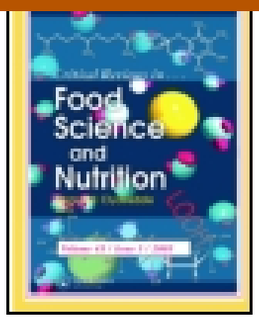


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# Obesity and sleep disturbance: the chicken or the egg?

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REVIEW



# Obesity and sleep disturbance: the chicken or the egg?

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**ABSTRACT**

Epidemiological studies suggested an association between obesity and sleep disturbances. Obstructive sleep apnea is the most prevalent type of obesity-related sleep disorder that lead to an increased risk for numerous chronic health conditions. In addition the increased visceral adipose tissue might be responsible for the secretion of inflammatory cytokines that could contribute to alter the sleep-wake rhythm. Unhealthy food characterized by high consumption of fat and carbohydrate seems to negatively influence the quality of sleep while diet rich of fiber is associated to more restorative and deeper sleep. Although obesity could cause through several pathogenetic mechanisms an alteration of sleep, it has been reported that subjects suffering from sleep disorders are more prone to develop obesity. Experimental laboratory studies have demonstrated that decreasing either the amount or quality of sleep increase the risk of developing obesity. Experimental sleep restriction also causes physiological, hormonal and food behavioral changes that promote a positive energy balance and a compensatory disproportionate increase in food intake, decrease in physical activity, and weight gain. Thus, the aim of this review is to provide observational evidence on the association of obesity with sleep disturbances and *viceversa* with emphasis on possible pathophysiological mechanisms (hormonal and metabolic) that link these two pathological conditions.

**KEYWORDS**

Sleep disturbances; sleep quality; sleep duration; obesity; obstructive sleep apnea

## 1. Introduction

In the last decade, the prevalence of obesity increased significantly in populations worldwide. A less dramatic, but equally important increase has been seen in *obesity-related* comorbidities (Type 2 diabetes, cardiovascular diseases, cancer) that are becoming a real burden for healthcare systems (Bauer et al. 2014). In addition to the most common complications of obesity, recently sleep disturbances rose to the prominence as one of *obesity-related* complication (Burman 2017).

In particular, obesity could increase the risk of developing obstructive sleep apnea (OSA), a condition that appears to independently increase metabolic impairment, including dyslipidaemia, insulin resistance and hypertension in both adults (Tahrani 2017; Said, Mukherjee and Whayne 2016) and adolescents (Patinkin, Feinn, and Santos 2017). Additionally, Sleep Quality (SQ) has been reported to be blunted by increased pro-inflammatory cytokines circulating levels, which are often associated to obesity (Gamaldo, Shaikh and McArthur 2012). Recent findings suggest that a further important mechanism that links obesity to Sleep Disturbances (SD) is represented by diet quality (Hargens et al. 2013), likely through the effects of nutrients that act on inflammation and/or hormonal responses involved in hunger-satiety mechanism, energy metabolism and circadian rhythm.

In turn, a number of evidence showed that SD may increase the risk of developing obesity and metabolic diseases, including type 2 diabetes (T2DM) (Shan et al. 2015). Sleep duration seems to be closely related to weight gain (Taheri et al. 2004; Taheri 2006; Chen, Beydoun, and Wang 2008; Doo, Chun, and Doo 2016; Alodhayani et al. 2017). Short sleep duration (between 5 and 6 hours), indeed, increased the risk of developing obesity (Alodhayani et al. 2017; Canuto et al. 2014; Broussard and Van Cauter 2016). Interestingly, the relationship between sleep duration and obesity risk described a U-shaped relation (Grandner et al. 2015).

The aim of this manuscript is to provide an overview of the current evidence on the association between obesity and SD and *viceversa*, tempting to provide insights on the hormonal and nutritional mechanisms involved in these associations.

