

Sleep and obesity in the causation of metabolic syndrome

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Sleep is essential for life. Modern lifestyle has generated several disorders. Sleep deprivation is known to cause glucose intolerance and snoring. Snoring and excessive daytime sleepiness are prominent symptoms of obstructive sleep apnea (OSA). Obesity is closely linked to OSA and diabetes. OSA itself can lead to diabetes. Although OSA is common in obese subjects, it is also observed in normal and low body weight subjects. Interesting close relationship exists between sleep, OSA, obesity, insulin resistance and metabolic syndrome. Polysomnography is the gold standard for diagnosis of OSA. Treatment of OSA by continuous positive airway pressure is rewarding. It is time that we closely attend to this relationship for better management of metabolic syndrome.

KEY WORDS: Metabolic syndrome, obesity, obstructive sleep apnea, type 2 diabetes.

Introduction

Sleep is a function of brain and is essential for life. Sleep is subdivided into two distinct states: non-rapid eye movement and rapid eye movement. There is a distinct 24-hour temporal pattern of endocrine functions and metabolism. Hormonal release obeys certain circadian rhythmicity and changes in sleep-wake cycle have a profound influence on the endocrine function and metabolic states. Hormones, active peptides and neurotransmitters have the capability to exert a modulatory influence over the neuroanatomic substrates

that generate sleep. These effects are reflected in several body systems. Errors in secretion of hormones in sleep are reflected in disorders of organ systems. Fast-paced modern lifestyle has given birth to sleep deprivation, which has profound effects in functioning of body systems. These effects may ultimately culminate into serious metabolic effects resulting in metabolic syndrome. Sleep is a metabolic regulator and sleep disorders affect metabolism. Obstructive sleep apnea (OSA) is closely linked to diabetes. A close relation exists between sleep, circadian rhythm, hormones, obesity, hypertension and cardiovascular morbidity and mortality.^[1]

Sleep and glucose metabolism

Glucose tolerance is markedly better in the morning than in the evening.^[2] Sleep loss is associated with impaired glucose tolerance and diabetes. Spigel *et al.*^[3] have demonstrated that sleep debt results in impaired glucose tolerance. Sleep debt also results in the elevation of evening cortisol and extended nocturnal secretion of growth hormone before and after sleep onset. Animal experiments have demonstrated that a slight degree of hyperactivity of hypothalamo-pituitary axis (HPA) at the usual trough of corticosterone levels is capable of exerting deleterious metabolic effects, including increased adiposity and insulin resistance.^[4] In humans a short-term elevation of cortisol in the evening results in a prolonged state of insulin resistance, while the same degree of elevation in the morning has insignificant effects on insulin and glucose levels.^[5]

Obesity and Sleep Apnea

Obesity is highly prevalent in western industrialized nations. Approximately 34 million American adults (26%) are overweight (body mass index >27.3) and 12.5

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million (9%) are obese (BMI ≥ 32), with greater numbers of women than men affected.^[6] In India we have observed in a sample population in urban area that 60% of 520 subjects who reported for diabetes prevalence study^[7] were recorded to have BMI of ≥ 25 kg/m². Gupta *et al.*^[8] have reported the prevalence of obesity as 21.8% in males and 44% in females. Metabolic syndrome was found to be present in 31.6%.

In a larger study, Ramchandran *et al.*^[9] reported that 30.8% of 3,453 subjects had a BMI of 25 kg/m² or more. He also observed that the subjects with diabetes were older and had higher BMI and waist-hip ratio as compared to subjects with normal glucose tolerance and impaired glucose tolerance. Also subjects with impaired glucose tolerance (IGT) were older and had a higher BMI compared to normal glucose tolerance (NGT) subjects. The prevalence of metabolic syndrome was reported to be 41%. Chennai urban population study^[10] also revealed that the proportion of obesity was significantly higher in those with impaired glucose tolerance (diabetes + IGT) than with those with NGT, and a similar trend was observed in the proportion of abdominal obesity.^[10]

