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Original Research Article

Associations Of Sleep Deprivation With Pathogenesis Of Obesity: An Overview

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Abstract

Sleep wake cycle is synchronized with the circadian clock fluctuations in Suprachiasmatic nucleus which are entrained with other diurnal rhythms in our body like feeding and fasting timings, temperature regulatory mechanisms and various hormonal level fluctuations. Due to change in our culture or lifestyle which lead to increased number of evening and night time work and leisure activities, less hours are available for sleep. Sleep deprivation alters both metabolism and endocrine function, including glucose tolerance and the hormone that controls hunger. This review looked at potential connections between sleep and factors that contribute to the pathogenesis of obesity.

Studies showed that suggested that sleep restriction has metabolic effects that predispose to weight gain. Sleep loss found to be associated with increase in appetite via increasing Ghrelin and endocannabinoids whereas decreasing Leptin hormone. Because of sleep disruptions, time spent awake gave more opportunity for night time snacking and daytime sleepiness which might lead to decreased activity level. Hence overall positive balance in spite of increased energy expenditure leading to weight gain. Increase in sleep debt subsequently leads to fatigue and daytime sleepiness making prone to sedentary lifestyle and can predispose to obesity. Sleep disorders were linked directly with obesity severity in literature. The sleep fragmentation in sleep disorders like OSA might lead to excessive daytime sleepiness, lack of physical activity and increasing food intake by influencing food choices and hence, to obesity. OSA patients with CPAP therapy (continuous positive airway pressure) showed improvement not only in OSA severity but weight loss also. Therefore, scheduling sleep might improve the obesity and further consequences of obesity like cardiovascular disorders or metabolic syndrome etc. Hence, sleep should be considered equally important as nutrition and exercise.

1. INTRODUCTION

Prevalence of obesity epidemic has been paralleled in modern society by a trend of reduced sleep duration which has become frequent these days because of lifestyle change and social media use. Growing evidence both from laboratory and epidemiological studies points to short sleep duration as a new risk factor for the development of obesity and its complications. Sleep deprivation alters both metabolism and endocrine function, including glucose tolerance and the hormone that controls hunger. In the present time, behavioural sleep reduction is increasingly widespread because of modernisation and social media use.(1) Due to this change in our culture which lead to increased number of evening and night time work and leisure activities, less hours are available for sleep. The exposure to artificial light after sunset and frequently before sunrise has had a significant impact on sleep duration and sleep quality. This has led to later bedtimes, shorter overall sleep duration, and the opportunity to be active and consume food during the natural night. A significant synchronizer of peripheral circadian clocks, which have been discovered in almost all tissues, is feeding. Desynchronization of the central circadian and peripheral clocks results from delayed feeding

brought on by extended night time awake (2-4). Therefore, this review looked at potential connections between sleep and factors that contribute to the pathogenesis of obesity, such as hormone changes, changes in energy intake and expenditure that result in a positive energy balance, weight gain, some neural mechanisms at play, and associations between sleep disorders and obesity.

2. SLEEP AND BMI

Various studies suggested that sleep restriction has metabolic effects that predispose to weight gain. A meta-analysis on 604 509 adults demonstrated a pooled obesity odds ratio (OR) of 1.55 (1.43–1.68; $P < 0.0001$) for <5 hours of sleep and a dose effect of sleep duration such that for each additional hour of sleep BMI decreased by 0.35 kg/m^2. (5)

Buxton and Marcelli demonstrated a 6% increase in the probability of obesity in adults for self-reported sleep duration of <7 hours per night. (6) Anic et al., in a cohort study demonstrated that the effect of short sleep duration was stronger for extreme obesity (OR of BMI ≥40 kg/m^2 was 3.12 for <6 h of sleep, CI 1.70–5.75). (7)

