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Summary

Obstructive sleep apnea (OSA) and more importantly its hallmark chronic intermittent hypoxia (CIH), are established factors in the pathogenesis and exacerbation of nonalcoholic fatty liver disease (NAFLD). This has been clearly demonstrated in rodent models exposed to intermittent hypoxia, and strong evidence now also exists in both paediatric and adult human populations. OSA and CIH induce insulin-resistance and dyslipidemia which are involved in NAFLD physiopathogenesis. CIH increases the expression of the hypoxia inducible transcription factor $HIF1\alpha$ and that of downstream genes involved in lipogenesis, thereby increasing β-oxidation and consequently exacerbating liver oxidative stress. OSA also disrupts the gut liver axis, increasing intestinal permeability and with a possible role of gut microbiota in the link between OSA and NAFLD. OSA patients should be screened for NAFLD and *vice versa* those with NAFLD for OSA. To date there is no evidence that treating OSA with continuous positive airway pressure (CPAP) will improve NAFLD but it might at least stabilize and slow its progression. Nevertheless, these multimorbid patients should be efficiently treated for all their metabolic co-morbidities and be encouraged to follow weight stabilization or weight loss programs and physical activity life style interventions.

Keywords: Obstructive sleep apnea; chronic intermittent hypoxia; nonalcoholic fatty liver disease

1. Introduction

Worldwide we are currently facing an epidemic of obesity [1]. This is leading to an increase in the prevalence of obesity-related chronic diseases, in particular metabolic syndrome, insulin resistance, type-2 diabetes (T2D), obstructive sleep apnea (OSA) and nonalcoholic fatty liver disease (NAFLD) [2]. Frequently clusters of comorbidities co-exist in the same patients, who are described as 'multimorbid'. The risk factors, pathophysiology and consequences of these chronic diseases share common pathways. This suggests that the concomitant presence of obesity related-metabolic comorbidities, in particular OSA, and its most important consequence chronic intermittent hypoxia (CIH), and NAFLD would mutually exacerbate the severity of each other. In this review, we will detail the clinical evidence suggesting a link between OSA and NAFLD, and describe the mechanistic pathways involved in this relationship to date studied mainly in animal models. Finally, we will discuss whether treatment for OSA might improve NAFLD.

2. Obstructive sleep apnea (OSA)

Obstructive sleep apnea (OSA) is characterized by the repetitive occurrence of partial (hypopneas) or complete (apneas) pharyngeal collapse during sleep. It is defined by the association of symptoms and an apnea + hypopnea index (AHI) above 5/hour of sleep. OSA is a major global health concern with multiple systemic consequences. OSA alters cognitive functions [3], daytime alertness (causing traffic accidents), and is associated with mood and neurological disorders (stroke). It is associated with obesity in more than 60% of cases [4] and causes considerable cardiovascular and metabolic morbidity and mortality [5,6]. OSA has been independently associated with the different components of metabolic syndrome, particularly visceral obesity, hypertension, insulin resistance [7] and abnormal lipid metabolism [8]. Furthermore, the severity of OSA has been linked with worse insulin resistance independently of the degree of obesity [9]. OSA induces the repetitive occurrence of the hypoxia-re-oxygenation sequence (i.e. chronic intermittent hypoxia (CIH)) that subsequently results in low grade inflammation, sympathetic over-activity and oxidative stress [10]. Currently, continuous positive airway pressure (CPAP) is the gold standard treatment of OSA [6]. CPAP applied during sleep aims at re-opening and stabilizing the upper airway, thereby suppressing abnormal respiratory events. It is highly effective in reducing daytime sleepiness [11] and improving daytime functioning. The beneficial effect of CPAP on

symptoms and quality of life is obtained after only a few days of treatment. Nevertheless its efficacy regarding cardio-metabolic outcomes and mortality remains to be established in large randomized controlled trials (RCT). Not all studies have shown a positive impact of CPAP alone on cardiovascular outcomes, and point to the need for a multimodal treatment strategy. Combination therapies (CPAP plus weight loss or CPAP plus physical activity) may be required to address both OSA and its co-morbidities [12]. Weight loss [13], either by diet intervention, or bariatric surgery [14] in the case of morbid obesity, is able to provide significant improvement in OSA [15].

3. NAFLD

Nonalcoholic liver fatty liver disease (NAFLD) is a highly prevalent condition and its prevalence is increasing in parallel with the epidemic of obesity and type-2 diabetes [16]. The prevalence of NAFLD varies from 6 to 33% in the general population and can reach 90% in the morbid obese patient population [16,17]. The diagnosis is based on histological examination and requires a liver biopsy. This disease starts with the accumulation of hepatic triglycerides known as steatosis. Although some patients remain at this stage, others develop further liver deterioration that leads to overt steato-hepatitis (NASH) defined as the presence of steatosis, hepatocyte ballooning and inflammatory infiltration [18–20]. NASH may be accompanied by liver fibrosis that can further progress towards cirrhosis and hepatocarcinoma [21]. A NAFLD activity score (NAS) has been validated in clinical studies, and NASH is defined as a NAS above 5 [22]. More recently, in order to take into account the presence and severity of liver fibrosis, which determines the disease's prognosis, a new scoring system, called SAF, has been proposed. SAF has been validated in liver biopsies in a large morbid obese cohort [23]. Non-invasive tools, such as a serum algorithm [24,25] or elastography [26] are being developed and enable patients to be screened for NAFLD, NASH and fibrosis. These tools have been validated in clinical studies that compared them to histological diagnosis using liver biopsy.

