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REVIEW ARTICLE

Sleep disturbances: one of the culprits of obesity-related cardiovascular risk?

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Abstract

Growing evidence suggested that Sleep Disorders (SD) could increase the risk of developing obesity and could contribute to worsen obesity-related cardiovascular risk. Further, obesity *per se* has been reported to blunt sleep homeostasis. This happens through several mechanisms. First of all, the excessive adipose tissue at neck and chest levels could represent a mechanical obstacle to breathe. Moreover, the visceral adipose tissue is known to release cytokines contributing to low-grade chronic inflammation that could impair the circadian rhythm. Also, nutrition plays an important role in sleep homeostasis. High fat and/or high carbohydrate diets are known to have a negative impact on both sleep quality and duration. In addition, obesity predisposes to a condition called "*obstructive sleep apnea*" that has a detrimental effect on sleep. SD could increase the risk and/or could contribute to worsen cardiovascular risk usually associated with obesity. The chronic low grade inflammation associated with obesity has been reported to increase the risk of developing hypertension, type 2 diabetes and dyslipidemia. In turn, improving quality of sleep has been reported to improve the management of these cardiovascular risk factors. Thus, the aim of this manuscript is to provide evidence on the association of obesity and SD and on how they could contribute to the risk of developing cardiovascular risk factors such as hypertension, dyslipidemia and type 2 diabetes in obesity.

Introduction

Sleep Disorders (SD) have been reported to increase the risk of developing obesity through several hormonal and metabolic mechanisms [1, 2]. In turn, obesity is currently considered a risk factor for SD. This could be due to several mechanisms, first of all the mechanical obstacle to breathe represented by the excessive adipose tissue at neck and chest levels. The release of inflammatory cytokines from visceral adipose tissue has been thought to be an additional mechanism able to blunt the sleep quality in obesity [1]. Further, the quality of food plays an important role in favoring falling asleep. A high fat diet has been associated with poor sleep quality; the two main mechanisms that link this nutritional pattern to sleep disturbances are represented by derangements of hormones regulating hunger/satiety and chronic inflammation [2]. SD could contribute to cardiovascular risk in obesity predisposing to or worsening several cardiovascular risk factors [3].

In particular, SD has been reported to increase the risk of developing hypertension. Several pathogenic mechanisms have been suggested to account for SD-related hypertension such as the hyperactivity of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS) activation, oxidative stress, activation of the endothelium and endothelial dysfunction [4].

SD is also a recognized factor that may increase the risk of developing metabolic diseases such as type 2 diabetes (T2DM); this happens because SD could increase the risk of developing a chronic stress condition that in turn could contribute to the onset of insulin resistance through stress-related hypercortisolism [5]. "Obstructive sleep apnea (OSA)" could also contribute to blunt sleep in obesity and

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to independently increase metabolic impairment, including dyslipidemia, insulin resistance and hypertension [6].

Therefore, the aim of this manuscript is to provide an overview of the current evidence on the association between obesity and SD and on the impact of SD on cardiovascular risk in obesity, mostly focusing on the following cardiovascular risk factors: hypertension, type 2 diabetes and dyslipidemia.

Search strategies

Articles were individually retrieved by each author up until August 2019, by search in PubMed (MEDLINE) using the following search terms: 'Sleep Disorders', 'Insulin resistance', 'Type 2 Diabetes', 'Obesity', 'OSA', 'C-PAP', 'glucose metabolism'. The reference lists of relevant articles and reviews were also searched manually.

Obesity and sleep disturbance

Obesity is a widespread phenomenon worldwide, which has tripled from 1975 to today. According to World Health Organisation (WHO) data [7], more than 1.9 billion adults over the age of 18 (39% of the adult population) were overweight in 2016. Of these, more than 650 million were obese (13%), 41 million were children under the age of 5, and over 340 million children/adolescents aged 5 to 19 were overweight or obese.