Patel et al, investigated the association between self-reported usual sleep duration and subsequent weight gain in 68,183 women who were followed for 16 years. In analyses, women sleeping 5 hours or less gained 1.14 kg (95% confidence interval (CI): 0.49, 1.79) more than did those sleeping 7 hours over 16 years, and women sleeping 6 hours gained 0.71 kg (95% CI: 0.41, 1.00) more, adjusted for age and body mass index. The relative risks for incident obesity (body mass index: >30 kg/m^2) were 1.15 (95% CI: 1.04, 1.26) and 1.06 (95% CI: 1.01, 1.11). (8) Fatima et al. published the first systematic review and meta-analysis looking at associations between sleep quality using the Pittsburgh Sleep Quality Index and overweight and obesity in youth. Poorer self-reported sleep quality, defined as higher sleep onset latency, more sleep disturbances, recurrent awakenings, and lower sleep efficiency, was associated with a higher odds of being overweight or obese (odds ratio of 1.46, 95% CI of 1.24–1.72), independent of sleep duration. (9)

Taheri et al, found a significant U-shaped relationship between average nightly sleep and BMI after adjustment for age and sex, ($p = 0.008$). Study showed that increased BMI was proportional to decreased sleep duration. An increase in BMI from 31.3 to 32.4 corresponded approximately to an average nightly sleep duration decrease from 8 h to 5 h.(10)

Few studies have been done assessing the link between sleep health and obesity in India. Among them, associations between few sleep parameters were done with BMI only. Mirdha et al, explored the relation between BMI and various sleep parameters using Likelihood Ratio. Among all the studied 7 individual components, sleep latency and sleep disturbance component were significant ($p<0.05$). (11) Khullar S et al, explored the link between sleep duration and anthropometric parameters and found thar sleep duration was significantly negatively correlated with hip circumference and W/H ratio (waist/ Hip circumference).(12)

3. CIRCADIAN RHYTHM AND FEEDING BEHAVIOUR

Sleep wake cycle is synchronized with the circadian clock fluctuations in Suprachiasmatic nucleus which are entrained with other diurnal rhythms in our body like feeding and fasting timings, temperature regulatory mechanisms and various hormonal level fluctuations.

A network of cerebral and peripheral impulses that control appetite can modify how each person responds to the foods being offered. The hypothalamus, brain stem, neuropeptide signalling systems (NPY (neuropeptide Y), proopiomelanocortin (POMC)- an anorexigenic effect), monoaminergic, and endocannabinoid systems all play a role in the central regulation of food intake. The gastrointestinal system sends signs of fullness via the hormones cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), and neuropeptide Y. (NPY). The vagus nerve carries signals to the solitary nucleus (SN) in the brain stem. Lateral hypothalamus and paraventricular nucleus regulation of feeding behaviour which are influenced by other factors like leptin, Ghrelin, insulin etc. These signals are believed to be integrated in Arcuate nucleus (integrating centre) from where POMC and NPY neurons originates to regulate feeding. (Figure-1) (3) Various studies explored associations of all these connections with poor sleep quality or decreased sleep duration of populations which will be discussed below.

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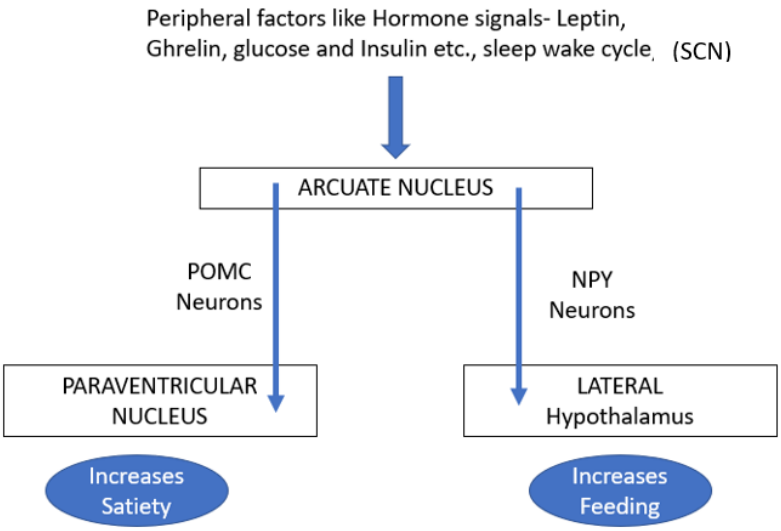

