fatty acid (NEFA), altered in patients with upper body obesity, might inhibit endothelium dependent vasorelaxation by protein kinase C (isoenzyme responsible for activation of serine and threonine phosphorylases) independent mechanisms [23]. If this hypothesis can be proved, consequently the therapies aimed at reducing NEFA-mediated endothelial dysfunction may help to improve blood pressure control in the metabolic syndrome [23].

Other important contributory factors for hypertension comprehend increased sympathetic activity [24], decreased baroreceptors sensitivity [25] and increased tumor necrosis factor alpha (TNF- α) concentration [26]. These alterations have all been described in patients suffering from OSAS [13]. Nevertheless, most of the OSAS patients are contextually obese and the studies are relatively small, so the independent effect of hypoxia, consequence of OSAS, could be hidden by the direct effect of adipose tissue.

Obstructive sleep apnoea syndrome is an independent risk factor for hypertension and renal and cardiac complications [27]. A possible mechanism by which OSAS may cause hypertension is via increased sympathetic activity and decreased baroreceptor activity [28]. This hypothesis is supported by the observation that treatment of OSAS reduces blood pressure (mostly important, with no change in body mass index, BMI) [29].

It has been shown that each additional apnoea or hypopnoea episode per sleep hour increases the fasting insulin level and IR by about 0.5% [30]. These findings suggest that OSAS is independently associated with IR and BMI [30].

Harsch et al showed that the effect of CPAP on insulin sensitivity is smaller in obese than in non obese patients, suggesting that in obese individuals insulin sensitivity is mainly determined by obesity and, to a smaller extent, by sleep apnoea [31]. More studies are required to clarify these effects.

VISCERAL OBESITY AND NAFLD

Non-alcoholic fatty liver disease occurs in 60% to 95% of people with obesity, as reported by Wang et al [32]. Visceral fat is a key mediator of NASH [32, 33], findings found in many animal models including *fa/fa* obese rats [32, 34].

Recent evidence suggests that visceral adipose tissue is a metabolic and inflammatory organ that signals and modulates the action and metabolism of the brain, liver, muscle and cardiovascular system [32, 35]. The imbalanced production of pro- and anti-inflammatory adipokines secreted from fat contributes to the pathogenesis of NAFLD [32]. Modulation of endocrine/immune/inflammatory interactions of adipose tissue may provide exciting pharmacologic targets for the treatment of NAFLD [32, 36]. In obesity-related NAFLD patients the plasma leptin concentration is high while the liver is resistant to the "anti-steatotic" effects of leptin [32, 37]. Tumor necrosis factor- α , a pro-inflammatory adipokine, interferes with insulin signaling and favors hepatic steatosis [32]. Circulating levels of TNF- α and hepatic expression of its type 1 receptor are increased in NASH [32, 38]. Neutralization of TNF- α activity improves fatty liver disease in human beings [38]. Conversely, nutritional steatohepatitis can still be produced experimentally

in both TNF- α and TNF- α type 1 receptor knockout mice [32, 39]. In contrast to leptin and TNF- α , adiponectin is more closely implicated in the pathogenesis of NAFLD/NASH. Unlike other adipokines, serum levels of adiponectin are decreased in obesity and its co-morbidities [32, 40]. Numerous epidemiological studies in diverse ethnic groups have identified lower levels of adiponectin as an independent risk factor for NAFLD [32]. Moreover, NASH patients with lower levels of adiponectin show higher grades of inflammation [32, 41]. In patients with T2D, plasma adiponectin concentrations are inversely associated with hepatic fat content [32, 42]. Some studies have demonstrated that adiponectin has potent protective activities against various forms of liver injuries [32, 43-45]. In animal models of NASH, exogenous adiponectin depletes lipid accumulation, decreasing hepatic expression and plasma concentration of TNF- α [32, 46]. In a NASH model in mice, the lack of adiponectin expression could accelerate the hepatocarcinoma formation [32, 47]. Among the known adipokines, adiponectin stands *per se* for its insulin-sensitizing and anti-inflammatory roles, and may be used as a promising drug candidate for the treatment of liver diseases [32].