The field of SD include a wide range of phenomena including insomnia, hypersomnia, sleep apnea, and many other disorders, overall classified as dyssomnias and parasomnias [8]. The prevalence of OSA, estimated as Apnea Hypopnea Index / Respiratory Disturbance Index (AHI/RDI) greater than 5, varies between 9% and 38% (men 13–33%, women 6–19%) in the adult population [9]. SD is a common finding in obesity; in fact it has been reported that almost 70% of patients with OSA are obese and most of them develop obesity-related cardiovascular risk factors [10–12].

Several pathways have been proposed to explain the link between SD and obesity (Fig. 1). Hyperphagia has been observed in rats with sleep deprivation [13] and in humans partial sleep deprivation showed a similar effect. To explain this phenomenon, biological and behavioral processes have been proposed, such as meal times, diet quality, "obesogenic" eating behaviors, and changes in hormones that regulate appetite [14].

Sleep deprivation (4 h per night over 2 days) led to an increase of appetite scores and hunger assessed using a visual analog scale compared to regular sleep duration (10 h per night over 2 days), and particularly for high carbohydrate and high fat food [15]. Interestingly these changes were accompanied by an increase in plasma ghrelin and decrease in plasma leptin in the sleep deprivation group.

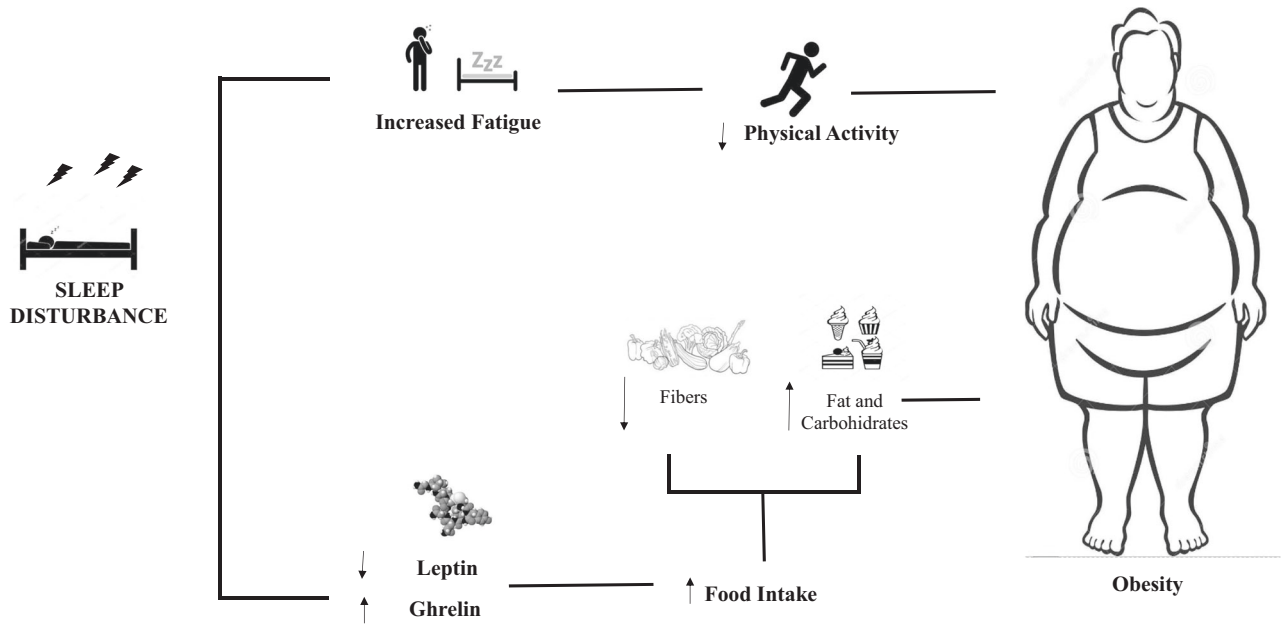

Fig. 1 Mechanisms of the association between sleep disorders (SD) and obesity. SD could represent a risk factor for the onset of obesity and could contribute to the development or worsening of obesity-related cardiovascular diseases. SD is associated to increased daily fatigue that consequently results in decreased physical activity. In addition, SD induces hormonal derangements mostly represented by an increase in ghrelin and a decrease in leptin levels. This hormonal change results in an increased food intake, mostly represented by fat and carbohydrates at the expense of fiber intake. All these mechanisms contribute to weight gain and thus to the development of obesity.