Although the complete physiopathology of NAFLD is not entirely understood, many factors such as insulin resistance, inflammation, oxidative stress and lipotoxicity have been proposed as being involved in the onset of NAFLD [27,28].

4. OSA and the progression from steatosis to steatohepatitis

It appears that OSA and NAFLD share common intermediary mechanisms. Thus, the presence of OSA, but most especially its consequence, severe CIH, has been suggested as being involved in the pathogenesis and exacerbation of the severity of NAFLD (Figure 1).

4.1 Studies in mice

Experimental studies with rodents exposed to CIH have allowed the mechanisms linking OSA and NAFLD to be elucidated. Rodents are caged in a device where the inspired oxygen fraction (FiO$_2$) is altered during their sleep period. The most commonly used pattern of exposure corresponds to cycles of 30 seconds of normoxia followed by 30 seconds of FiO$_2$ reduced to 5% for 8 hours, mimicking severe sleep apnea [29–31]. Animals had continuous access to food and water and a 12h day/night cycle. Short term CIH exposure (2 weeks) using this experimental design did not affect liver histology in lean mice [29]. However, when diet-induced obese mice or genetically obese mice [29,32], are subjected to induced CIH, histological liver damage mimicking the NAFLD phenotype is observed after both short (4 weeks) [33] and longer duration exposure (12 weeks or 6 months). Histological liver analysis using Trichrome Masson staining demonstrated increased red staining marking hepatic steatosis as well as fibrosis. Overall, these results suggest that CIH is indeed involved in NAFLD pathogenesis in obesity. In lean mice, CIH exposure over a longer period or a second toxic hit may be needed to induce NAFLD.

4.2. Studies in Adults

There is now a strong evidence for a link between NAFLD and the presence of OSA. This link seems even more obvious in the presence of severe OSA consequences, namely CIH. Only a few studies have found no adverse effect of OSA on the liver, however these presented some limitations. In a cohort of morbidly obese patients, while those with OSA had raised liver enzymes [34], there were no correlations between the AHI and different components of histological liver alterations (of which all are not included in the diagnosis of NASH), nor was there more NASH in patients with or without OSA. However, the authors did not look at the effects of CIH on liver alterations. Likewise, another study found no relationship between OSA and NAFLD severity, but the authors had included OSA patients

already treated by CPAP, which might have limited the effects seen in the OSA group since they did not display severe CIH anymore [35].

In contrast, the majority of studies demonstrate a link between these two chronic conditions. Using non-invasive surrogate markers of liver injury to diagnose NAFLD, Türkay et al. showed that the presence of OSA increased the severity of steatosis as evaluated by ultrasound [36], independently of BMI. A recent meta-analysis by Sookoian and Piorola included 11 studies, with 668 OSA patients compared to 404 control subjects. They demonstrated that OSA was associated with a significant increase in liver enzymes (in particular ALT) suggesting, again using a non-invasive surrogate of NAFLD, that OSA is associated with liver deterioration independently of BMI and diabetic status [37]. A recent study performed in overweight Indians that used an indirect diagnostic tool (elastography) to detect NAFLD, concluded there to be a very high prevalence of NAFLD in OSA patients. Furthermore, in multivariate analysis, AHI was found to be the only significant predictor of liver fibrosis. Most importantly, the severity of CIH correlated with increased fibrosis as determined by liver elastography [38]. Other human studies using liver biopsies had suggested this relationship [39,40]; however, the studies had some limitations. In particular, Tanne et al. performed liver biopsies solely in patients with abnormal liver enzymes. Yet, since it is known that 40% of patients with biopsy proven diagnosis of NAFLD or NASH actually have normal liver enzymes [41,42], they might have found a stronger association if they had performed a liver biopsy in the entire cohort.