VISCERAL FAT AND OSAS RISK

The prevalence of OSAS shows a close correlation with adiposity, rising from a prevalence of 2-4% in the general population [48] to a prevalence of at least 40% in severely obese patients [48, 49]. However, the prevalence and severity of OSAS in overweight and obese patients have been shown to be more dependent on the fat distribution than on the level of total fatness [48]. Waist circumference was a better predictor of OSAS than BMI in moderately obese undergoing a sleep study for suspected sleep-disordered breathing [48, 50]. Vgontzas et al [51] demonstrated that male obese patients with OSAS had a greater amount of visceral adiposity determined by computed tomography than a group of BMI-matched men without sleep-disordered breathing.

The neck, as a part of the body, is a potent anthropometric predictor of OSAS [48, 52]. Decreased pharyngeal patency was considered the most important pathogenetic mechanism leading to OSAS in obese patients [1]. A reduction in pharyngeal size has been attributed to a reduction in lung volume. In visceral obesity the accumulation of fat inside the abdomen pumps the diaphragm upwards, causing a reduction in lung volumes [48, 53]. The reduction of lung volume has been found to be enhanced by the supine position and during sleep [48, 54].

Whatever the mechanism, it is possible that intraabdominal fat accumulation and fat deposition around the pharynx coexist in obese patients [48].

LOW-GRADE CHRONIC INFLAMMATION: THE MAIN ROLE OF INTERLEUKIN 6 (IL-6)

Growing evidence links a low-grade, chronic inflammatory state to obesity and its coexisting conditions such as T2D, metabolic syndrome, NAFLD [55] but also OSAS (see below). It should be emphasized that the spleen also plays a key role

in this chronic process. Normal values of spleen longitudinal diameter and IL-6 are strongly associated with fatty liver [55]. Anti-inflammatory drugs can reverse IR [56], which suggests that inflammation is directly involved in its pathogenesis. Insulin resistance is strictly linked to anti-apoptotic serum Bcl-2 values [57]. Those were higher in fatty liver than in NASH patients suggesting a protective role of the anti-apoptotic process in liver and perhaps in other areas. Apoptotic cell death is caspase-dependent and associated with mitochondrial membrane depolarization and cytochrome C release [58]. Inflammatory mediators that are biosynthesized in the liver and are increased in the serum of NAFLD patients include C-reactive protein (CRP) [55], IL-6 [55], fibrinogen and plasminogen activator inhibitor-1 (PAI-1) [59]. Hepatocytes, beyond adipocytes, independently contribute to synthesis of inflammatory mediators. In support of a sequence of cellular and molecular events that mediate hepatic IR in NAFLD, recent data lend credence to the fact that hepatic steatosis activates I κ B kinase (IKK)- β and the nuclear factor (NF)- κ B [60]. Among the inducible transcription factors that control inflammatory gene expression, NF- κ B plays a central and evolutionarily conserved role in coordinating the expression of various soluble pro-inflammatory mediators (cytokines and chemokines) and leucocyte adhesion molecules. In non-stimulated cells, NF- κ B is sequestered in the cytosol by the inhibitor of NF- κ B (I κ B) that masks the nuclear localization signal present along the NF- κ B protein sequence.

Exposing cells to pro-inflammatory cytokines, i.e. TNF- α and IL-1, or lipopolysaccharide, leads to the activation of a specific-IKK complex that phosphorylates I κ B and consequently tags it for ubiquitination and degradation by the proteasome [61]. The degradation of I κ B thus allows NF- κ B to translocate into the nucleus where it can act as a transcription factor that upregulates IL-6 production and secretion. IL-6, working locally through paracrine and/or endocrine mechanisms to activate IL-6 signaling, induces IR in hepatocytes [62]. Hepatic production of IL-6 also explains the muscle involvement in IR. NF- κ B target genes are not upregulated in transgenic mouse muscle, but IL-6 target genes are, including suppressor of cytokine signaling and signal transducer and activator of transcription proteins. These genes are reversed during IL-6 neutralization, which is consistent with the pathogenic involvement of IL-6. Activation of NF- κ B leads to a severe syndrome of muscle wasting, surprisingly without IR [63].

Obesity, aging, and fat mass influence the growth hormone/insulin-like growth factor (IGF)-I axis, key regulator of insulin sensitivity, and chronic inflammation might reduce IGF-I signaling. In a recent study population, lower IGF-I status is associated with higher FM, spleen longitudinal diameter, CRP and more severe hepatic steatosis [64].

