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REVIEW

Sleep apnea and fatty liver disease: The growing link and management issues

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Abstract

Obstructive sleep apnea (OSA) is associated with metabolic, cardiovascular and neuropsychological disorders, with substantial morbidity and economic costs. OSA has been estimated to affect 4%-11% of the population, depending on age. Obesity is a significant risk factor for OSA. Non alcoholic fatty liver disease (NAFLD) has emerged as an integral component of the metabolic syndrome, with insulin resistance as the central pathogenic feature. Estimates based on imaging and autopsy studies suggest that about 20%-30% of adults in the United States and other Western countries have NAFLD. Evidence now suggests that NAFLD is independently correlated to insulin resistance regardless of adiposity. Some authors have suggested that OSA may be another contributor to NAFLD development. In complex diseases, several or many different genes interact with environmental factors in determining disease presence or its phenotype. Individual genes only have a small effect on disease risk and can therefore be very difficult to identify. The genetic and hormonal determinants of OSA and NAFLD have received little attention. A wide variety of intermediate phenotypes and genes are involved in OSA and NAFLD which makes this syndrome genetically complex. Various adipokines, the most important of which are leptin, adiponectin, tumor necrosis factor-alpha, resistin and interleukin-6, have a key role in NAFLD and OSA. Some studies have suggested that oxidative stress may also contribute to the development of NAFLD and OSA. Lifestyle intervention, insulin sensitizer drugs and bariatric surgery aim to improve metabolic syndrome, OSA and NAFLD but need further investigation.

Key words: Body mass index; Inflammation; Asian Indian; Insulin resistance; Metabolic syndrome

Core tip: Obstructive sleep apnea (OSA) is associated with non alcoholic fatty liver disease (NAFLD) in animals and humans. Importantly, OSA can aggravate the development of NAFLD to nonalcoholic steatohepatitis in obese individuals. OSA has also been linked to other features of the metabolic syndrome, including dyslipidemia, insulin resistance and hypertension. A wide variety of intermediate phenotypes and genes are involved in sleep apnea and fatty liver which makes this syndrome genetically complex. Lifestyle intervention should be first line treatment for all NAFLD and OSA patients. Several drugs aim to improve metabolic syndrome but need further investigation. Bariatric surgery may improve conditions associated with metabolic syndrome, OSA and NAFLD in the morbidly obese.

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INTRODUCTION

Obstructive sleep apnea

Sleep apnea was first described in the context of the

Pickwickian syndrome[1]. Since then, sleep apnea has been recognized as a common problem, conservatively estimated to occur in over 5% of the population worldwide[2]. The hallmark of obstructive sleep apnea (OSA) is the sleep-related obstruction of the upper airway. There are significant drops in the oxygen saturation, changes in cardiac rhythm, arousals from sleep and increases in sympathetic tone due to the apnea. Sleep apnea is a disorder in which a person fails to breathe properly during sleep[3]. The three types of apnea are obstructive, central and mixed. OSA is characterized by repetitive collapse of the upper airway during sleep[4]. OSA is cause by either complete obstruction of the airway (obstructive apnea) or partial obstruction (obstructive hypopnea), both of which can cause arousal from sleep. Apnea is defined as cessation of airflow at both the nose and mouth for at least 10 s. OSA is defined in clinical and research setting as the apnea-hypopnea index (AHI = number of total apnea + number of total hypopnea/total time of sleep in hours). A person with severe OSA may have more than 100 waking episodes per hour in a single night. OSA prevalence is different in different populations.

The prevalence of OSA in habitual snorers is 35%-64% (25% of men and 20% of women in the normal adult white population)[5]. OSA is prevalent but largely undiagnosed in adults. According to estimates, in the United States approximately 12 million people between 30-60 years of age have obstructive sleep apnea[2]. It is estimated that approximately 4% of men and 2% of women in the middle age working population suffer from OSA[2]. The prevalence of OSA in habitual snorers is reported as 35%-64%[6].

A study indicates that about 60%-70% of patients with OSA are obese[7]. OSA is independently associated with insulin resistance[8]. OSA is more common in men aged 30-65 years, although it can occur in all age groups. The prevalence of OSA syndrome (OSAS), which is different from OSA in that it has an additional component of excessive daytime somnolence, has been reported to be between 0.3% and 7.5% in the general population in different studies[9]. Young and colleagues reported the prevalence of OSAS as 2% and 4%, respectively, for women and men in the United Kingdom population[2]. Moreover, the prevalence of OSAS in middle-aged men and women from Hong Kong was reported to be 4.1% and 2.1%, respectively[10].