Recent studies have proposed that the presence of OSA with or without CIH (the latter reflecting the severity of OSA) exacerbated NAFLD severity and favored the development of NASH [43–45]. These studies based their conclusion on liver biopsy diagnosis but the sample size was rather small or an indirect measurement was used to determine the severity of OSA. Furthermore, a subgroup analysis from a recent study demonstrated that the severity of CIH was associated with increased severity of NAFLD and fibrosis, in those patients that benefited from both polysomnography and liver biopsy [46]. Finally, in a large cohort of 100 morbid obese patients with biopsy proven NAFLD/NASH we demonstrated that there was a dose response effect of CIH on the exacerbation of NAFLD severity [47] independent of all metabolic confounding factors. Furthermore, CIH was also an independent risk factor for the development of liver fibrosis. A recent study demonstrated that morbidly obese patients with liver fibrosis had higher AHI and more severe oxygen

desaturations than those without liver fibrosis [48]. Interestingly, in an OSA population with a wide range of BMI [from lean to morbidly obese), where NAFLD was diagnosed according to a non-invasive systemic algorithm (i.e. Fibrotest®, Nashtest® and Steatotest®), the prevalence of NAFLD increased with OSA severity. Importantly, the severity of nocturnal hypoxia was independently associated with steatosis. However, the dose-response relationship between the severity of nocturnal hypoxia and liver injury was established only in the morbid obese subgroup and not in lean OSA patients [49]. The results of a recent study are in agreement with this; in a large cohort of non-obese individuals who systematically underwent polysomnography and had NAFLD diagnosed using ultrasound (i.e liver steatosis) the authors showed that patients with steatosis had greater severity of CIH. Furthermore, in multi regression analysis the severity of CIH, BMI and triglyceride concentrations, were independent predictors of NAFLD development. However, it was impossible to demonstrate a dose-response relationship in this study since the severity of NAFLD cannot be graded by using ultrasound alone. [50]. Likewise, in a population including both lean and overweight NAFLD patients diagnosed using ultrasound, the severity of CIH was an independent predictor of increased liver enzymes in the multiple regression analysis [51]. Overall, OSA even in non-obese patients seems to be associated with NAFLD development.

Finally, in a recent meta-analysis using biopsy proven liver fibrosis, OSA patients displayed a 2.6-fold higher risk of liver fibrosis when they had NAFLD [37]. The severity of OSA was associated with the severity of liver disease, as defined by the presence of NASH or advanced fibrosis [46]. It was also demonstrated that the absence of OSA seemed protective of NAFLD development in morbidly obese patients [47].

4. 3. Studies in children

The growing worldwide epidemic of obesity also affects children, with an increase in obesity related-diseases. Consequently, NAFLD has been more systematically investigated in child populations than previously [48,49]. The prevalence of NAFLD reaches 10% of the paediatric population and attains 60% in obese children [56]. Therefore, expanding literature in the field of paediatric NAFLD describes its epidemiology, diagnostic procedures, and studies of the mechanistic pathways [57]. It was demonstrated that OSA was more frequent in children with NAFLD even in non-obese individuals. A study using surrogate markers of NAFLD found that OSA was associated with an increase in liver enzymes in paediatric

populations [58]. Interestingly, circulating surrogate markers of liver apoptosis and inflammatory markers are elevated in children with OSA [59]. Furthermore, the dose-response relationship between the amount of oxygen desaturation during the night and the severity of liver injury that has been established in adults also seems to prevail in children [60,61]. Indeed, in a large cohort of 81 children who benefited from polysomnography and liver biopsy analysis, NAFLD was again found to be associated with OSA severity [62].

Overall, both murine and human studies in adults or in children (summarized in Table 1) are concordant and show a strong link between OSA and NAFLD. Most importantly, the strongest factor associated with the exacerbation of NAFLD and fibrosis aggravation during OSA is its consequence i.e the severity of chronic intermittent hypoxia, independently of confounding metabolic factors.

5. Physiopathology linking CIH and NAFLD

There is an organ-specific response to intermittent hypoxia and the liver is highly sensitive to this stimulus. In rodent models of exposure to CIH, the severity of pO_2 oscillations was closely reproduced in the liver, whereas other organs such as fat tissue were less affected [63] both in lean and obese mice. Regarding molecular pathways, during normoxia, transcription factor HIF1α is degraded in the proteasome. In contrast, during sustained hypoxia or CIH, HIF1α appears to be stabilized and can reach the nucleus, bind to DNA and subsequently induce its target genes [64].

5.1. *CIH induces metabolic abnormalities*

It has been shown in murine models that one night of CIH significantly increased fasting glycaemia, both in obese and lean mice, with an exacerbation of abnormal glucose control occurring in obese animals [63]. Most importantly, many studies confirm that CIH induces insulin-resistance in lean mice and to a much greater extent when they are obese [33]. There is also a dose response relationship between the duration of CIH and insulin-resistance exacerbation in obese animals [65]. It has been suggested that this increase in glycemia originates from increased neoglucogenesis during CIH. Indeed, selective inhibition of HIF1α reduces fasting glycemia, insulin levels and glucose output as well as decreasing phosphoenolpyruvate carboxykinase (PEPCK) gene expression, the main enzyme involved in neoglucogenesis [66].

Short duration CIH also induces increased systemic concentrations of triglycerides as well as the levels of other lipids [29] both in lean and obese animals [9]. This phenomenon is further exacerbated with a longer duration of CIH [67]. Interestingly, the inhibition of HIF1α prevents this increase in systemic lipid concentrations [68], even upon CIH exposure. This increase in systemic triglycerides originates from a decrease in lipoprotein clearance, due to a 5-fold reduction in adipose tissue lipoprotein lipase activity during CIH [67].