Other studies showed reduced levels of leptin and increased levels of ghrelin in short sleepers suggesting that short sleep may affect appetite modifying appetite regulating hormones level [15, 16]. Leptin levels were also modified in subjects who experienced partial sleep deprivation for 6 consecutive days showing a reduction in leptin levels which persisted for 24 h [17]. Obstructive Sleep Apnea (OSA) is accompanied by increased leptin resistance, which is already present in obesity, so that in OSA the weight-reducing effects of leptin are blunted, therefore inducing a cycle of weight gain and worsening OSA. Potential effects of leptin on respiratory control may also contribute to disorders of breathing in the obese, hyperleptinemic patients with OSA. Therefore, the detection of reduced leptin concentrations and increased ghrelin in patients with short duration of sleep, regardless of BMI, corroborated the hypothesis that some hormonal changes promote over-eating, leading to an increased risk of obesity [16].

Otherwise, it has been argued that reduced sleep time may offer an increased chance to eat if most of wake time is spent in an environment with readily available food [18]; however no clear relationship has been shown between sleep duration and dietary consumption [19–21].

A feeling of fatigue increases when subjects experience chronic partial sleep deprivation [22], and consequently the derived tiredness may cause a decrease in exercise. Studies in children showed that short sleep duration is associated with increased sedentary lifestyle (e.g., viewing television and reduced sport time) [20]. In adults the same trend has been observed [20, 23].

Acute sleep deprivation led to a drop in body temperature, which may be a sign of reduced energy expenditure through thermoregulation; however a study using doubly labeled water, the gold standard measurement for energy expenditure, failed to find an association between reported sleep duration and total energy expenditure [24].

Among the pathophysiological mechanisms identified, one of the major triggers is the OSA-induced intermittent hypoxia which increases the levels of Angptl4 (angiopoietin-like4), a lipoprotein lipase inhibitor, which leads to a reduction in lipoprotein clearance and increases serum triglycerides and fasting VLDL cholesterol [25]. Moreover, the persistent pro-inflammatory state increases cytokines, serum A-amyloid and C-reactive protein (CRP). SD and obesity share the same pro-inflammatory pattern that can cause hypercoagulable states. Adipocyte hypertrophy also determines an altered expression of adipokines, which play a crucial role in vascular function, affecting lipid and glucose metabolism.

It is probable that OSA can cause metabolic changes independent of obesity. The association between abnormal glucose metabolism (e.g., insulin resistance) and sleep-disordered breathing has been investigated in several studies that have provided substantial evidence supporting an independent association between insulin resistance and OSA. Although increased insulin resistance was also related to obesity, in multiple regression analysis the association between OSA and insulin resistance was independent of obesity status (central obesity assessed as waist to hip ratio) and has been reported in people with and without obesity [26–28].

The majority of clinical studies in people without obesity have reported an independent association between OSA and insulin resistance/sensitivity, with a dose-dependent effect of OSA on metabolic impairment, although some studies found that the association was abolished after adjusting for BMI and/or other measures of adiposity [29].

The relationship between OSA and obesity may also be associated to variations in patients' lifestyle, so that subjects with OSA may be prone to weight gain because of daytime somnolence and a reduction in physical activity [26].

Increased adipose and soft tissues around the upper airway narrow the pharyngeal caliber and increase the likelihood of airway collapse during sleep [29].

The link between "short sleep" and obesity was also supported by a 16-year longitudinal study in which women who slept less than 5 h per night gained 1.14 kg more than those who slept 7 h per night (age and BMI adjusted) [19].

Although the wide body of evidence in the scientific literature linking sleep deprivation with obesity, there are some important limitations which limit the possibility to clearly state that short sleep duration causes quicker weight gain. The methods used to measure sleep duration and quality have some limitations (e.g., polysomnography may itself interfere with sleep) and most of the questionnaires used do not take into consideration day-time sleep time, underestimating total sleep duration (e.g., in populations where napping or shift-work is common). The problem of reverse causation is another concern, in fact, obesity increases medical conditions that can cause reduced sleep duration (e.g., osteoarthritis, gastroesophageal reflux, asthma, and heart failure, OSA) [30, 31]. Further studies using reliable measures of sleep duration, with experimental study designs that influence sleep are warranted to clarify the causal relationship between sleep deprivation and obesity.