As observed in various studies, with growing urbanization and nutrition transition, obesity and metabolic syndrome (MS) are increasing in Asian Indians[11]. Asian Indians are predisposed to develop central obesity[11], which can predispose them to the development of OSA. Our group is working extensively on the genetic and metabolic aspects of obesity[12,13]. In the context of OSA, studies reported in India are mainly on ethnic differences[14], awareness issues[15], relationship of OSA with heart disease[16] and the prevalence[17] of OSA. One questionnaire-based published study showed a positive family history of snoring[18] but few studies have been done to document the genetic and hormonal aspect in OSA. Singh *et al*[19] found that OSA symptoms were prevalent in 46 patients, with aminotransferase (AST) levels, imaging or biopsy findings suggestive of non alcoholic fatty liver disease (NAFLD). The prevalence of OSA symptoms tends to be even higher (63%) among the subset of patients whose liver biopsies showed a more advance disease. Udwadia *et al*[14] studied urban men between 35 to 65 years of age presenting to the hospital for a routine checkup and reported the estimated prevalence of OSA as 19.5% and that of OSAS as 7.5%.

NAFLD

NAFLD is a spectrum of liver disorders, ranging from isolated fatty infiltration of the liver to steatohepatitis (fatty infiltration with accompanying inflammation), to end stage cirrhosis. Normal liver contains approximately 5 g of lipids per 100 g of wet weight. Hepatic steatosis (fatty liver) is a term used when lipids, predominantly triglycerides, in liver are more than 5% of the liver weight. Size and weight of liver increases in the presence of hepatic steatosis and lipids may then account for up to as much as 50% of the liver weight[20]. Current evidence indicates that NAFLD is an integral manifestation of MS which consists of obesity, dyslipidemia, insulin resistance (IR) and hypertension. NAFLD is the most common form of liver disease in various countries and is estimated to affect nearly 20%-25% of the population of developed countries. The prevalence of NAFLD in type 2 diabetes (T2DM), obesity and dyslipidemia varies from 40%-75%[21]. Estimates based on imaging and autopsy studies suggest that about 20%-30% of adults in the United States and other Western countries have NAFLD[22]. Current data suggest that approximate 2%-3% of the same population have nonalcoholic steatohepatitis (NASH)[23]. The prevalence of NAFLD was 14%-16% in Asians, 31%-33% in African-Americans and 45% among Hispanics, differences partly explained by different visceral adiposity distribution. NASH affects 3% of the general population, 20%-30% of the obese and diabetics and 35%-40% of morbidly obese subjects[24].

The data on the prevalence of NAFLD in Asian populations is limited. Chitturi *et al*[25] highlighted the potential burden of NAFLD in the Asia-Pacific area, with an estimated 1.8 million Asians and at least 400000 Australians with NASH, thus eclipsing the disease burden of hepatitis B and C. In Japan, the gender specific prevalence of NAFLD was reported to be 3.3% and 3.8% in the non-obese and 21.6% and 18.8% in obese males and females, respectively[26]. In a hospital-based study in Taiwan, the prevalence of NAFLD was 36.9% and was greater in males than in females[27]. According to our data from North India, the prevalence of NAFLD was 32%[28].

OSA and NAFLD

Some authors have suggested that OSA may be another contributor to NAFLD development. Like NAFLD,

OSA is more prevalent in but not confined to obese individuals[29]. OSA has also been linked to other features of the metabolic syndrome, including dyslipidemia[30], IR and hypertension[31]. Singh *et al*[19] found that OSA symptoms were prevalent in 46% of patients with AST levels. The prevalence of OSA symptoms tended to be even higher (63%) among the subset of patients whose liver biopsies showed more advanced disease[19]. A case series of 163 patients undergoing evaluation for OSA showed that 20% had elevated liver enzymes and that the presence of severe OSA (AHI > 50) was a far stronger predictor of elevated liver enzymes than elevated body mass index (BMI). The presence of severe OSA was also associated with greater degrees of steatosis, necrosis and fibrosis on liver biopsy[32]. Chin *et al*[33] found that 35% of obese OSA patients had abnormal AST levels and that AST levels rose at night in OSA patients prior to therapy. Furthermore, continuous positive airway pressure (CPAP) therapy reduced the nighttime rise in AST levels, both immediately and over 1 and 6 mo of CPAP therapy. These studies demonstrate that, like the MS, OSA is common in patients with NAFLD and may play some role in its pathogenesis.