Interleukin-6 drives CRP production by the liver, but it is abundantly produced also by visceral adipose tissue in obese patients. The confounding effect of visceral obesity colors the findings of much of the published data investigating IL-6 in OSAS. As with CRP, a number of case control studies favor an independent effect of OSAS on IL-6 levels [65], while other researchers show some criticism to this interpretation [66].

SPLEEN INVOLVEMENT

Emerging data point towards an important role for macrophages in the priming of naïve T cells. Accordingly, macrophages derived from spleen can have an important role in regulating T-cell responses; furthermore, the spleen is one of the centers of activity of the reticulo-endothelial system [67]. In humans, the spleen does act as a reservoir for platelets that are major carriers of serotonin (5-HT) in the blood. 5-HT has been reported to modulate T cell and natural killer (NK) cell proliferation, thus providing an important link between this neurotransmitter and the immune system [68]. Another study, examining the mRNA expression of 5-HT receptors in the cells of lymphoid tissues of isolated spleen of the rat, confirmed 5-HT receptors in mitogen-stimulated spleen cells [69]. As intriguing link, platelets are attracted to the liver following systemic inflammatory stimuli.

OBSTRUCTIVE SLEEP APNOEA SYNDROME, INFLAMMATION AND IMMUNITY

There is emerging evidence that inflammatory processes leading to endothelial dysfunction play a pivotal role. Various studies, considered by Kent et al [70] have demonstrated elevated inflammatory markers in OSAS patients in comparison to matched control subjects with a significant fall after effective treatment with CPAP [71]. Cell culture and animal studies have significantly enhanced understanding of the pathophysiology of inflammation in OSAS [71]. Intermittent hypoxia, the hallmark feature of OSAS, leads to a preferential activation of inflammatory pathways with the downstream consequence of expression of pro-inflammatory cytokines, chemokines and adhesion molecules that may contribute to endothelial dysfunction [71].

Although the etiology of OSAS is uncertain, intense local and systemic inflammation is present in these patients. This process, in the upper airway, may promote oropharyngeal inspiratory muscles dysfunction with their subsequent collapsibility and may amplify upper airway narrowing with the effect of worsening the frequency and duration of apnoea episodes during sleep [71]. The presence of systemic inflammation, characterized by elevated levels of certain potent pro-inflammatory mediators (CRP, leptin, TNF- α , IL-1 β , IL-6), reactive oxygen species (ROS) and adhesion molecules, not always evidenced, may predispose to the development of cardiovascular complications observed in patients with OSAS [71]. Treatment with nasal CPAP in part abrogates local and systemic inflammation in these patients. Clearly, further research is necessary to elucidate the mechanisms of inflammation in inducing and maintaining OSAS [71]. Sources of cytokine production other than monocytes/macrophages and inflammatory cellular trafficking need to be better defined in OSAS [71].

Furthermore, the effect of OSAS in the immune system appears to be systemic. Increased plasma levels of TNF- α , CRP, and its major regulator, IL-6, which is secreted by monocytes (again the role of spleen is determinant) in response to hypoxia, have been demonstrated in OSAS patients [72-75].

A significant decrease in the levels of these factors has been reported after application of CPAP [76]. Also, the Th1 cytokine pattern in OSAS is further accompanied by functional and numerical alterations of peripheral blood lymphocytes. An activated phenotype is exhibited in CD8+ cells of OSAS patients, which is characterized by overexpression of perforin and TNF- α and excessive cytotoxicity against various cell lines, all of which decrease after CPAP therapy [77].