Figure 1: Figure showing neural circuits influenced by external factors

These behavioural and physiological rhythms are coordinated by the neuronal circadian clock found in the hypothalamic suprachiasmatic nucleus (SCN), which runs on a 24-hour cycle. In mice, disruption of the circadian clock gene network can result in obesity and the metabolic syndrome. This network affects a number of central and peripheral tissues that are involved in energy balance. Studies reported that Clock mutant animals were associated with altered expression of neuropeptides involved in appetite regulation and energy balance. Compared to wild type animals, clock mutant animals showed higher energy intake, positive balance and weight gain indicating the energy homeostasis and metabolic regulations operating at central level. Desynchronization at suprachiasmatic nucleus or sleep wake rhythm disruptions can lead to various metabolic changes leading to obesity.(4)

4. SLEEP ASSOCIATION WITH HORMONES CONTROLLING APPETITE

Sleep deprivation can cause disturbances in various hormones involved in various metabolic processes like glucose metabolism, regulating appetite and satiety (feeling of fullness), fat metabolism, insulin sensitivity or feeding habits.

4.1 Sleep and Leptin

It is believed that paraventricular nucleus of hypothalamus act as satiety centre and lateral hypothalamus as feeding centre along with arcuate nucleus which act as integrated centre for feeding behaviour. Ther are various peripheral hormones which can influence these connections and hence affect feeding behaviour such as leptin and ghrelin. Leptin is an appetite suppressant hormone produced by adipose tissue, and ghrelin is released from the stomach primarily in response to fasting and promotes the feeling of hunger. Leptin has been shown to rapidly increase or decrease in response to caloric deficiency. Studies showed the mean leptin levels for half-hour increments of average sleep duration, showed a significant increasing trend in leptin for average nightly sleep duration ($p = 0.01$). When evaluated at the average values and sex distribution of sample, decrease from 8 to 5 h in average nightly sleep was associated with a predicted 15.5% decrease in leptin.(10)

4.2 Sleep and Ghrelin

Same study also evaluated Ghrelin levels and found a significant decreasing trend in ghrelin with total sleep time ($p = 0.008$). When evaluated at the average values of Ghrelin, a decrease from 8 to 5 h of polysomnographically defined total sleep time was associated with a predicted 14.9% increase in ghrelin. Higher leptin levels in sleep deprived population were also found in some studies,

independent of body fat content, suggested that sleep deprivation could be associated with resistance to the weight-reducing effects of leptin.(10,16) Few studies also confirmed an interaction between elevated plasma orexin-A concentrations and poor sleep that contributes to fluctuations in body mass index.(17)

4.3 Sleep and Endocannabinoids

The endocannabinoid system (ECS) is an endogenous signalling system formed by specific receptors (cannabinoid type 1 and type 2 (CB1 and CB2)), their endogenous ligands (endocannabinoids), and enzymes involved in their synthesis and degradation. The ECS, centrally and peripherally, was found to be involved in various physiological processes, including regulation of energy balance, promotion of metabolic process, food intake, weight gain, promotion of fat accumulation in adipocytes.(18) The ECS was associated with reduction in the feeling of satiety, which could increase the frequency and quantity of food intake via stimulating NPY signalling in lateral nucleus of hypothalamus.(18) The Endocannabinoids level found to be decreased when we sleep. Poor sleep was found to be associated with increased endocannabinoids level, hence increased food intake.(19)

Growth hormone is typically elevated at onset of sleep with highest levels during slow wave sleep (SWS) while cortisol levels are greatly increased during the second half of the sleep, predominantly in REM sleep. (13,14) There is a relative state of insulin resistance during early phases of sleep cycle. During the latter part of sleep cycle, the glucose and insulin levels fall despite continuous infusion of glucose. Other studies have shown similar findings suggesting increased glucose utilization during REM phase of the sleep and increased glucose levels in the evening with reduced insulin sensitivity (15).