## 2. Obesity as cause of sleep disturbance

Obesity is considered one of the most important risk factor of SD (Marks and Landaira 2016; Xiao et al. 2016; Ma et al. 2017). An increase of 6 units in body mass index (BMI) resulted in four time greater risk of OSA (Quintas-Neves, Preto, and Drummond 2016) that is characterized by recurrent narrowing and closure of the upper airway, leading to

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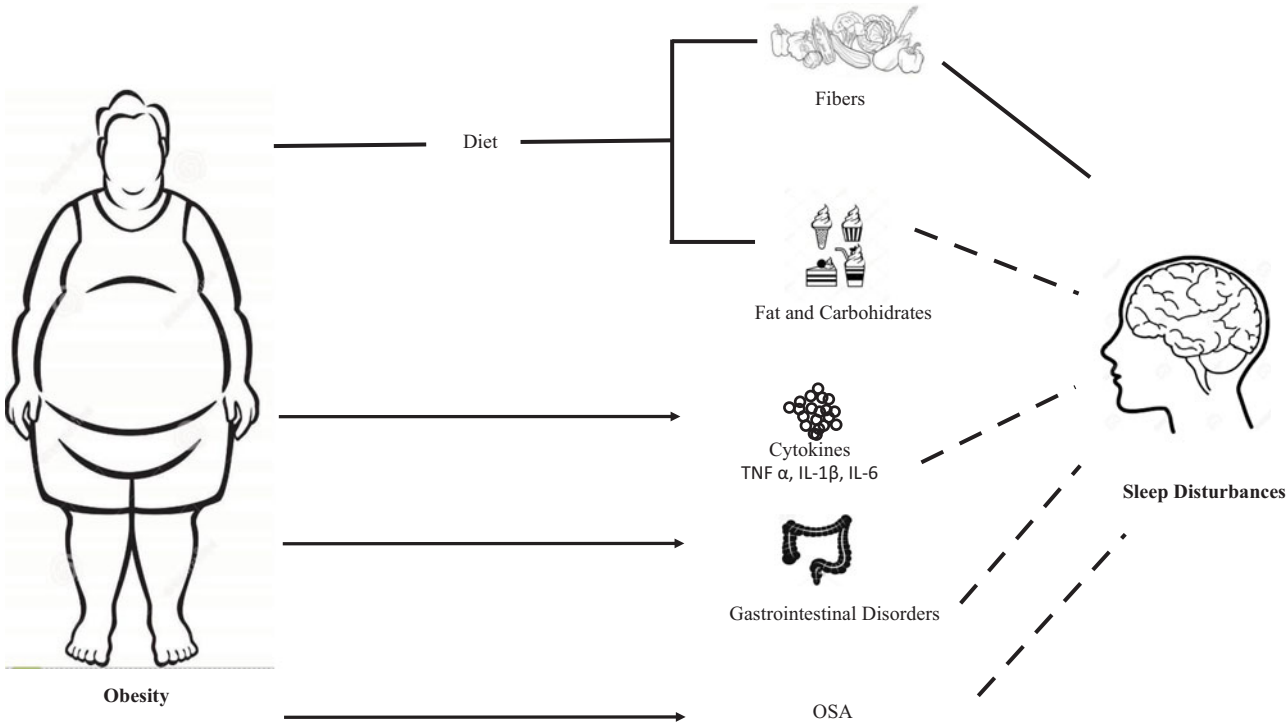


**Figure 1.** Mechanisms linking sleep disturbances and obesity. Obesity represents a risk factor of developing Sleep Disturbances. Several obesity-related factors could interfere with normal sleep quality and/or duration. In particular the consumption of fat and carbohydrates, mostly in the evening, have been reported to have a detrimental effect on sleep while the consumption of fibers is associated with more restorative and deeper sleep. Further, as well known the visceral adipose tissue is the main source of cytokines that could have a role in disrupting the sleep. The gastrointestinal disorders such as irritable bowel syndrome and functional dyspepsia could have an additional effect in disturbing the sleep quality. In addition severe obesity could be associated to OSA that is characterized by recurrent narrowing and closure of the upper airway, leading to intermittent oxyhemoglobin desaturation, sleep fragmentation and daytime sleepiness. ————: positive effect; – – – – – – –: negative effect

intermittent oxyhemoglobin desaturation, sleep fragmentation and daytime sleepiness (Dewan, Nieto and Somers 2015). The excessive body size could represent a mechanical barrier to normal breathing thus resulting in OSA that is associated to frequent nocturnal awakenings, with impaired SQ and sleep duration (Quintas-Neves, Preto, and Drummond 2016; Shigeta et al. 2008; Tirado et al. 2017).