Likewise, these metabolic changes observed in mice that could mediate the effects of OSA/CIH on the liver are also seen in humans. Firstly, OSA exacerbates metabolic abnormalities such as insulin resistance and overt Type-2 diabetes independently of BMI [69–71]. Secondly, OSA also plays a role in aggravating dyslipidemia in humans [72]. Thirdly, CIH increases systemic inflammation in humans [47,70]. Furthermore, gene expression of the inflammation transcription factor Nf-κβ is increased in the liver of adult NAFLD patients [73]. In the paediatric population, liver local inflammation is also increased in intrahepatic leucocytes and activated macrophages (Kupffer cells) particularly in children with the most severe CIH [54].

5.2. CIH induces gene expression involved in lipogenesis

In mice, a short exposure to CIH (i.e. 5 days) induces the expression of genes involved in lipogenesis such as Sterol Regulatory Element-Binding Protein 1c (SREBP1c), Acetyl-CoA carboxylase (ACC) and Fatty acid synthase (FAS) [29] and this is translated into increased levels of liver triglycerides [29,32]. Importantly, liver triglyceride content is increased upon CIH compared to normoxia both in lean and obese animals [74], but the increase is even greater in the obese [29]. The duration of CIH also affects the severity of liver lipid content and fibrosis deposition as seen after 6 months of CIH [32]. In contrast, selective inhibition of the HIF1α pathway led to a reduction in liver triglycerides in transgenic mice as compared to wild type animals [75]. This reduction in liver triglyceride content after inhibition of the HIF1α pathway originates from a reduced expression of genes involved in lipogenesis such as ACC [66]. Overall, these data confirm that CIH increases lipogenesis by inducing the HIF1α pathway.

5.3. CIH induces LOX expression which is involved in extra-cellular matrix rigidity

CIH induces HIF1α which in turn induces the expression of LOX (lysyl oxidase)enzyme. LOX is involved in the cross linking of collagen fibers in the extra-cellular matrix and is implicated in

increased fibrosis and rigidity in various tissues.[76]. It was recently demonstrated that patients with OSA and severe liver fibrosis had an elevated systemic concentration of LOX [48]; the authors suggested that LOX could be a useful biomarker of liver fibrosis in OSA patients. In-vitro models also demonstrated that submitting hepatocytes to hypoxia induced LOX gene expression and increased LOX protein concentration suggesting a new mechanism linking CIH and fibrosis [48].

5.4. *CIH induces oxidative stress and lipid peroxidation*

Oxidative stress is among the mechanisms involved in CIH induced NAFLD. Indeed, the production of reactive oxygen species favours liver lipid peroxidation, which can be prevented by the use of antioxidants [32,77]. In murine studies, CIH induces increased lipid peroxidation in the livers of obese animals [32,78]. In contrast, in lean mice, 4 weeks of exposure to CIH did not induce this oxidative stress [79]. Nevertheless, exposure of lean mice to 12 weeks of CIH increased lipid peroxidation in the absence of obesity [78]. Conversely, when the oxidative stress pathway was blocked using a pharmacological agent, lipid peroxidation decreased in the liver even after CIH exposure [77].

5.5. *CIH induces mitochondrial dysfunction*

During hypoxia, HIF1α activates the metabolic pathway leading to the conversion of pyruvate into lactate, thereby inhibiting its entry into the mitochondria and the β-oxidation process. Furthermore, HIF1α also inhibits mitochondrial biogenesis [80]. Finally as discussed earlier, CIH induces liver inflammation as seen by the increased expression of liver TNFα [63]. In *in-vitro* models, hepatocytes incubated under normoxia in the presence of TNFα displayed an increased concentration of HIF1α which led to a decrease in oxygen consumption by all the mitochondrial respiratory chain complex [81]. Furthermore, the incubation of hepatocytes with TNFα has been associated with increased oxidative stress, which *per se* is able to induce the HIF1α gene and protein expression, thus creating a vicious circle [82]. Overall, these results suggest that liver inflammation *per se* participates in mitochondrial dysfunction. During hypoxia, mitochondria may be unable to process the increased free fatty acid (FFA) flux leading to the production of other lipotoxic lipid metabolites favouring NAFLD development. An alternative hypothesis is that FFA are rerouted towards the peroxisome where they undergo lipid peroxidation, as seen earlier.

5.6. CIH induces intestinal permeability and disrupts the gut-liver axis

Finally, a recent study in children adds to our understanding of the mechanism of OSA induced NAFLD. Nobili et al. showed that OSA increases intestinal permeability resulting in increased systemic levels of lipopolysaccharides (LPS), and as a result an up-regulation of Toll‑like receptors 4 (TRL-4) in hepatocytes, Kupffer cells and hepatic stellate cells (HSC) [62]. These results suggest that the microbiota might be involved in OSA-related NASH; in line with previous studies linking dysbiosis of the gut microbiota with NASH physiopathology, reviewed in [83]. Indeed, Kheirandish-Gozal et al. demonstrated in a large cohort of 219 children, that systemic LPS levels increased in relation to OSA severity [84]. It is known that the gut microbiota might play a role in NAFLD pathogenesis as reviewed in [83] CIH might exacerbate gut microbiota dysbiosis and therefore participate in NAFLD exacerbation.