5. SLEEP AND ENERGY BALANCE

Bedtime restriction was accompanied in literature by increased consumption of energy from snacks ($P = 0.026$) and a shift toward more carbohydrate and relatively less fat consumption. (20) Change in sleep duration from 8 hours to 5 hours was found to be associated with decreased leptin concentration. Mean energy expenditure was high in short sleeper group compared to long sleepers. In spite of higher energy expenditure, overall energy balance was also found more in short sleepers. This could be explained by night time snacking in short sleepers causing significantly high energy intake during sleep debt periods and decreased leptin concentration and increased ghrelin concentration which further support it.(20,21)

Sleep duration was also found to be negatively associated with visceral and subcutaneous fat deposition and weight gain in younger adults (<40 years).(22)

Activity level was also explored in previous studies where obese children with and without sleep deprivation were compared with respect to intake, nutrient choices and activity level. It has been observed that obese children with OSA (Obstructive sleep apnea) were significantly found to be least active, consumed more snacks and ate less fruits and vegetables with high level of ghrelin levels. (23)

Hence, sleep deprivation could might lead to not only hormonal modulation but also change in food choices and fat deposition and can predispose to obesity.

6. DAYTIME SLEEPINESS AND OBESITY

Increase in sleep debt subsequently leads to fatigue and daytime sleepiness making prone to sedentary lifestyle and can predispose to obesity. Excessive daytime sleepiness (EDS) is commonly assumed to be the result of disturbed or inadequate sleep, for example, daytime sleepiness observed in those with sleep disordered breathing (SDB) is commonly assumed to be due to the sleep disturbance caused by frequent arousals associated with the apneas or hypopneas. EDS has been shown to be associated with obesity in the absence of SDB.(24) Recent studies also associated EDS with the metabolic syndrome (e.g., obesity, diabetes, insulin resistance). (25) BMI-specific prevalence, showed a dramatic increase in the prevalence of EDS around the threshold of BMI

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which was considered to be overweight (BMI>28). When associations of EDS were evaluated with various sleep components, EDS was found to be significantly associated with sleep duration. Presence of EDS might be responsible for decreased activity level, fatigue and sedentary life style which is risk factor of obesity.(24)

7. SLEEP DISORDERS AND OBESITY

Decreased sleep duration and quality was associated with an increase in body weight and adiposity. Insomnia, obstructive sleep apnoea, and restless legs syndrome are three of the most prevalent types of sleep disorder that lead to an increased risk for numerous chronic health conditions. Various studies have examined the impact of these sleep disorders on obesity, and are an important link in understanding the relationship between sleep disorders and chronic disease.

OSA is characterized by recurrent episodes of complete or partial obstruction of the upper airway during sleep associated with progressive respiratory effort to overcome the obstruction. These events lead to cortical micro-arousals and oxygen desaturation and overall sleep fragmentation, chronic sleep loss, and increased sympathetic nervous activity. Wisconsin Sleep Cohort Study used a sample of 700 subjects, showed a direct association of weight gain with severity of OSA. 10% weight gain predicted a 32% increase in AHI score; conversely a 10% weight loss predicted a 26% decrease in AHI score over a 4-year period. Connection with OSA and obesity is evolving and might involves a two-way relationship affecting both the contribution of obesity to OSA and the implications of OSA contributing to obesity. (26)(27) The sleep fragmentation of OSA could lead to excessive daytime sleepiness, lack of physical activity and increasing food intake by influencing food choices and hence, to obesity. OSA patients with CPAP therapy (continuous positive airway pressure) showed improvement not only in OSA severity but weight loss also. Parameters of OSA severity AHI (apnea-hypopnea index - time spent below 90% saturated or arousal frequency) were significantly more severe in the obese group with OSA compared to OSA without obesity.(16) (26)