The result of four randomized controlled trials showed that weight loss achieved through behavioral or surgical interventions could be useful in the management or resolution of SD (measured as AHI modification) [32–36].

A double-blind, placebo-controlled trial of 86 patients with moderate-to-severe OSA, showed that 3 months of C-PAP therapy reduced blood pressure and partly also improved metabolic syndrome [37].

The impact of weight loss through bariatric surgery on OSA was analyzed through specific questionnaires for

symptom assessment, changes in pressure levels required for C-PAP, and pattern changes to polysomnography. The results showed a reduced rate of apnea in subjects with obesity after bariatric surgery [11, 38].

Weight loss may exert its positive influence on sleep apnea reducing the effect of adiposity on the upper airway function during sleep. Throughout weight loss intervention, the upper airway collapsibility during sleep is reduced and this effect may be attributed to the decrease in mechanical loads or improvements in the control of pharyngeal neuromuscular action [39]. In addition some alterations in humoral factors correlated to changes in weight and body adiposity (e.g., ghrelin, adiponectin and leptin) can be related to these mechanisms [39].

Hypertension and sleep disturbance

In 2015 the global prevalence of hypertension in adults is around 30–45% [40]. Among patients with hypertension, the frequency of OSA is ~50%; conversely, hypertension is present in 28–57% of patients with OSA [41–43]. Baguet and coworkers observed in 130 patients with newly-diagnosed OSA and without cardiovascular history, a prevalence of hypertension around 35.4%, and among them, 30% had undiagnosed hypertension [44]. Disrupted autonomic balance is associated with impaired sleep, characterized by reduced parasympathetic dominance and elevated sympathetic nervous system activity during sleep [45]. Patients suffering from insomnia have significantly increased sympathovagal imbalance [46]. Autonomic dysfunction has been linked to hypertension and to decreased nocturnal dipping of blood pressure [45–47]. Adiposity and metabolic dysfunction (e.g., T2DM and obesity) in SD may also increase hypertension risk. Moreover chronic sleep deprivation can lead to circadian misalignment which in turn may modify the blood pressure diurnal pattern [45], inducing increased hypertension risk, reducing nocturnal dipping and increasing blood pressure variability [45, 48, 49].

Several pathophysiological mechanisms play a role in determining the onset of hypertension in patients with SD. Intermittent hypoxia and hypercapnia: the sudden re-oxygenation would lead the cells, used to working at low oxygen pressure, to produce free radicals, causing the ischemia-reperfusion phenomena. Also, the changes in intrathoracic pressure have repercussions on cardiac dynamics and lead to an increase in the afterload. Besides, reduced production of Nitric Oxygen (NO) and increased production of endothelin-1 in the vessels can predispose to systemic hypertension and cardiovascular diseases. The accumulation of reactive oxygen species contributes to the pathogenesis of endothelial dysfunction in patients with OSA. Hyperactivity of the sympathetic nervous system, altered sensitivity of the baroreceptors, activation of the RAAS system, hyperinsulinism and leptin resistance, states of hypercoagulability and microarousals have also been observed in this subset of patients. OSA is also associated with increased levels of urinary catecholamines which are reduced by treatment with C-PAP, and nocturnal awakenings are associated with changes in the pulsatile release of cortisol. Angiotensin II and aldosterone also increased in patients with OSA compared to controls [50, 51].

In children sleep apnea impacts on blood pressure regardless of age, gender, race, BMI or waist circumference and SD also affect the cardiac remodeling of the left ventricle [52].