6. Impact of CPAP treatment on liver injury

In general, OSA is associated with metabolic comorbidities and in particular NAFLD development and severity. Since CPAP is the gold standard treatment for OSA, one might expect CPAP to have beneficial effects on metabolic parameters and limit liver degradation.

6.1. Effects of CPAP on metabolic parameters

Some trials have evaluated the impact of effective CPAP compared to sham placebo on various clinical and metabolic parameters [85]. A 6 week RCT in obese non-diabetic patients demonstrated that CPAP was effective in significantly reducing arterial blood pressure but was unable to improve or modify insulin-resistance [86]. These results were confirmed in another RCT of around 60 obese non-T2D patients randomized to 12 weeks of CPAP or sham CPAP. Although the intervention was longer the authors observed no reduction in visceral fat mass or in insulin-resistance [87]. These results were further confirmed in a RCT that included OSA patients with T2D, treated with CPAP or sham CPAP for three months. Again no difference in corpulence or insulin-sensitivity parameters was observed [88]. Thus it was not surprising that a meta-analysis confirmed that CPAP treatment had no significant effect on glucose and insulin-resistance parameters [89]. Finally, a recent review summarized the effects of CPAP on several metabolic parameters

and concluded to the absence of improvement in metabolic or inflammatory markers, including lipids levels or the proportion of patients with metabolic syndrome [8].

6.2. *Effects of CPAP on NAFLD*

Since OSA is associated with NAFLD development and severity, a growing literature reports studies on the effect of CPAP on NAFLD. Some observational studies have suggested that CPAP treatment could induce a significant reduction of liver enzymes, even after a first night of effective treatment. Chin et al. reported that this beneficial effect on surrogate markers of NAFLD was maintained after 1 and 6 months [90]. Likewise, similar results were observed in children [52]. However, these non-randomized observational studies had limitations and bias since they used very indirect surrogate markers of NAFLD [91].

In contrast, a randomized study comparing the evolution of liver enzymes after 4 weeks of effective CPAP treatment versus sham CPAP did not show any differences in this surrogate marker of NAFLD. Indeed AST did not show any evolution and ALT levels decreased similarly in both groups without any significant intergroup differences [92]. Likewise, a randomized crossover study comparing the effect of CPAP or sham CPAP on obese patients with NAFLD and OSA did not display any effects of effective CPAP. Indeed, effective CPAP did not change fatty liver content or liver enzyme levels in the two months of treatment [91]. Similarly, in an earlier study comparing sham versus effective CPAP, in which liver fat was estimated by CT-scan, a surrogate marker of NAFLD, was unchanged after 12 weeks. This was in line with the lack of improvement in lipid profile and glycemic control. After the first 12 weeks the sham group was switched to effective CPAP treatment and again no significant change was observed in liver fat levels or any other metabolic parameters [87].

Finally, a recent RCT using more robust non-invasive markers of NAFLD (i.e. Fibrotest®, Nashtest® and Steatotest®) showed no impact of effective CPAP treatment on NAFLD regression [93]. Thus, it appears that although OSA and more importantly CIH is associated with NAFLD, short term CPAP treatment alone does not improve liver damage. In our view, it is not surprising that short term CPAP treatment did not lead to any improvement in histological liver alterations. Indeed, in other intervention models, there is a need for either a longer duration of treatment or associated interventions to see any effect on all metabolic parameters. For example, liver biopsy alterations improve only one year after post-bariatric surgery [94]. However, it is important to recall that, after such surgery

patients not only lose weight but also improve their metabolic complications and OSA [14]. This further suggests, that in order to correct liver alterations, there might be a need to improve all the metabolic parameters involved in NAFLD. Overall, since, CIH plays a role in NAFLD development and NASH exacerbation; we strongly believe that alleviating any of the deleterious mechanisms will be helpful for the patient. This might at least stabilize the disease and limit NASH progression.

Furthermore, it might be that synergic treatments such as a diet intervention program with weight loss and/or bariatric surgery together with CPAP are needed to improve NAFLD although this remains to be demonstrated. Weight loss has been demonstrated to improve metabolic parameters [95] and to lead to NAFLD improvement. However, the goal of at least 10% weight loss, which is the demonstrated cut-off to obtain clinical benefit [96], is very difficult to achieve and maintain over time [97,98]. Finally, it was also demonstrated that untreated OSA patients have more difficulty to losing weight [99], again suggesting that CPAP when needed CPAP should be prescribed. Overall, we believe that it is not only of utmost importance to try to induce weight loss in every patient with NAFLD, but also to take all possible steps to improve their metabolic parameters, including the treatment of OSA.