One Indian study explored role of OSA in non-obese with respect to metabolic syndrome. Metabolic syndrome was observed in approximately one in three patients with OSA and BMI < 25 kg/m2. Approximately two of every three lean waist non-obese patients with OSA had at least two markers of metabolic syndrome indicating role of OSA in the development of metabolic syndrome in non-obese participants.(28)

8. CONCLUSION

Sleep disruption in form of sleep duration majorly was found to be associated with every link in pathogenesis of obesity. Decreased sleep duration and quality increased appetite via increasing Ghrelin and decreasing Leptin hormone.

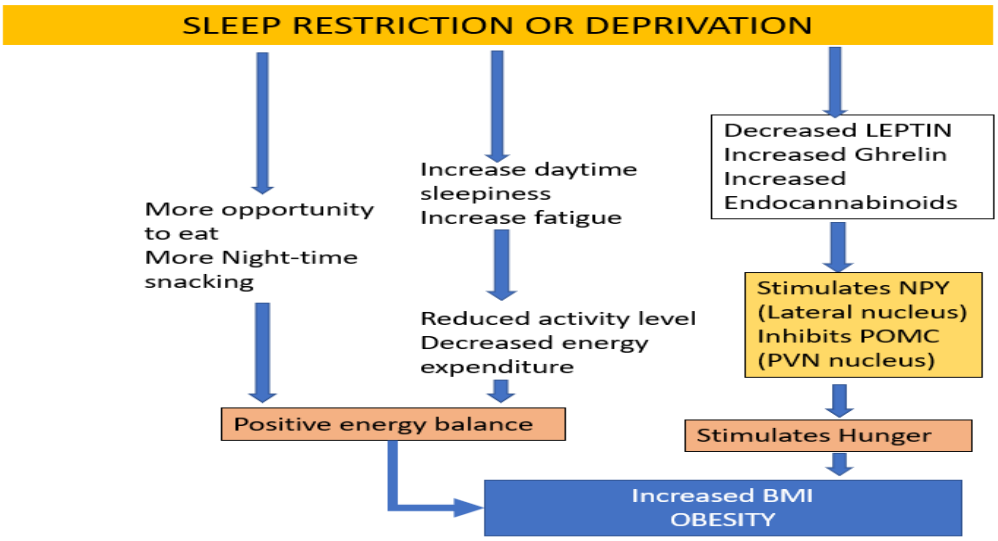

Figure-2: Figure showing the proposed connections between sleep deprivation and pathogenesis of obesity

Poor sleep was associated to increase in endocannabinoids which further enhanced hunger. Because of sleep disruptions, time spent awake gave more opportunity for night time snacking and daytime sleepiness which might lead to decreased activity level. Hence overall positive balance in spite of increased energy expenditure. (Figure-2) Sleep disorders also showed clear relationship with weight gain. Clock gene showed role of circadian rhythm generator in energy balance and weight gain. These links associated sleep disruption with obesity explained the importance of sleep in prevention of obesity. With sleep hygiene techniques like scheduling sleep timing and giving importance to our sleep health, the risk of obesity, cardiovascular disorders and metabolic syndrome can be prevented. Hence, sleep should be considered equally important as nutrition and exercise.

9. FUTURE DIRECTIONS

Most of the previous studies explored sleep duration only with obesity. There is need of more longitudinal studies focussed on various sleep parameters linked to factors involved in pathogenesis of obesity with polysomnographic studies. There is scarcity of literature about all these links associations in Indian population.

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