SD such as Periodic Limb Movements (PLM) and Narcolepsy could affect blood pressure control, but the link between them is not yet fully understood. The prevalent hypothesis reports that the qualitative-quantitative changes in sleep affect the physiological nocturnal blood pressure dip which occurs typically during Non-Rapid Eyes Movements (REM) sleep. The loss of nocturnal dip is attributable to an increase in sympathetic activity, which consequently leads to an increase in sympathetic tone also during the day [53, 54]. Additional intervention studies that investigate the effects of mild to severe sleep restriction on blood pressure level are needed to clarify the association of objectively assessed sleep with blood pressure level.

If it is clear that hypertension requires a specific blood pressure lowering treatment, it is less clear if treating SD in patients with hypertension can improve hypertension itself.

Several studies have shown that C-PAP reduces blood pressure in patients with OSA, while in others the data were uncertain. A randomized controlled trial, in which 340 patients with hypertension and OSA were enrolled, showed that a three-month treatment with C-PAP resulted in a small, but significant, reduction in blood pressure [55, 56].

A randomized controlled trial showed that there was an additive effect of the antihypertensive medication valsartan, an angiotensin II receptor antagonist, and C-PAP on hypertension, but the pharmacological intervention was superior. This study reinforces the idea that C-PAP has a limited effect on the management of arterial hypertension. However, the result of the study suggests not precluding the prescription of C-PAP in patients with OSA and hypertension [43].

In another study, the effect of the potassium-sparing diuretic spironolactone therapy for 8 weeks was evaluated based on the results of polysomnography. Blood pressure measured in the clinic and at home was reduced after administration of spironolactone; also, a significant reduction in OSA severity (from severe to moderate severity) was observed [57].

Another study showed a modest reduction in OSA severity after improvement and intensification of diuretic therapy (metolazone and spironolactone) in patients with uncontrolled hypertension. A reduction in nighttime overflow of fluids at the declivity level and in the neck circumference was shown, accompanied by a reduction in the apnea-hypopnea index in patients undergoing intensive diuretic treatment. Based on these results, the redistribution of body fluids during the night helps to determine the severity of OSA in people with hypertension and could be an essential link between these two conditions [58].

Type 2 diabetes and sleep disturbance

Since the global prevalence of type 2 diabetes among adults (18 years-old and over) has risen from 4.7% to 8.5% in last two decades, this chronic illness has to be considered as increasing epidemic of worldwide proportions according to WHO data [54].

Several studies demonstrated that SD are associated with several factors, including insulin resistance, glucose intolerance, reduction in the disposition index and a reduced insulin response to glucose, leading to a predisposition to T2DM [59].

Indeed, it has been reported that increasing post-prandial plasma glucose and decreasing resting metabolic rate could be correlated with both prolonged sleep restriction and circadian disruption due to inadequate insulin secretion, thus causing adverse effects on glucose and insulin metabolism as a result of poor sleep quality and of sleep outside the timing of the circadian cycle [60].

From this specific point of view, Broussard JL et al. showed in their study that sleep deprivation was associated with a reduction of 30% in phosphorylation of Akt, which is an indicator of reduced peripheral insulin response. This in turn determined a reduction in total body insulin sensitivity in humans [61].

Sleep restriction can also lead to an up- and down-regulation of the expression of numerous genes that play important roles not only in the regulation of circadian rhythms and sleep homeostasis but also in metabolism and oxidative stress [62]. This evidence was also supported by an experimental metabolic profiling in which specific "metabolic phenotypes" were characterized by comparing patients during sleep deprivation and normal controls. More than 27 metabolites were associated with a disruption of markers of the circadian rhythm, among which the most relevant were: serotonin, tryptophan, 8-acylcarnitines, taurine, 3-sphingolipids and 13-glycerophospholipids. The presence of specific metabolites released during sleep deprivation in the study may also explain the association of acute sleep deprivation with their anti-depressive effect [63].

From a clinical point of view, an analysis of the data from prospective longitudinal studies, provided evidence that in people sleeping less than 6 h per night there is an increased risk of 28% in developing T2DM compared with controls [64].

This finding was also confirmed by a recent meta-analysis and systematic review, in which sustained sleep deprivation was highly associated with the risk of developing T2DM. However, the higher prevalence of T2DM in subjects suffering from sleep deprivation was also associated with other well-known metabolic risk factors such as family history, overweight, and sedentary lifestyle [65].