7. **Conclusion**

In summary, studies in rodents provide some evidence that OSA and particularly its major adverse consequence, CIH, is implicated in the pathogenesis and exacerbation of NAFLD. Data in humans (adults and children) also suggest a strong link between OSA, CIH and NAFLD. However, the causative role of OSA and CIH in the development of NAFLD or the exacerbation of NASH exacerbation remains to be more clearly demonstrated in humans. There is a need for longitudinal studies investigating whether pre-existing OSA can lead to NAFLD in order to definitively confirm this causal relationship. Another definite demonstration would be a positive impact of OSA treatment in slowing the evolution of NAFLD.

The several physiological pathways involved are outlined in Figure 2. OSA and CIH induce inflammation and oxidative stress leading to insulin-resistance and dyslipidemia, all of which are involved in the physiopathogenesis of NAFLD. CIH also exacerbates NALFD by inducing *HIF1α* gene expression and consequently the expression of particular genes involved in

lipogenesis, thereby increasing β-oxidation and thus exacerbating oxidative stress. In addition, a recent study in children suggested that OSA leads to disruption of the gut-liver axis, increasing intestinal permeability and possibly implicating the gut microbiota in the link between OSA and NAFLD [100]. Further studies in adults are needed to confirm these recent observations.

In brief, patients with OSA should be screened for NAFLD and vice versa those with NAFLD for OSA. Importantly, patients with NAFLD or NASH with increased excessive daytime sleepiness have worse liver alterations than others, emphasizing the importance of treating OSA in these patients even when they are not overly obese [101]. However, NAFLD patients seem to have a low prevalence of daytime sleepiness [38,101].

This suggests that a sleep study should be systematically performed in NAFLD patients to detect OSA, even in pauci-symptomatic patients. This recommendation is supported by the results of a recent study that showed that in newly diagnosed NAFLD patients (lean and overweight) systematically assessed by polysomnography, 83% exhibited OSA. [51]. The evidence currently available does not suggest that treating OSA with CPAP will reverse NAFLD exacerbation, although it might at least stabilize it or slow the progression. However, screening and treating OSA with CPAP have been shown to be beneficial on OSA specific outcomes and metabolic alterations such as hypertension. Therefore even if CPAP has not yet been shown to have any specific effects on improving liver pathology, its use should be encouraged whenever possible so as to alleviate some of the metabolic conditions also implicated in NAFLD. More studies and especially long-term RCTs are needed to determine whether treating one would benefit the outcome of the other. In any case, these patients should be efficiently treated for all their metabolic comorbidities and encouraged to follow weight stabilization or weight loss programs.

Conflict of Interest

None of the authors have a conflict of interest with respect to this work

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Legends to figures

Figure 1: Evolution of NAFLD severity according to corpulence and severity: *Taken together, studies performed in lean mice and in murine obese models suggest that CIH induces the expression of genes involved in NAFLD such as lipogenesis, inflammation and extra cellular matrix deposition without significant histological changes. Both murine and human studies performed in the overweight or obese demonstrate that CIH induces liver triglyceride deposition with proven histological steatosis. Finally, CIH exacerbates NAFLD in the obese leading to increased severity manifested as NASH and fibrosis induction.*

Figure 2: pathophysiological pathways involving CIH and NAFLD: *Red arrows represent what is known to occur during NAFLD: an increase in FFA flux coming from increased lipolysis in the adipose tissues in the obese and accumulating in the liver, which participates towards increased lipogenesis. Subsequently, it induces increased β-oxidation and ROS production as well as lipotoxic metabolite production that contribute to liver injury. Blue arrows represent pathways activated during OSA and CIH. CIH induces increased adipose tissue lipolysis with greater FFA flux. It also induces liver inflammation. CIH blocks β-oxidation but provokes mitochondrial dysfunction thus exacerbating ROS production and oxidative stress. Gut microbiota and altered intestinal permeability also seem to be involved in the mechanism linking OSA to NAFLD.*

Table 1. Human studies correlating obstructive sleep apnea and NAFLD.

Study	Population	Number	Tools to diagnose NAFLD/NASH	Tools to diagnose OSA/CIH	Findings	Limits
Adults						
Qi et al 2015	Lean and overweight	175	Ultrasound	PSG	↗ Steatosis with CIH severity	Indirect NAFLD diagnosis (steatosis and no quantifications)
Lin et al 2015	Lean and overweight	85	Ultrasound	PSG	↗ Steatosis with CIH severity	Indirect NAFLD diagnosis (steatosis and no quantifications)
Minville et al 2014	Sleep clinic lean, overweight and obese	226	Nash test , steatotest, fibrotest	PSG	↗ Steatosis with CIH severity Exacerbation of NASH with CIH severity on obese individuals	Indirect NAFLD diagnosis
Angrawal et al 2015	Indian overweight patients		Liver enzymes Liver elastography	PSG	↗ Fibrosis with the severity of CIH and increased AHI	Indirect marker of liver fibrosis
Petta et al	Lean, overweight and obese patients	126	Liver biopsy	PSG (50) Questionnaires (Epworth and stop bang)	↗ NAFLD and fibrosis severity with increasing CIH severity	PSG performed in a subgroup of 50 patients Indirect OSA diagnosis for more than 50% of the cohort
Tanne et al 2005	Overweight	163	Liver biopsy and liver enzymes	PSG	AHI predicted liver histology independently of age and BMI	Liver biopsies performed only in patients with elevated liver enzymes
Turkay et al 2012	Sleep unit patients Overweight and moderate obesity	112	Ultrasound (steatosis) Liver enzymes	PSG OSA diagnosed with AHI>15/h	↗ Prevalence and severity of steatosis in OSA patients AHI and ODI independently predicted NAFLD	Surrogate NAFLD diagnostic tool
Pulixi et al 2014	BMI<35	159 patients vs. 80	Ultrasound	Questionnaires (Epworth and Berlin)	↗ NAFLD prevalence in OSA patients with excessive daytime sleepiness	Indirect OSA diagnosis Indirect NAFLD diagnosis (steatosis and no quantifications)