OSA is associated with an increase in liver enzyme concentrations in 14 of 44 (35%) obese individuals[32]. Furthermore, CPAP therapy decreases concentrations of liver enzymes. In contrast, in a randomized controlled trial, administration of CPAP for 4 wk had no effect on liver enzymes[34]. Jouët *et al*[35] reported that in morbidly obese patients who required bariatric surgery, OSA was found to be a risk factor for increased liver enzyme concentrations but not for NASH. However, Kallwitz *et al*[36] showed that in obese patients with NAFLD, OSA is associated with elevated alanine transaminase (ALT) levels and a trend toward histological evidence of progressive liver disease. This finding was endorsed by Mishra *et al*[37] who showed that in patients awaiting bariatric surgery, OSA was a risk factor for progression of NAFLD to NASH. Histopathological evidence has shown that OSA is associated with NASH and IR. Norman *et al*[38] showed that in OSA, serum AST levels were better predicted by markers of oxygen desaturation than by factors traditionally associated with the metabolic syndrome. Markers of hypoxia were correlated significantly with AST and ALT levels, whereas the AHI, BMI, blood pressure, fasting glucose, triglyceride and cholesterol levels were not significant. Ahmed *et al*[39] reported that OSA aggravates NAFLD in the absence of obesity and MS. The presence of MS and obesity with OSA can aggravate NAFLD.

Genetics of NAFLD and OSA

As with most of the common diseases today, NAFLD and OSA are considered to be genetically complex disorders. In complex diseases, several or many different genes interact with environmental factors in determining disease presence or its phenotype. Individual genes only have a small effect on disease risk and can therefore be very difficult to identify. Methods for detecting genes in complex disorders have included family-based linkage studies, hypothesis-based candidate gene allele association studies, genome wide single nucleotide polymorphism (SNP) scanning and, recently, microarray and proteomic studies. Almost all of the data available on genes associated with OSA and NAFLD has so far come from the candidate gene association studies, where candidate genes are usually selected on the basis of their suggested role in disease pathogenesis, and the frequency of one or more known SNPs within or close to those genes is compared in cases and controls in the search for a positive or negative association with the disease. Asian Indians are predisposed to obesity and hence can be at risk to develop NAFLD and OSA. Most of the studies carried out in the Indian context are related to the prevalence of OSA and NAFLD. We hypothesize that not only environmental influence but also genetic predisposition makes obese Indians susceptible to OSA and NAFLD.

Few genetic studies have been carried out in obese Asian Indians. A recent paper by Petersen *et al*[40] describes an association of two SNPs in apolipoprotein C3 (APOC3) with NAFLD and IR. Ninety-five healthy Asian Indian men were genotyped for APOC3 C-482T and T-455C. NAFLD was present in 38% of APOC3 variant allele carriers and none of the wild-type homozygotes. The association between APOC3 variants and NAFLD was confirmed in a validation study of 163 healthy non-Asian Indian men. Misra *et al*[41] studied the association of *APO-B* gene polymorphism with dyslipidemia and obesity. Our group reported that TNF alpha gene polymorphism was significantly associated with OSA[13]. We studied 207 obese subjects; 104 with OSA and 103 without OSA. We found that the frequency of '-308A'allele in TNFα gene was significantly higher in obese subjects with OSA (28.8%) when compared with obese subjects without OSA (12.6%, $P = 0.001$). Also, serum TNFα levels were significantly higher in obese subjects with OSA when compared with obese subjects without OSA[13].

Genetic susceptibility for cardiovascular manifestations of OSA may be mediated by gene polymorphisms associated with regulation of body weight, lipid metabolism, inflammatory response and autonomic vascular function[42]. The G-allele of a single nucleotide polymorphism in the pro-inflammatory *IL-6* gene is associated with 6-fold increased odds of having OSA after adjustment for obesity[43].

Hypoxia decreases insulin sensitivity in mice and might ultimately increase expression of the lipogenic genes sterol-regulatory element-binding protein-1c, peroxisome proliferator-activated receptor-γ (PPAR-γ), acetyl CoA carboxylase 1 (ACC1) and ACC2. Furthermore, hypoxia also decreases expression of genes that regulate mitochondrial β oxidation (*e.g.*, PPAR-α and carnitine palmitoyltransferase-1[44]).