A recent cohort study reported that the incidence of T2DM was significantly higher in patients with insomnia than in patients without insomnia (34.7 vs 24.3 per 1000 person-years), and the longer was the duration of insomnia, the higher the risk tended to be [66].

Among the different types of SD, OSA is a well known manageable sleep breathing disorder that is very common among adults with overweight and obesity, who currently accounts for almost two-thirds of the U.S. population [67–70].

In addition, OSA has been indicated as an independent risk factor for diabetic kidney disease, with a more pronounced association in women rather than men [67]. Indeed, a longitudinal population-based study in Finland showed that patients with OSA had a 1.75-fold increased risk of diabetic kidney disease. Moreover, in this study it was also reported that OSA was associated with all-cause mortality in people with diabetes (HR = 1.35, 95% CI 1.06 to 1.71, $p = 0.016$) [71]. However, the study did not find a significant correlation between obesity and OSA-dependent T2DM.

The probability to develop T2DM is higher in people with OSA than those without [68–71]: in fact, the risk of developing T2DM ranges from 15% to 30%, being higher in those who suffer from severe OSA [72–75]. However, in T2DM patients managed by primary care providers, OSA remains largely undiagnosed [76].

A large cross-sectional study demonstrated that 30.1% of patients affected by OSA had T2DM, whilst 20% had impaired glucose tolerance [77]. Another recent meta-analysis showed that an increase in the incidence of T2DM was dependent on the severity of OSA [78, 79].

OSA and T2DM have several risk factors in common, the two major ones being age and obesity, which are also important risk factors in the development of cardiovascular diseases. Obesity can be considered as a prominent risk factor: for every 10% increase in weight, there is a six-fold increase in risk of OSA development [80].

The direct link between obesity and OSA can be explained by the state of hypoxia that occurs during OSA, as shown in Fig. 1. Hypoxia stimulates sympathetic activity, which in turn stimulates oxidative stress and chronic inflammation; these factors are likely to disturb the homeostasis of glucose metabolism. Moreover, hypoxia may also act by directly blunting pancreatic beta cell, liver and adipose tissue function, the major tissues involved in the maintenance of glucose homeostasis. Also sleep fragmentation and deprivation caused by OSA may have a negative impact on insulin sensitivity. This may occur either through sympathetic activation, or following oscillations in the secretion of growth hormone and cortisol [81].

The hypothesis that hypoxia in OSA patients may promote obesity led to investigate if respiratory techniques could improve metabolic conditions. Two studies have been carried out in patients with pre-diabetes aiming to investigate the effects of C-PAP on glucose metabolism [82, 83]. A significant increase in insulin sensitivity and an improved response to glucose overall have been found in patients in C-PAP arm compared with the control group. Another study showed that 8 weeks of C-PAP usage at home (average mean adherence of 4.8 h/night) had a positive outcome on insulin sensitivity and 2-h insulin levels only in the severe OSA group [83].

However, different variables could be responsible for the conflicting results of the studies in patients without diabetes, such as various degrees of CPAP adherence, the different baseline glycemic status and different methods used to assess glucose metabolism. Four of these studies were included in a meta-analysis, in which no changes have been found in terms of fasting glucose levels or homeostatic model assessment (HOMA) index after C-PAP, although fasting insulin levels were significantly reduced [84, 85].

However, it has been shown that in the treatment of patients with OSA, weight loss should be priority. In fact, when weight loss was successfully achieved, there is an improvement of both glucose control and OSA. However, it is still debatable whether OSA treatment with CPAP has a positive outcome on glucose metabolism. Moreover, it is yet to be established what is the precise amount and duration of C-PAP necessary to improve the metabolic outcomes.

Six randomized controlled trials (RCTs) in a recent systematic review and meta-analysis with a total of 581 participants, showed that treatment with C-PAP had no effect on changes of glycated hemoglobin (HbA1c) levels following 12 or 24 weeks of treatment. Analysis of the subgroups based on C-PAP adherence (>4 h or <4 h) also confirmed the same results [86]. Change in fasting glucose levels, considered as an indirect outcome of the study, was not significant in the C-PAP population and the placebo group [87].