Nevertheless, both SQ and sleep duration might be impaired in obese individuals without OSA. These data come from an interesting study of Resta et al performed in severe obese subjects without OSA (BMI $39.7 \pm 5.94\,kg/m^2$) or diseases that are known to be associated with SD such as endocrine, psychiatric, and neuromuscular diseases (Resta et al. 2003). In this study, SD, characterized by choking, awakening and unrefreshing sleep, were more frequent in obese (17%, 25%, 50% and 50%, respectively) than in normal-weight subjects (2.5%, 1%, 3% and 9%, respectively). In addition, these Authors reported that the percentage of snoring was higher in obese subjects (47%) than in controls (8.1), and the daytime sleepiness, evaluated by the Epworth Sleepiness Scale (ESS), was lower in normal control group ($2.7 \pm 2$) than in obese subjects ($7.7 \pm 4.6$), with a linear correlation between ESS score and snoring severity ($P = 0.0169$). Indeed, in addition to OSA, SD in obesity could be due to other *obesity-related* pathological conditions, such as functional gastrointestinal disorders, including irritable bowel syndrome and functional dyspepsia (Dixon, Schachter, and O'Brien 2001; Eslick and Talley 2016), nicturia, asthma and ostearticolar pain (Dixon, Schachter, and O'Brien 2001). Although obesity has been associated to SD, several studies attempt to investigate if it was just obesity or instead body composition that could have a role in explaining the effect of the excess of weight on sleep. In both males and females waist circumference (WC) has been reported to be the most predictive factor of SD (Davidson and Patel 2008). These results were also confirmed in a study performed in 463 community-dwelling older Spanish women reporting a significant positive correlation between SD, assessed by the Jenkins Sleep Scale, and WC. Since WC is an indirect measure of visceral adipose tissue, the results of these studies lead to hypothesize that visceral adipose tissue could play an additional role in the pathogenesis of SD (Moreno-Vecino et al. 2017). As well known visceral adipose tissue is the main site of secretion of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-$\alpha$ that determine chronic low-grade inflammation (Hotamisligil 2006). Several studies showed that pro-inflammatory cytokines could be involved in sleep regulation and classified as "*sleep-regulatory substances*" (Gamaldo, Shaikh and McArthur 2012; Perrini et al. 2017). TNF-$\alpha$ and IL-1$\beta$, whose secretion follows a circadian rhythm, with the highest TNF-$\alpha$ and IL-6 secretion during the night (between 01:00 and 02:00 h), are involved in the physiological regulation of sleep in both animals and humans (Opp, Kapás and Toth 1992), playing an important role in the slow-wave sleep (SWS) (Covelli et al. 1992). In 1997, Vgontzas et al showed that in overweight and obese subjects with OSA, narcolepsy, idiopathic hypersomnia, TNF-$\alpha$ and IL-6 levels were elevated during the morning

(between 06:00 and 07:00 h), with a positive association between TNFα and Il-6 with SD and BMI, respectively (Vgontzas et al. 1997). Thus, a possible vicious circle operating within the interactions between obesity, pro-inflammatory cytokines levels and sleep abnormality, could be hypothesized (Figure 1).

Another important mechanism that relates obesity to SD is represented by diet food components (Hargens et al. 2013). In fact dietary fatty acids have been reported to be involved in sleep regulation, through their effect on the dynamics of biochemical compounds, including complex lipids, prostaglandins, neurotransmitters and aminoacids which exert an important role for the initiation and maintenance of sleep (Yehuda, Rabinovitz, and Mostofsky 1998; Irmisch et al. 2007; St-Onge et al. 2016), indeed, showed that poor diet quality (characterized by high fat and low fiber intake) was associated with SD. In this study normal weight adults subjects were randomized in two groups: short sleep (four hours in bed) and normal sleep (nine hours in bed). After 4 days controlled diet, in the fifth day self-reported free diet was allowed. Diet quality analysis revealed that free diet was characterized by higher intake of saturated fatty acids, sugar and/or non-sugar/non-fiber carbohydrates. During controlled diet period, SQ did not differ between the two groups. After free diet period, impaired sleep parameters were observed, in particular, less slow wave sleep (SWS) and longer sleep onset latency (SOL); in addition free diet was associated with poor SQ (St-Onge et al. 2016). On the contrary polyunsaturated fatty acids and n-3 fatty acids have been observed to be positively associated to SQ parameters, after controlling for age, gender and obesity (Papandreou 2013). At first, fatty acids (specifically, n-3 and n-6 fatty acid) contribute to the generation of prostaglandin D2 (PGD2), an inflammatory signaling molecule that has a role in sleep regulation which is involved in the maintenance of normal sleep (Mizoguchi et al. 2001); in addition, n-3 fatty acids are related to the regulation of serotonergic neurotransmission, being serotonin a well-known substance that promote the normal sleep and helps the melatonin production (Machado and Suchecki 2016).