INTERMITTENT HYPOXIA AND OSAS: A MAJOR STIMULUS

The desaturation–reoxygenation sequence is a classic pattern coupled with a great number of respiratory events. This sequence, defined as intermittent hypoxia (IH), conducts to oxidative stress, with production of ROS. Several studies [78–80] have shown increased oxidative stress using various biological markers, even if co-morbid conditions such as T2D, hypertension and obesity may account for some of these results. The increased levels of ROS contribute to the generation of adhesion molecules [81], activation of leucocytes [82] and production of systemic inflammation [73]. Together, these mechanisms generate vascular endothelial damage and dysfunction [83]. Furthermore, a high sympathetic output, as frequently found in OSAS, may lead to IR, even in non-obese OSAS patients [84], representing an additional source of oxidative stress. Oxidative stress is characterised by an imbalance between the production and degradation of ROS. It has been proposed that oxidative stress driven by IH may initiate systemic inflammation in OSAS [85]. Oxidative stress occurs when production of ROS exceeds antioxidant supply, as seen in ischaemia–reperfusion injury. Data from animal

models support a role for ROS, particularly in the generation of cardio-respiratory instability by chronic IH [86]. Similarly, some investigators have found increased circulating markers of oxidative stress in OSAS patients, while leucocytes from OSAS patients have been found to be more potent producers of ROS than those isolated from controls [86–88]. Furthermore, this increase in ROS production can be eliminated or drastically reduced by CPAP treatment.

Oxidative stress generates an inflammatory cascade via NF- κ B activation. Nevertheless, there is still much discussion regarding the confounding influence of obesity and the associated metabolic morbidity on the relationship between sleep apnoea severity and inflammatory markers [89]. This is probably responsible for the conflicting results obtained regarding CRP in OSAS. Even if CRP levels were found to be elevated in several studies, other reports failed to demonstrate any linear relationship to the severity of OSA [72, 90]. Beyond sleep fragmentation and sleep deprivation, the only form of hypoxia in OSAS, with recurrent short cycles of desaturation followed by rapid reoxygenation, termed IH, is probably thought to play an important role in the initiation of the inflammatory process (Fig. 2).

NF- κ B is a key player in inflammatory and innate immune responses and a master regulator of inflammatory gene expression. Genes like TNF- α or IL-8, which are central to the atherosclerotic process, and which have also been found to be upregulated in OSAS, are under the control of this transcription factor [86]. Obstructive sleep apnoea leads to NF- κ B activation, which may constitute an important pathway linking OSAS with systemic inflammation and cardiovascular disease [86]. Furthermore, it has been showed that NF- κ B-mediated, delayed apoptosis of polymorphonuclear cells in

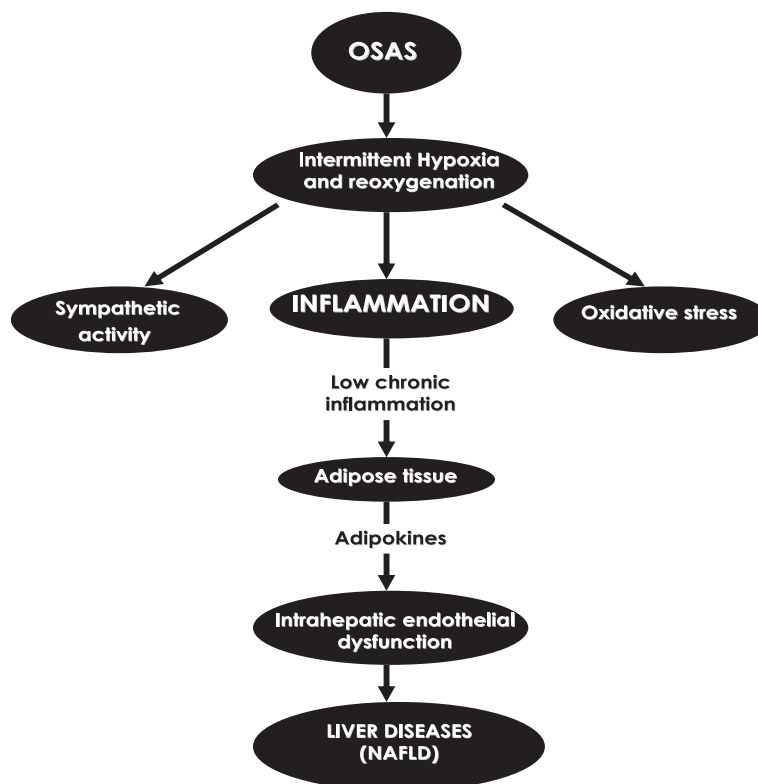


Fig. 2. Proposed pathways leading to liver diseases (NAFLD) in obstructive sleep apnoea (OSAS).