In a study performed by Martinez-Ceron et al., patients with sub-optimally controlled T2DM and OSA showed a significant improvement in glycemic control (HbA1c levels) and insulin resistance compared to a control group, following a 6-months C-PAP treatment [88].

Bariatric (or metabolic) surgery can be used as a treatment in patients with both type 2 diabetes and OSA in order to improve both [89, 90]. In conclusion, results gathered from the literature concerning the use of C-PAP remain controversial in terms of improvement of glycemic control. Although most of the studies support its use and demonstrate its efficacy in patients with diabetes and OSA, particularly if they are symptomatic. In fact, increasing evidence demonstrates that patients with T2DM and severe OSA who highly adhered to CPAP therapy are likely to obtain a greater metabolic benefit [81, 91].

Hypercholesterolemia and sleep disturbance

Hypercholesterolemia is considered one of the major risk factors for cardiovascular diseases and mortality from all causes [92]. It has been estimated by the WHO that there were 17.3 million deaths related to CVDs in 2008 and the burden will rise to more than 23 million people by 2030. Moreover, from epidemiology studies it appears that American adults over the age of 20 have a prevalence rate of hypercholesterolemia of 16.2%, accounting for 35.7 million of people affected.

Recently, it has emerged from the literature that SD can contribute, to some extent, to increase the risk of hypercholesterolemia and diseases associated to this. SD can come in many forms and are generally divided into insomnia (described as total sleep-hours < 6) and prolonged sleep duration (described as >8 sleep-hours).

Different epidemiological studies have assessed the relationship between an abnormal lipid profile and SD. For instance, Kaneita et al. studied in a Japanese population this association. The study involved the recruitment of 1666 men and 2329 women that were more than 20 years old [93]. Categorization of sleep duration was based on a single question asked to the participants, which allowed distinguishing long and short sleepers. The results revealed that short sleepers accounted for nearly a quarter (23.3%) of men and a third (31.2%) of women, whilst long sleepers were 13.6% men and 8.2% women. Results from this study revealed a U-shaped association in women between triglyceride levels and sleep duration, with both shorter (adjusted odds ratio [OR]: 1.51; 95% CI: 0.96–2.35, for less than 5 h sleep) and longer (adjusted OR: 1.45; 95% CI: 1.00–2.11; for more than 8 h of sleep) sleep duration having the highest levels of triglycerides compared to the baseline, which was represented by people that slept anaverage of 6–7 h.

Another interesting finding was that in women only, an inverted U relationship was reported, with HDL-cholesterol levels in the short (adjusted OR: 5.85; 95% CI: 2.29–14.94) and long (adjusted OR: 4.27; 95% CI: 1.88–9.72) sleep duration groups, being much lower compared with the baseline group. Conversely, men sleeping more than 8 h had a significantly reduced OR (adjusted OR: 0.45; 95% CI: 0.27–0.76) of having high LDL-cholesterol compared with the baseline group.

Other groups reported no association between sleep duration and total cholesterol content. For instance, Williams et al. performed a study on 935 women with T2DM recruited from the US Nurses' Health Study [94]. Even in this study, assessment of sleep duration was based on a single question asked to participants. No association was found between the duration of sleep and total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels. The differences found were the lower serum HDL-cholesterol levels among short and long sleepers in normotensive women only.

Bjorvatn et al. studied the association between sleep duration and body mass index (BMI). In this cross-sectional study, 3531 men and 5329 women from the Hordaland Health Study were assessed for sleep efficiency, calculated as time in bed (from bedtime to wake time) minus self-reported sleep latency. Beside the U-shaped association between sleep duration and BMI, the other interesting finding was that short sleep duration was associated with higher levels of non-fasting total cholesterol and triglycerides. However, these associations were non-significant after controlling for smoking, gender and BMI [95].