In addition to fat, a single carbohydrates-rich meal in the evening has been reported to increase core body temperature ad heart rate and reduced nocturnal secretion of melatonin within the eight hours after the end of the meal consumption healthy normal weight subjects (Touitou, Reinberg and Touitou 2017; Kräuchi et al. 2002). On the other hand, fiber consumption is associated with more restorative and deeper sleep (St-Onge et al. 2016). These findings suggest that diet quality might have a great influence on SQ, probably due to the effects of foods, or more specifically nutrients, on hormonal responses and circadian rhythms. In this context, the understanding of the relationship between nutrition and sleep could pave the way to the recent concept of *chronobiology*, or more specifically *Chrono nutrition*, as a way for Nutritionists to manage not only obesity and obesity-related diseases by using proper diets, but also SD.

Finally, several evidence have widely demonstrated an association between vitamin D deficiency and SD (McCarty et al. 2013; Bertisch et al. 2015). Although no studies were carried out in obese population, it could be hypothesized that since vitamin D deficiency is a common finding in obesity (Muscogiuri et al. 2010), it could act as an additional detrimental factor on obesity-related SD.

## 3. Sleep disturbance as cause of obesity

### 3.1. Dietary factors

Although a number of evidence showed that obesity is one of the main cause of SD, several studies investigate the role of SD as predisposing risk factor of obesity (Hargens et al. 2013; Lyytikainen et al. 2011; Markwald et al. 2013;). Indeed, several meta-analysis and systematic reviews showed that subjects with SD or poor quality sleep are more prone to develop obesity, in particular central obesity (Broussard and Van Cauter 2016). A four-years follow-up prospective study conducted on 14,000 young adults (24.3–34.7 years) showed that self-reported short sleep persistent exposure leads to an 1.45 times increase in obesity and elevated WC development, suggesting that lower sleep duration may represent an important obesity risk factor, acting with a dose-response association (Krueger et al. 2015). Similar results were reported by Canuto et al. demonstrating that *shift work- induced* sleep deprivation ($\leq$ 5 hours of continuous sleep *per* day) increases the risk of obesity compared to normal sleep duration ($>$ 5 hours of continuous sleep *per* day) (Canuto et al. 2014). A retrospective study performed by Kubo and colleagues carried out on about 10,000 shift workers reported that shift workers had an increased obesity risk in a follow-up period of 6 years, compared to daytime workers (Kubo et al. 2011).

The increased prevalence of obesity in subjects with sleep restriction could be explained by an effect on calorie intake (Cain et al. 2015). Subjects undergoing a simulated night shift experienced a significant increased consumption of high-fat foods compared to controls, although differences in food amount or total caloric intake were not significant, thus suggesting that an impaired SQ could lead to unhealthy food cues and thus to an increased risk of developing obesity.

Modern lifestyle could contribute to alter our physiological *chronobiology*. Both shift workers/businessmen and young people tend to go to bed late and to wake up early, resulting in a blunted sleep duration (Burman 2017; Wittmann et al. 2006). This pathological condition has been called "*Social Jet-lag (S-jl)*" and seems to be strongly linked with increased risk of developing both obesity and metabolic syndrome (Burman 2017; Espitia-Bautista et al. 2017; Pinto et al. 2017) due to an excessive consumption of high caloric food, carbohydrate and high fat-rich foods. Espita-Bautista and colleagues investigated the effect of S-jl on metabolism in an experimental model founding that S-jl can cause the propensity towards an increased consumption of unhealthy food resulting in obesity and *obesity-related* metabolic consequences such as dyslipidaemia and hyperinsulinemia

**Table 1.** Mechanism of action of sleep disturbance-related hormones in promoting obesity.

| Hormones | Sleep disturbance – related changes | Mechanism of action |
|---|---|---|
| Cortisol | ↑ | High cortisol levels causes overeating, impairs glucose homeostasis, insulin-resistance, and increases visceral fat accrual |
| Ghrelin | ↑ | High ghelin levels increase calorie intake, mostly sweet foods |
| Leptin | ↑ | Sleep disturbance has been associated to leptin-resistance and consequent increased leptin levels which results in increased hunger. |
| Endocannabinoid System | ↑ | 2-arachidonoylglycerol (one of the most abundant ligand of endocannabinoid receptors) rhythm is amplified and the peak is delayed and extended, increasing hunger |
| Melatonin | ↓ | Decreased levels of melatonin causes weight gain, chronic inflammation and increased oxidative stress, thus blunting glucose metabolism. |