The prevalence of adult obesity in United States has more than doubled from 15% in the late 1970s to 31% in 2001. The prevalence in adolescents has tripled from 5 to 15% over the same period.^[11] At the same time, the prevalence of chronic sleep deprivation has also increased. Thirty-nine percent of adults reported sleeping less than 7 h per night in 2002.^[12] Chronically reduced sleep times are associated with obesity.^[13] Such prospective data lends further credence to the hypothesis that sleep deprivation may play a causal role in the development of obesity. Sleep deprivation induces or aggravates snoring by increasing muscular hypotonia and delaying contractions of the dilator muscles of the pharynx.^[14] Snoring and excessive daytime sleepiness (EDS) are prominent symptoms of obstructive sleep apnea (OSA).

The association of obesity and sleep apnea is well known. The prevalence of sleep apnea in obese clinical population appears to be as high as 40% for morbidly obese men (BMI ≥ 39) and 3% for premenopausal morbidly obese women. A strong association between obesity and sleep apnea has been observed.^[15,16] However, in India Udawadia *et al.*^[17] reported 46% of subjects with sleep disordered breathing (SDB) had a BMI of less than 30, whereas 27% of subjects with SDB had BMI less than 27, suggesting that a significant percentage of the subjects were not obese by western or

Asian standards but still had SDB. Sleep apnea promotes obesity principally due to lack of physical activity. Obesity also aggravates sleep apnea (a vicious cycle). The predominant pattern of body fat distribution in sleep apnea subjects is central. It has also been demonstrated that it is the intra-abdominal fat (visceral fat and not generalized obesity) that predisposes to the development of sleep apnea.^[18,19] There is increase in fat content with loss of lean muscle mass as age advances. This visceral adipose tissue is also metabolically active. Increased visceral adiposity has been associated with several metabolic abnormalities, including insulin resistance, dyslipidemia, type 2 diabetes mellitus, hypertension and cardiovascular problems.^[20] Sleep deprivation induces stress and stress causes obesity. The connection between stress, cortisol production and obesity is an important feature of syndrome X. The addition of OSA to syndrome X is now labeled as syndrome Z.^[21]

Increased waist-hip ratio is a symptom of chronic hypothalamic arousal. HPA may be aroused even in utero. It is interesting to note that sleep disordered breathing in pregnant women may have adverse effects on both mother and fetus (pregnancy-induced hypertension and small gestational age birth).^[22] Approximately 28% of children born in India are of low birth weight, and low birth weight is associated with elevated glucocorticoid levels in later life.^[23] A story from the womb to the tomb!

The prevalence of SDB increases with age, ranging from 5-15% in middle-aged adults to approximately 24% in community-dwelling older adults.^[24,25] OSA tends to be more common in older individuals. Recently it has been reported that age distribution of metabolic syndrome is similar to the age distribution of symptomatic sleep apnea.^[26]

Sleep Apnea and Diabetes

Sleep disorders are common in diabetic subjects. In one large study, diabetes was associated with more frequent complaints of difficulty in initiating sleep (21.1%), difficulty in maintaining sleep (21.9%) and excessive daytime sleepiness (12.2%).^[27] Sridhar *et al.*^[28] reported increased prevalence of sleep disturbances – primarily, difficulty in initiating sleep – in a clinical group of 184 diabetic subjects compared to controls. Sleep disruption is common in diabetic subjects and is often due to nocturia and/or physical complications of the disease. Nocturia is also a symptom of OSA due to secretion of

atrial natriuretic peptide from the right atrium.^[29] Several studies have shown an increased prevalence of sleep apnea and sleep disordered breathing in patients with type 2 diabetes. Diabetes may be a cause or consequence of SDB or possibly both. Snoring, which is a prominent symptom of SDB, has also been shown to predict the onset of diabetes in both men and women.^[30,31] Mondini and Guilleminault^[32] reported an increased frequency of abnormal breathing during sleep in lean and obese diabetic subjects. Brooks *et al.*^[33] reported that 70% of obese diabetic subjects had moderate to severe OSA.