response to IH potentially augments inflammatory responses [87]. All these mechanisms lead to endothelial dysfunction and its damage. Furthermore, IH is associated with significant cyclical hemodynamic changes that may contribute to endothelial dysfunction. Whang et al showed that OSAS and its characteristic chronic IH can cause injuries to multiple organs, including the cardiovascular system, urinary system, and liver in rats with a high-fat diet [91]. Moreover, in rodent models, it has been evidenced that IH leads to liver damage and that it can result from a cascade of signals initiated by oxidative stress, inflammation and apoptosis [92]. It is noteworthy to stress that endurance-training with chronic IH does not alter general basal liver mitochondrial function, but may attenuate some adverse effects of salicylate [93]. Chouker et al showed that because liver protective effects of hypoxic preconditioning are negated when the adenosine A2B receptor is nonfunctional, the hypoxia→adenosine→A2B receptor pathway plays a critical role in the prevention of warm ischemia-reperfusion injury in vivo [94]. Hypoxic activation of this pathway warrants use of selective A2B receptor agonists or even intermittent hypoxia (e.g., in deceased organ donors) to protect from liver ischemia-reperfusion injury [94]. Jun et al have showed that acute hypoxia increases plasma triglycerides due to decreased tissue uptake, not to increased hepatic triglycerides secretion [95]. Drager et al have highlighted that chronic IH exacerbates IR and induces steatohepatitis in diet-induced obesity in mice, suggesting that chronic IH may account for metabolic dysfunction in obesity [96].

The prevalence of NAFLD, as reported by Turkay et al [97], was higher in patients with severe OSAS, suggesting a role for nocturnal hypoxemia in the pathogenesis of NAFLD.

Finally, it has been shown that in morbidly obese patients undergoing bariatric surgery during which a liver needle biopsy as well as surgical subcutaneous and omental adipose tissue biopsies were obtained, IH was strongly associated with more severe liver injuries but did not worsen obesity-induced macrophage accumulation in adipose tissue depots [98].

PREVENTION OF SYSTEMIC INFLAMMATION

A large body of evidence supports a role for adipose tissue-derived pro-inflammatory cytokines in the pathogenesis of T2D and atherosclerotic diseases, as reported by Huffman et al [99]. Therefore, Ohman et al [100] administered pioglitazone, which has been shown to reduce monocyte chemoattractant protein-1 (MCP-1) levels and fat inflammation, to ApoE^{-/-} mice that received a visceral fat transplant or sham-operated controls. Pioglitazone treatment lowered MCP-1 levels and macrophage content in the visceral fat transplant and reduced atherosclerosis development in visceral fat-transplant mice, but not in sham-operated mice [101]. Another study in obese mice showed that short-term treatment with a pharmacological antagonist of chemokine (C-C motif) receptor 2 (CCR2) lowered macrophages content in adipose tissue and systemic inflammation, resulting in improved insulin action [102]. Therefore, drugs that can interfere with the infiltration of macrophages into fat, and in particular visceral fat, may provide an effective strategy for the prevention of cardiovascular risks,

OSAS, NAFLD and metabolic syndrome due to abdominal obesity [99-101].

UNANSWERED QUESTIONS

Taking into account that low-grade chronic inflammation is fundamental in the progression of NAFLD toward liver cirrhosis, what role does the systemic inflammatory status in obesity play in triggering NAFLD and OSAS? Although an inflammatory state appears to be ameliorated with diet or lifestyle for NAFLD [102] and nasal CPAP therapy for OSAS [71], is the treatment of obesity (with its attendant inflammatory state) necessary to prevent recurrence of NAFLD and OSAS?

Recent evidence suggests that hypoxia could play a pivotal role in the pathogenesis of NAFLD but also NASH and cirrhosis [103].

CONCLUSION

Currently, it appears clear that there are complex bidirectional relationships between NAFLD, obesity and OSAS, with many factors affecting these diseases. Whether OSAS could worsen NAFLD and obesity is less clear at this time, although there are several potential mechanisms that support such a sequence. Whatever, the intriguing observations of reduction in visceral fat deposition [104] deserve further studies to delineate mechanisms and methods.

Conflicts of interest: No conflicts to declare.

Authors' contribution: The authors equally contributed to drafting the manuscript.

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