(Espitia-Bautista et al. 2017). Prolonged sleep restriction or sleep duration of less than 6.5 hours has been associated to unhealthy dietary patterns, mainly characterized by increased consumption of high glycaemic index (GI) food and beverages (Felső et al. 2017). Subjects with sleep disruption, indeed, tend to have a low quality diet (Hargens et al. 2013; Alodhayani et al. 2017; Markwald et al. 2013), including increased carbohydrate intake (Hargens et al. 2013; Doo, Chun, and Doo 2016; Moreno-Vecino et al. 2017; Markwald et al. 2013), that might contribute to develop central obesity. A study conducted on 4th and 7th grade children showed that sleep pattern tightly influence food choice (Franckle et al. 2015). During annual screening, students provided information about diet and sleep. Results showed that shorter sleepers (< 10 hours per day) consumed less frequently vegetables and more frequently soda than other students. A randomized cross-over study conducted on adolescents evaluated the effects of sleep restriction (6.5 h in the bed) *versus* normal sleep duration (10 h in the bed) on food preferences (Simon et al. 2015). Short sleepers showed more appealing towards sweets, higher sweets consumption and calories intake, even if self-reported hunger was not affected, suggesting that prolonged short sleep duration may contribute to *obesity* and *obesity-related* disease development, acting by this mechanism. The preferences of unhealthy food could be ascribed to an increase in brain activity in areas associated with reward, including the putamen, nucleus accumbens, thalamus, insula, and prefrontal cortex in response to food stimuli, consequent to sleep deprivation (St-Onge et al. 2012).

Sleep deprivation not only influences the food preferences but also it is associated to an increased food intake. The function of sleep in humans is to preserve energy and that some of the energy saved is redistributed to support other critical sleep-dependent physiological processes (Jung et al. 2011). Sleep restriction seems to lead to an increased energy expenditure that in turn results in an increased food intake in daytime, probably as a compensatory mechanism (Broussard and Van Cauter 2016; Alodhayani et al. 2017, Pinto et al. 2017). When the food intake overcomes the energy expenditure, weight gain is the logical consequence. Among the dietary factors that could improve SD, tryptophan (Trp) deserves a prominent role. Tryptophan is an essential amino acid in humans that must be absorbed in the small intestine from protein-rich foods (for example, milk, eggs, meat, and beans). As Trp is metabolized into melatonin *via* the serotonin pathway, several previous studies have suggested that eating food rich in Tryptophan at evening could improve nocturnal sleep quality in humans (Wyatt et al. 1970). This could be due to the fact that Tryptophan is the precursor of melatonin, a hormone that is produced by the pineal gland and regulates sleep and wakefulness.

### 3.2. Hormonal aspects

Several studies showed interesting correlations between SQ and hormonal status. In particular, sleep restriction seems to impair the hormonal system that regulate energy balance at brain level and which involves different hormones, including cortisol, insulin, ghrelin, leptin and melatonin (Hargens et al. 2013; Taheri et al. 2004; Broussard and Van Cauter 2016; Pinto et al. 2017; St-Onge et al. 2012; Leproult and Van Cauter 2010; Beccuti and Pannain 2011; Lowry et al. 2012) (Table 1).

### 3.3. Cortisol

There is an overall agreement across different studies that sleep deprivation and/or reduced sleep quality is more commonly associated with a modest but functionally important activation of the hypothalamus-pituitary-adrenal axis (HPA) activity as the consequence of a chronic stress induced by long-time altered sleep and consistent with a disorder of central nervous system hyper arousal (Vgontzas and Chrousos 2002; Kumari et al. 2009; Ruan et al. 2015; Balbo et al. 2010). The impaired function of the HPA axis, in turn, is involved in a number of healthy problems (Anagnostis et al. 2009). In particular, high concentrations of cortisol are recognized as one the main cause of impaired glucose homeostasis, insulin-resistance, and visceral fat accrual (Di Dalmazi et al. 2015). In addition, functional HPA hyperactivity with increased cortisol levels are proposed as one of

the main cause of overeating in presence of palatable foods [56].

### 3.4. Ghrelin

Insufficient sleep duration might induce changes in satiety and hunger hormones, thereby altering food intake and EE (Markwald et al. 2013).