OSA and development of DM

The development of diabetes in a subject with OSA is largely due to the cyclical hypoxemia and associated sympathetic stimulation resulting in catecholamine secretion and metabolic errors. OSA often causes fasting

hyperglycemia with normal or near normal postprandial blood sugar levels. Such subjects can have impaired glucose tolerance. This is important to recognize since treatment of OSA by continuous positive airway pressure increases insulin sensitivity, thereby preventing development of DM. Also OSA should be strongly suspected in subjects having fasting hyperglycemia. OSA can be observed in lean subjects, and therefore it is possible that OSA may be an etiological factor for type 2 diabetes in lean and in normal body weight individuals.^[1] Figure 1 highlights the path taken by nocturnal events to culminate in the development of diabetes in a subject with OSA.

Sleep and metabolic syndrome

Several studies have reported an association between OSA and insulin resistance. It is interesting to note that Ip and associates^[34] observed an association between

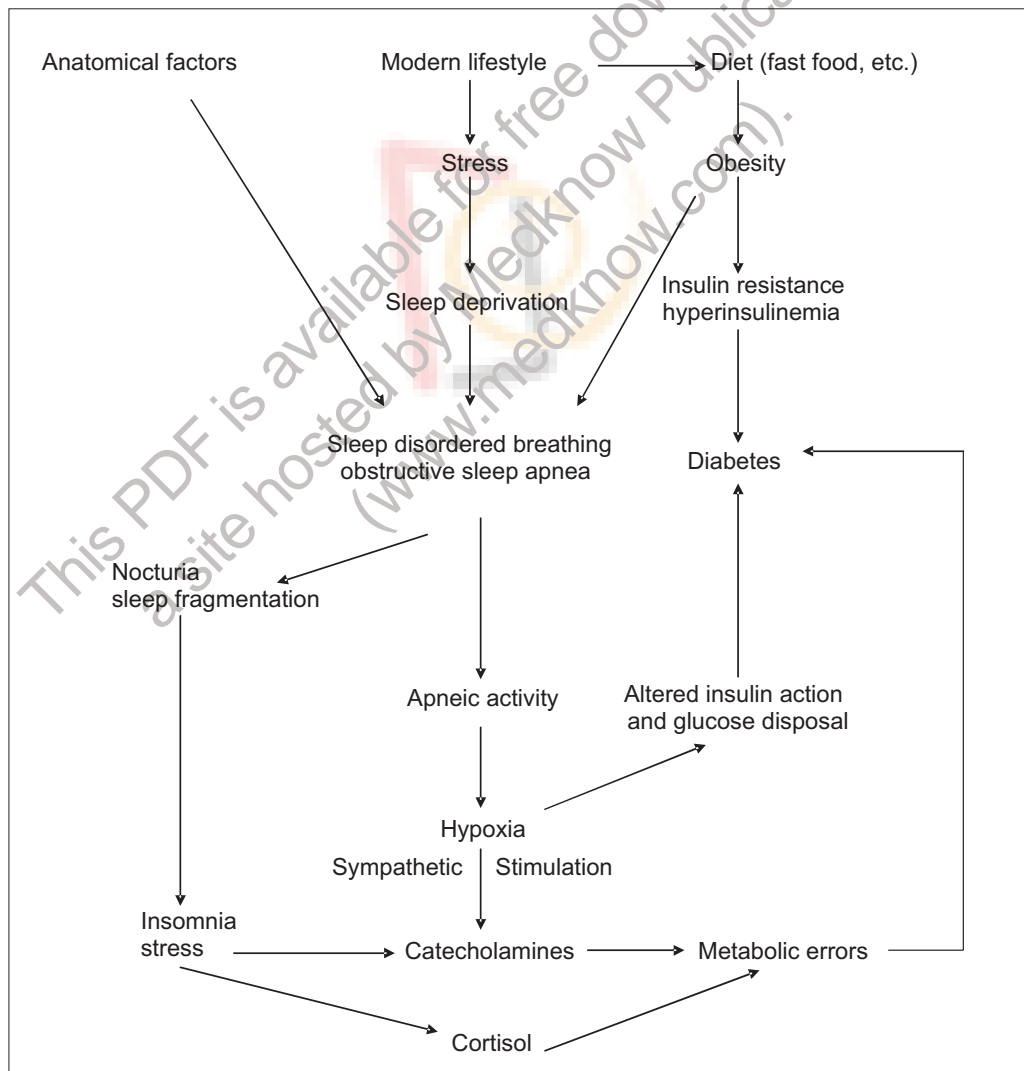


Figure 1: Flow Chart highlighting the path taken by nocturnal events to culminate in the development of diabetes in a subject with OSA

OSA and insulin resistance, even in non-obese subjects. This statement indicates that OSA may have a bearing in development of diabetes in lean and normal body weight subjects, which is commonly observed in India.^[1] Visceral fat accumulation is an important risk factor for OSA in obese subjects,^[35] and AHI is significantly correlated to intra abdominal fat but not with subcutaneous fat in the neck or parapharyngeal regions.^[36] Punjabi *et al.*^[16] reported insulin resistance even in mild forms of sleep apnea. Evidence is accumulating that sleep apnea is closely linked to metabolic syndrome. OSA is independently associated with an increased prevalence of metabolic syndrome.^[37] Strohl *et al.*^[38] demonstrated a modest correlation between severity of sleep apnea and indices of insulin resistance. Subsequently Vgontzas *et al.*^[19] in a well-controlled study concluded that visceral obesity/insulin resistance determined by both genetic and constitutional or environmental factors may be the principal culprits of obstructive sleep apnea. This study comprised of three groups of patients:

- a. Obese patients with sleep apnea
- b. Obese patients without sleep apnea
- c. Normal weight controls

None of the patients with sleep apnea or obesity had developed overt diabetes. It was observed that sleep apnea patients had significantly higher levels of fasting plasma insulin and glucose than obese controls. Sleep apnea subjects had a higher degree of visceral but not subcutaneous fat.

Prevalence of metabolic syndrome is high in Asian Indians. It has been hypothesized that excess body fat and low muscle mass may explain the hyperinsulinemia and high risk of type 2 diabetes in Asian Indians. This may also explain the high prevalence of metabolic syndrome among this population.^[10,39,40]

Sleep apnea is not totally an anatomic abnormality, since a large majority of adult sleep apneics do not demonstrate structural abnormalities in their upper airways.^[41] The converse is also true. There are various risk factors for sleep apnea, like thick neck, large neck, increased BMI and gain in waist circumference during adult life. Of these, the last has a stronger association than neck size with sleep disordered breathing.^[42]

The Sleep Heart Health Study^[43] concluded that diabetes is associated with periodic breathing, a respiratory abnormality associated with abnormalities in the central

control of ventilation. Some sleep disturbances may result from diabetes through the deleterious effects of diabetes on central control of respiration. The high prevalence of SDB in diabetes, although largely explained by obesity and other confounders, suggests the presence of a potentially treatable risk factor for CVD in the diabetic population. It is to be appreciated that diabetes is a cardiovascular disease.

The following features suggest that OSA is closely linked to metabolic syndrome:

1. Strong association with obesity
2. Male gender prevalence
3. Postmenopausal increase of its prevalence in women
4. Systemic effects like hypertension and diabetes
5. Increase of prevalence of sleep apnea with advancing age, the peak being 55 years for male and 65 years for female (postmenopausal)

Recently Vgontzas,^[44] in a theoretical review, has suggested that sleep apnea is a manifestation of the metabolic syndrome.