Gene expression

Microarrays analyses are increasingly being used to evaluate potential molecular signatures of disease[45]. The advantages are providing a broad unbiased approach to

study changes in gene expression of thousands of genes simultaneously and the ability to discover new pathways and molecules affected by a disease such as OSA[46]. The main disadvantage is the cost of this high-throughput technology. To date, there have been two studies of gene expression profiling in OSA patients. In the first study in adults, gene expression was measured both before and after sleep, albeit in a small sample (4 OSA patients, 4 controls), therefore allowing for the assessment of overnight changes in gene expression[47].

Zheng *et al*[48] identified the role of micro ribonucleic acid (miRNA) in regulating the steatosis level by directly targeting PPAR-α mRNA in a steatotic L02 cell model. This newly-identified miRNA-10b-PPARα-steatosis pathway provides a new clue that the pathogenesis of steatosis formation in NAFLD and miRNA-10b might become the potential target for the treatment of NAFLD. Ma *et al*[49] showed that the expression of miRNA-10b was induced by the transcription factor Twist through directly binding to the putative promoter of miRNA-10b (MIRN10B). Moreover, previous reports demonstrated that PPARα exerted its influence on hepatic lipid metabolism through activating genes encoding for fatty acid oxidation, lowering the hepatic substrate for triglyceride synthesis by limiting its output from other organs and upregulating the level of malonyl-CoA decarboxylase to increase translocation of fatty acid into mitochondria for oxidation[50]. Therefore, the potential regulatory axis Twist-miRNA-10b-PPARα-downstream effector molecule-hepatic lipid metabolism might play an important role in the pathogenesis of NAFLD.

OSA, NAFLD and insulin resistance

Obesity is associated with an increased risk of developing IR and T2DM[12]. Unlike obesity which is clinically obvious, the diagnosis of IR is often missed for many years and patients present to a wide variety of specialists, including endocrinologists, diabetologists and internists. On a population-wide basis, severe obesity is by far the commonest cause of IR. Daltro *et al*[51] reported that OSA was associated with IR but not with the severity of NASH.

One of the consequences of obesity and IR is NAFLD. Studies suggest that OSA may also contribute to the progression of NAFLD[31,35,38]. NAFLD includes a spectrum of disease severity, ranging from steatosis without inflammation to NASH and liver cirrhosis[52]. Day *et al*[53] proposed a "two-hit" model to explain the evolution of NAFLD. The "first hit" involves the accumulation of triglyceride in hepatocytes and has been specifically attributed to obesity and IR. The "second hit" induces progression of hepatic steatosis to NASH.

OSA, NAFLD and inflammation

Obesity and OSA have been independently associated with metabolic dysfunction and systemic inflammation. OSA causes low-grade inflammation and hypercytokinemia. Severe obesity leads to chronic inflammation which has been implicated in poor cardiovascular outcomes[54]. In mice with diet-induced hepatic steatosis, but not in mice with normal livers, increases in liver levels of proinflammatory cytokines IL-1β, IL-6, macrophage inflammatory protein-2, and TNFα as well as α1(I) collagen and indices of lobular inflammation and fibrosis are seen[55].

Chronic inflammation is indicated by an increased expression of proinflammatory cytokines and elevated infiltration of macrophages into adipose tissue. In recent years, it has become clear that obesity also gives rise to a heightened state of inflammation. The link between obesity and inflammation has been further illustrated by the increased plasma levels of several proinflammatory markers, including cytokines and acute phase proteins like hs-CRP in obese individuals[56]. Although increased visceral fat[57] and adipocyte hypertrophy have been linked to a higher degree of adipose inflammation, until recently the exact pathways leading to a proinflammatory state of adipose tissue in obese individuals remained unidentified. Recently, much attention has been diverted to the role of macrophages. The inflammation markers (IL-6 and CRP) are increased in the plasma and reduced after improvement of breathing by surgery in OSA patients[43].

Oxidative stress

OSA is characterized by apnea-related multiple cycles of hypoxia which is accepted to promote the formation of ROS and induce oxidative stress[58]. The imbalance between oxidant-producing systems and antioxidant defense mechanisms determine oxidative stress, which results in excessive formation of ROS or RNS. Ordinarily, maintenance of homeostasis is provided by this tightly regulated balance system. The superoxide anion radical is the predominant ROS molecule. In particular, of importance in the vasculature is the reaction of superoxide with the powerful vasodilator NO, which promotes the formation of peroxynitrite while diminishing the bioactivity and bioavailability of NO. This activity is a major contributor of oxidative stress in the vasculature and hence greatly affects endothelial function, vascular inflammation and atherosclerosis.