In fact it has been reported an increase in ghrelin (Markwald et al. 2013), which is an orexigen hormone, associated to insufficient sleep duration (Broussard and Van Cauter 2016; Beccuti and Pannain 2011). To investigate the effect of sleep restriction on ghrelin levels, nineteen normal weight (mean BMI: 23.1 ± 0.4 kg/m2) young healthy subjects were recruited (Broussard and Van Cauter 2016). Participants underwent a normal sleep (8.5 hours in bed for 4 consecutive nights) and restricted sleep (4.5 hours in bed for 4 consecutive nights) period. SQ was assessed by polysomnography and diet strictly controlled by Nutritionists, blood samples were collected within the 24 hours, and biochemical parameters and hormones were assessed. Sleep restriction significantly increased the diurnal and nocturnal ghrelin profile, in particular during postprandial periods. As expected, sleep restriction was also associated with increased caloric intake, particularly higher carbohydrates intake. Interestingly, increased ghrelin profile was associated with higher sweets consumption.

### 3.5. Leptin

Several evidence showed that obese subjects with OSA have higher circulating levels of leptin compared to non-OSA obese subjects (Quintas-Neves, Preto, and Drummond 2016; Beccuti and Pannain 2011; Marik 2000; Wolk, Shamsuzzaman and Somers 2003), suggesting that OSA exacerbate the leptin-resistance, which characterize the obesity. In addition, OSA treatment with nasal continuous positive airway pressure (nCPAP) seems to improve the leptin levels (Marik 2000). This mechanism could explain the increased food intake in subjects with sleep disruption, resulting in higher risk to develop obesity, overweight or metabolic alterations.

### 3.6. Endocannabinoid system

The sleep deprivation could affect also the endocannabinoid system which, in turn, regulates either food intake and metabolism [70]. In a well-designed clinical study, Hanlon and colleagues (2015) showed that 2-arachidonoylglycerol (2-AG), one of the most abundant ligand of endocannabinoid receptors, follows a circadian secretion, with a peak in the early mid-afternoon and a nadir in mid-sleep (Hanlon et al. 2015). According to these Authors, circadian levels of 2-AG regulate the daytime food intake, suppressing hunger during the sleep and enhancing it during mid-afternoon. Interestingly, the same Authors, in another study, showed that restricted sleep causes an increase in daily 2-AG circulating levels (Hanlon et al. 2016). Healthy adults were randomized in 2 groups: sleep restriction (4.5 hours) and normal sleep (8.5 hours) for 4 nights. In restricted sleep group, 2-AG rhythm was amplified and the peak was delayed and extended. In addition, participants of this latter group reported increased hunger and appetite in concomitance with the afternoon peak of 2-AG, and an inability to inhibit the palatable foods intake.

### 3.7. Melatonin

Subjects with SD showed decreased nocturnal levels of melatonin. Melatonin is involved in sleep timing and is empirically used in the treatment of SD (Auld et al. 2017). Melatonin is secreted in humans during the dark phase of the light–dark circadian cycle but it exerts antioxidant, anti-inflammatory and immune-modulatory effects (Reiter, Tan and Fuentes-Broto 2010). In addition, several studies showed that melatonin is involved also in the regulation of body weight gain and energy metabolism in some rodents. In particular, the administration of melatonin in a model of obesity-related type 2 diabetes, such as Zücker diabetic fatty rats, has been shown to reduce obesity and to improve the low-grade inflammation, oxidative stress, and the metabolic profiles in this strain of rats, without affecting food intake and activity (Agil et al. 2013). Misalignment in circadian rhythm and deficiency of melatonin, as the consequences of sleep deprivation, have been accounted for one of the mechanisms to explain why shift workers tend to gain weight (Touitou, Reinberg and Touitou 2017). The possible links between the deficiency of melatonin and obesity or its potential role in the prevention of obesity and its complications have been supported by several studies during recent decades (Cipolla-Neto et al. 2014; Reiter et al. 2012; Szewczyk-Golec, Woźniak and Reiter 2015). However, despite the growing body of evidence indicating the association of melatonin with obesity, the mechanisms of melatonin action are far from being fully understood.

## 4. Conclusion

SD represents a common complications of obesity that could contribute to the pathogenesis and/or to worsen *obesity-related* complications. Thus, it is of paramount importance to investigate SD in obese patients and to include the treatment of SD in the management of obesity in order to prevent or improve metabolic and cardiovascular diseases. On the other hand, SD although not associated to obesity, should not be underestimated because they could foster the onset of hormonal and metabolic patterns that in turn increase the total intake and the unhealthy food consumption thus encouraging the weight gain.

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