					controls	
Morbidly obese Adults						
Jouet et al 2007	Bariatric surgery setting	62	Liver biopsy	Polygraphy No OSA: AHI<10/h	- ↗ Liver enzymes in OSA patients - No associations between histologic NAFLD and OSA	No evaluation of CIH severity effects (ODI)
Daltro et al 2010	Bariatric surgery setting	40	Liver biopsy	PSG Comparison of patients with AHI< or > 15/h	- No associations between histologic NAFLD and IAH or Sat O2min	No evaluation of CIH severity effects (ODI) IAH cut-off to be discussed
Campos et al 2008	Bariatric surgery setting	200	Liver biopsy	Clinical diagnosis confirmed by PSG	OSA is an independent predictive factor of NASH vs. normal or simple steatosis	Included patients with CPAP treatment No evaluation of CIH severity effects
Ulitsky et al 2010	Bariatric surgery setting	253	Liver biopsy	Retrospective data from medical records	↗ Prevalence of OSA in NASH patients as compared to NAFLD and normal liver	Indirect diagnosis of OSA No evaluation of CIH severity effects
Polotsky et al 2009	Bariatric surgery setting	90	Liver biopsy and Liver enzymes	PSG	OSA and increased CIH exacerbate NAFLD development and NASH severity	Liver biopsies performed only in patients with elevated liver enzymes (smaller sample)
Mishra et al 2008	Bariatric surgery setting	101	Liver biopsy	PSG	OSA in associated with NASH development ↗ CIH is associated with NAFLD exacerbation and fibrosis	
Aron-wisnewsky et al 2012	Bariatric surgery setting	101	Liver biopsy	Polygraphy	OSA in associated with NASH development Dose-response effect of CIH on the exacerbation of NAFLD, NASH and fibrosis	
Mesarwi et al 2015	Bariatric surgery setting	35	Liver biopsy	PSG	↗ Fibrosis with the severity of CIH and increased AHI	

Children						
Kheirandish et al 2008	Children from 4 to 17	376	Liver enzymes	PSG	↗ Liver enzymes in children with OSA vs. without	Indirect diagnosis of NAFLD
Nobili et al 2014	Lean overweight children	65	Liver Biopsy	PSG	↗ severity of NAFLD with the severity of CIH	
Nobili et al 2015	Lean overweight children	81	Liver Biopsy	PSG	↗ severity of NAFLD with the severity of CIH Alteration of liver-gut axis with the severity of OSA	
Sundaram et al 2014	Obese children	25	Liver Biopsy	PSG	↗ severity of NAFLD with the severity of CIH	