Some studies have demonstrated increased lipid peroxidation and generation of ROS by blood cells in OSA[59]. Vasoreactivity in OSA can be improved by antioxidants such as ascorbate and allopurinol, suggesting that oxidative stress contributes to endothelial dysfunction[60]. The reoxygenation/reperfusion phase of the hypoxia/reoxygenation cycle appears to promote production of ROS, leading to oxidative stress in OSA[61]. Barceló *et al*[62] reported an alteration in antioxidant capacities, with a reduction in total antioxidant status (TAS) and a decrease in vitamin A and vitamin E levels in OSA patients. In the same study, CPAP treatment normalized TAS.

Oxidative stress, due to increased generation of ROS and decreased antioxidant defenses, is observed in human and experimental models of steatohepatitis[63]. Enhanced mitochondrial and microsomal fatty acid β oxidation, cy-

tochrome P450 (CYP) 2E1 induction and leukocyte infiltration can all lead to oxidative stress. Several groups have studied markers of oxidative stress in liver samples, as well as plasma samples from subjects with NAFLD and NASH. Thus, oxidative stress may contribute to the development of both steatosis and steatohepatitis, although in some studies, in the latter condition the level of oxidative stress markers is higher than simple steatosis alone.

Treatment

Treatment of patients with NAFLD and OSA has typically been focused on the management of associated conditions such as obesity, diabetes mellitus, hyperlipemia and cardiovascular disease. Weight loss has been shown to improve insulin sensitivity and NASH may resolve with weight reduction. IR seems to be the common denominator in many cases of NAFLD and OSA. Different modalities of treatment have been advocated for the management of OSA and NAFLD. These include lifestyle modifications and weight reduction, CPAP therapy, insulin sensitizer drugs and bariatric surgery.

Life style modifications and weight reduction

Weight gain is a significant risk factor for the development of NAFLD and OSA. In the vast majority of OSA cases the illness can be improved, if not eliminated, with significant weight loss. However anatomic abnormalities may cause the condition to persist. The amount of weight a patient needs to lose to achieve these benefits varies. Some may need only a modest reduction in weight to gain improvement, while others may require significant weight loss. It is usually not necessary to slim down to an "ideal body weight" to achieve these benefits.

As NAFLD is most commonly associated with obesity, weight loss is a reasonable initial step towards treating this condition. The theoretical advantages of weight loss include decreasing insulin resistance and, if combined with exercise, increasing muscle insulin sensitivity. Weight reduction has been clearly associated with improvement in liver biochemical tests and prevention of hepatic injury. One study indicated that moderate amounts of weight loss as well as exercise were associated with improvement in insulin sensitivity and thus logical treatment modalities for patients with NAFLD who are overweight or obese[64].

Continuous positive airway pressure therapy

CPAP is an effective therapy for OSA. The CPAP machine sends air under pressure through the tube into the mask, where it imparts positive pressure to the upper airways. This essentially acts as "splints" and keeps the upper airways open and prevents them from collapsing. CPAP is the most commonly prescribed treatment for OSA. The advantages of CPAP are that it is safe, completely reversible and generally quite well tolerated. Chin *et al*[33] reported that CPAP therapy reduced the nighttime rise in aminotransferase levels, both immediately and over 1 and 6 mo of therapy. Another study indicated that CPAP treatment may also be helpful in reducing elevated biochemical and liver enzyme levels in people with both NAFLD and OSA[19].

Drugs

As we previously described, IR is associated with NAFLD and OSA. Therefore, treatment strategies targeting IR are becoming increasing popular. Thiazolidinediones improve insulin sensitivity in adipose tissue by activating the nuclear transcription factor peroxisome-proliferator activated receptor[65]. Improvements in IR and biochemical and histological parameters have been noted in a number of studies[19,21].