Short and long sleep duration can also be associated with metabolic syndrome. Hall et al. studied 1214 subjects aged 32–50 years, and found that self-reported short or long sleep duration were associated with the metabolic syndrome, along with abdominal obesity, elevated fasting glucose and hypertriglyceridemia [96]. In the study it was found that, short sleepers were 53% more likely to have these values compared to baseline subjects.

Also, Choi et al. studied the association between sleep duration and metabolic syndrome, using data from the 2001 Korean National Health and Nutrition Survey [97]. Their results showed a U-shaped association with sleep duration and most of the elements associated with metabolic syndrome. Findings showed that although abdominal obesity and hypertension were higher in people who sleep ≤5 h a night, hyperglycaemic and hyper-triglyceridemic subjects were more likely to sleep ≥ 9 h/night. A study assessing the correlation between metabolic syndrome and sleep disturbance in 388 Chinese participants of the Guangzhou Biobank Cohort Study, also found an association with metabolic syndrome and long hours of sleep (OR: 1.13; 95% CI: 1.02–1.24). Moreover, subjects who were over 61 years of age with the longest total sleep duration had increased risk of high triglycerides levels (OR: 1.18; 95% CI: 1.02–1.37) [98].

SD are not only a problem that concerns the adult population. In fact, in modern society children are also exposed to poor sleeping hours, increasing therefore the risk of developing CVD and obesity in their adulthood. By assessing sleep duration in 308 children over 4–10 years of age, Spruyt et al. found, using wrist actigraphy, that patterns of sleep in obese children were shorter during the week compared to weekdays, with more inconsistent patterns during weekends compared to weekdays. In overweight children, short sleep duration was associated for most part of the cases with altered lipid biomarkers, such as LDL levels and high-sensitivity C-Reactive Protein, as well as altered plasma insulin levels [99].

Speculation on different mechanisms by which SD causes hypercholesterolemia has led to various hypotheses. For instance, decreased sleep duration might alter the levels of ghrelin and leptin, the hormones responsible for appetite stimulation and suppression; this leads to an increased intake of saturated fat-rich food. SD might also lead to activation of the sympathetic nervous system and lead to increased catecholamine secretion, which in turn increases adipose tissue lipolysis [100, 101]. Other studies have demonstrated that subjects with short sleep duration had abnormal glucose metabolism [17], along with the development of daytime fatigue, resulting in decreased activity and decreased lipolysis [102]. McNeil et al. [103] demonstrated that indeed SD lead to an increased food intake and higher sensitivity to high-energy density food and carbohydrates.

However, OSA, which is one of the main causes of insomnia, can offer a clearer explanation of the link between SD and hypercholesterolemia. In fact, as the concentration of blood oxygen decreases during apnoea, the level of triglyceride increases. On the other hand, low oxygen levels in blood might activate the sympathetic nervous system, which results in accelerated synthesis of lipids in the liver and decreased lipid enzymes activity, which in turn leads to an abnormal lipid profile, such as increased LDL and decreased HDL [104].

In conclusion, despite there being evidence from meta-analyses and cross-sectional studies performed on a vast number of human subjects, it is still debatable whether SD may play a critical role in the development of hypercholesterolemia, and whether SD have to be taken into account in the clinic when assessing for obesity-related risk factors. This is also due to the fact that most of the time these studies are based on patient's opinion and sleep quality is generally evaluated through questionnaires, limiting the validity of most studies. Moreover, SD are often associated with other confounding factors; in fact, people with poor

quality of sleep often have poor lifestyles (e.g., a stressful job), sedentary lifestyle and an unbalanced diet and are more likely to smoke. All these factors heavily contribute to abnormal lipid profile and increased risk of exposure to CVD and obesity [105].

Conclusions

SD have been identified as a common finding in obesity that could potentially have a role in predisposing or worsening obesity-related cardiovascular complications. Thus, it becomes of paramount importance to identify SD in people with obesity and to take into account the treatment of SD in the management of obesity. On the other hand, when SD are not associated to obesity, it should not be underestimated because it could represent a risk factor for obesity and cardiovascular derangements. In fact, SD-related hormonal changes could encourage the increase of food intake and in particular of unhealthy food; in addition, fatigue consequent to SD results in decreased physical activity thus favouring weight gain.

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