Clinical implications

Daytime sleepiness is a marked characteristic of obese patients, and EDS has a strong association with BMI. Diabetes and insulin resistance themselves contribute to EDS, and therefore diabetes should be considered in any subject experiencing EDS. Postprandial drowsiness is often complained by diabetic subjects. This is also observed in sleep apnea. EDS must be differentiated from physical tiredness, mental tiredness and sleepiness. All of them might coexist in the diabetic subject. Hypersomnia is a reflection of disturbed nocturnal sleep (quality and/or quantity), physical tiredness (a consequence of the disease process) and mental tiredness (due to underlying stress and depression). Patients with OSA are often compelled to sleep on one side to reduce the burden of snoring and apneic episodes. This may result in compressive neuropathies, particularly radial nerve palsy (personal observation). Also periarthrititis of the shoulder can get aggravated due to an abnormal posture while sleeping. It is to be appreciated that supine posture is ideal for sleep. Drawing an analogy between ancient healing practices and modern medicine, it would be appropriate to mention that sleeping in supine position maintains the body *chakras* (energy receiving centers) in alignment. This facilitates the smooth flow of energy of the body systems and thereby promotes good health at all levels of existence.

Table 1: Comparison of type 2 diabetes and obstructive sleep apnea

| Particulars | Type 2 Diabetes | Obstructive sleep apnea |
|--|--|--|
| Increasing prevalence with advancing age | Yes | Yes |
| Obesity | Often | Often |
| Lean subjects | Affected | Affected |
| Sleep disturbances | Often insomnia, EDS, early awakenings, may have associated OSA | Snoring + EDS. Sleep architecture disrupted. May have associated DM (OSA risk factor for DM) |
| Nocturia | Yes. (Glycosuria) | Yes (ANP) release |
| Metabolic syndrome | Part of metabolic syndrome | ? A manifestation of metabolic syndrome. If associated with Syndrome X = Syndrome Z. |
| Sleep study | Essential | Essential |
| Management of OSA | Rewarding for metabolic control | Rewarding and may prevent development of DM in IGT subjects |

OSA - Obstructive sleep apnea

Management of OSA by continuous positive airway pressure (CPAP) is rewarding and beneficial. CPAP rapidly improves insulin sensitivity.^[45] It also enables the patient to sleep in supine position. Table 1 compares features of type 2 diabetes with OSA.

EDS, cytokines and insulin resistance

EDS is a prominent symptom of OSA. It is also observed in type 2 diabetes and polycystic ovarian syndrome. Tumor necrosis factor TNF- α , interleukin-1 β and interleukin-6 (IL-6) are involved in physiological sleep regulation. Their increased secretion or exogenous administration to humans is associated with sleepiness and fatigue.^[46] Vgontzas *et al.*^[47] reported that TNF- α was significantly elevated in sleep apneics and narcoleptics, while IL-6 concentration was markedly and significantly elevated in sleep apneics as compared to normals. Both these cytokines were positively correlated with the presence of EDS. Also plasma levels of IL-6 were positively correlated with BMI. In a study controlled for obesity,^[19] it was demonstrated that sleep apneic men had higher plasma concentrations of TNF- α , IL-6 and leptin, than non-apneic, obese men, who had intermediate values; or lean men, who had lowest values. Sleep apnea is associated with insulin resistance independently of obesity. Sleep disordered breathing is very frequent in disorders in which insulin resistance is a primary pathophysiologic abnormality (e.g., polycystic ovarian syndrome).^[48]

It is reported that Indians have a higher C-reactive protein (CRP) than do European whites.^[49,50] It is also likely that Indians have higher levels of TNF- α and IL-6.^[51,52] Elevated plasma TNF- α levels have been associated not only with obesity and insulin resistance but also with hypertriglyceridemia and glucose intolerance, and

negatively correlated with HDL cholesterol.^[53,54] Therefore a close relation exists between TNF- α , CRP, IL-6 and metabolic syndrome.

Conclusions

It would be interesting to study the association of SDB in normal body weight/underweight diabetic subjects in India. The association of sleep disorders with obesity and metabolic syndrome demands sleep history to be recorded and polysomnography performed on these subjects. Diagnosis of SDB in a diabetic subjects will pave the way for better management and possibly reversal of metabolic errors.

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