Metformin is a biguanide, a class of oral hypoglycemic drugs with insulin sensitizing properties. It acts by decreasing the hepatic glucose output, increasing the insulin mediated glucose utilization in peripheral tissues, and lowering the serum free fatty acid concentrations. Metformin was associated with a significantly higher normalization of serum ALT and an improvement of liver echographic response was also seen. Additionally, an improvement of fatty infiltration was observed in a limited number of patients who underwent liver biopsies[66]. Several smaller clinical studies initially reported improvement in serum aminotransferase levels and IR after 6 mo of treatment; although after 1 year of treatment there was no clear effect on aminotransferase levels, liver histology and insulin sensitivity.

Bariatric surgery

Bariatric surgery is currently being recommended for morbidly obese patients[67]. Except for jejunoileal bypass surgery which has been largely abandoned, all the other types of bariatric surgical techniques seem to decrease excess body weight by at least 50%. Overall, patients undergoing bariatric surgery (regardless of the type of intervention) showed an average reduction of 15 kg/m^2 in BMI and 36 events/h in the AHI, suggesting that every 1 unit reduction in BMI translated to a reduction of 2.3 units in the AHI. Lettieri *et al*[68] reported that surgical weight loss reduces AHI but many patients had residual OSA 1 year after bariatric surgery. Bariatric surgery may be an alternative treatment of severe or complicated obesity. Important and sometimes impressive changes have been noted in cardiovascular risk factors, metabolic markers and OSA severity.

Historically, there is a reduced prevalence and severity of liver disease after bariatric surgery. Previous studies indicate that bariatric surgery decreases concentrations of liver enzymes and the degree of hepatic steatosis. The effect on hepatic inflammation and fibrosis has been more variable[69]. In a recent meta-analysis consisting of 15 studies and 766 paired liver biopsies, Mummadi *et al*[24] showed that all components of NAFLD show significant improvement following foregut bariatric surgery.

CONCLUSION

OSA is associated with NAFLD in animals and humans. Importantly, OSA can aggravate the development of NAFLD to NASH in obese individuals or those with

metabolic syndrome. OSA might induce NAFLD in the absence of obesity and metabolic syndrome and the link with hypoxia might be instrumental in precipitating fatty liver development. Several epidemiological studies have demonstrated that sleep related disorders are an independent risk factor for obesity and hypertension, probably resulting from a combination of intermittent hypoxia and hypercapnia, arousals, increased sympathetic activity and altered baroreflex control during sleep. Additionally, arterial hypertension, obesity, T2DM and coronary artery disease which often coexist with OSA are independent predictors of left ventricular dysfunction. Some authors have suggested that OSA may be another contributor to NAFLD development. NAFLD and OSA are more prevalent in but not confined to obese individuals. OSA has also been linked to other features of the metabolic syndrome, including dyslipidemia, IR and hypertension. The presence of severe OSA was also associated with greater degrees of steatosis, necrosis and fibrosis on liver biopsy. Hypoxia from OSA has been associated with serum markers of liver fibrosis.

The genetic and hormonal determinants of OSA and NAFLD have received little attention. A wide variety of intermediate phenotypes and genes are involved in sleep apnea and fatty liver which makes this syndrome genetically complex. In a linkage analysis study, genes associated with obesity were shown to be relevant for further study of OSA and NAFLD. With growing urbanization and nutrition transition, obesity and MS are increasing in Asian Indians. Although these diseases are multifactorial, genetic associations and hormonal determinants have been suspected but not researched. The interplay of various adipokines, the most important of which are leptin, adiponectin, TNFα, resistin and IL-6, has a key role in this process. Oxidative stress may contribute to the development of NAFLD and OSA. Clinical studies suggest that serum levels of the above cytokines differ among patients with NAFLD/NASH, OSA and healthy controls. Importantly, individuals with OSA require a full evaluation of their CVD risk and clinicians should be aware that these individuals are also at increased risk of NAFLD. It is important to investigate these issues in view of the large burden of IR, MS and coronary heart disease in Asian Indians. We feel strongly that supports a relationship between OSA and NAFLD. Further studies are needed to elucidate the precise nature of this relationship.

Lifestyle intervention should be first line treatment for all NAFLD and OSA patients. Several drugs aim to improve metabolic syndrome but need further investigation on their exact anti-steatotic effect. The most promising drugs are the insulin sensitizers but most studies have a small sample size and have been done for a short duration only. Bariatric surgery may improve conditions associated with metabolic syndrome, OSA and NAFLD in morbidly obese patients. There is currently no well established treatment for patients with NAFLD and OSA. Whether newer drugs will emerge which can treat both NAFLD and OSA together is unclear and needs more research.

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