PSG: polysomnography; AHI: apnea/ hypopnea index; ODI oxygen desaturation index reflects CIH severity; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steato-hepatitis.
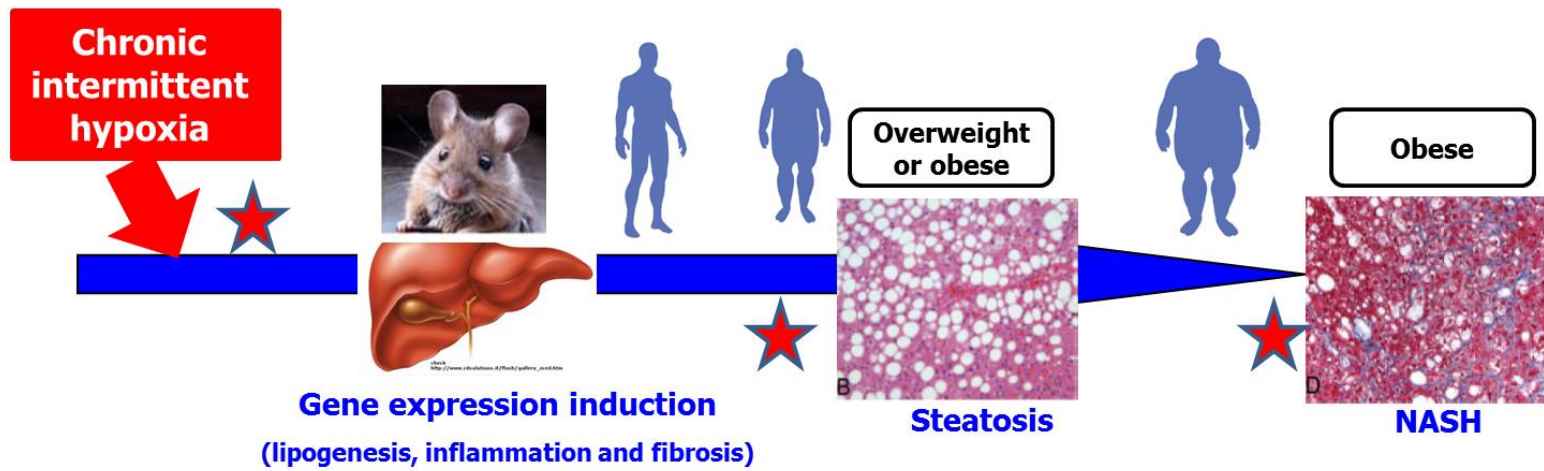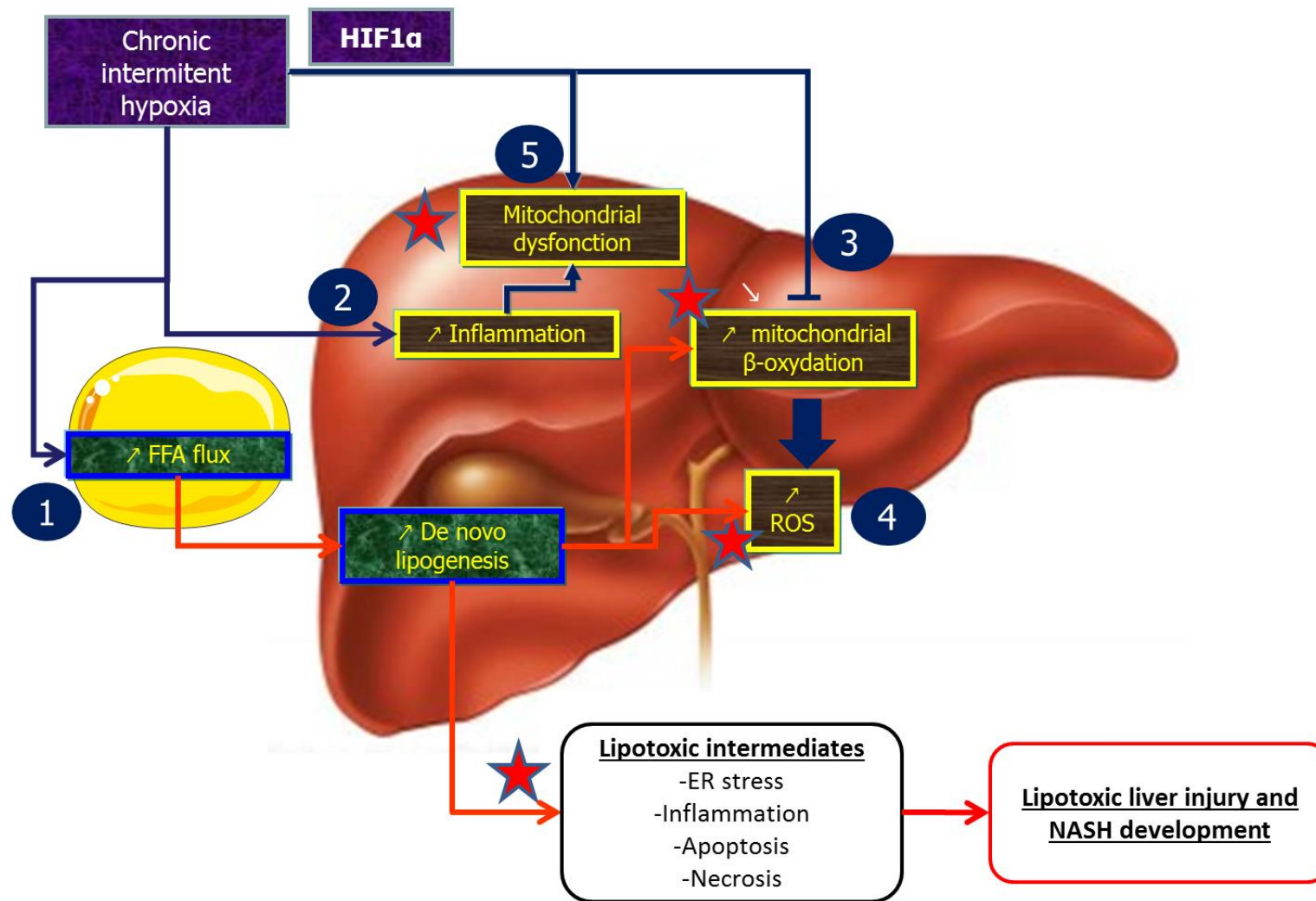
Figure 1

Figure 2