REVIEW ARTICLE

Sleep Apnea is an Independent Risk Factor for Metabolic Syndrome

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Introduction

Sleep is essential for life. Sleep is a metabolic regulator and sleep disorders affect metabolism. Obstructive sleep apnea (OSA) is a common disorder but seldom recognized in clinical practice. This disorder has wide ranging ill effects on body systems. There are many features common to OSA and metabolic syndrome. OSA has been closely linked to type 2 diabetes mellitus. Several studies have demonstrated that sleep apnea is an independent risk factor for metabolic syndrome. Management of OSA by CPAP reduces insulin resistance which occupies the center stage in metabolic syndrome.

OSA and Insulin Resistance

Approximately 4% of men and 2% of women from the middle aged work force have OSA, as defined by apnea hypopnea index of $\geq$5 and daytime hypersomnolence.[1] In India Udwadia etal[2] reported that the estimated prevalence of of sleep disordered breathing was 19.5 % and that of obstructive sleep apnea hypopnea syndrome (SDB with daytime hypersomnolence) was 7.5%. The prevalence of SDB increases with age, ranging from 5-15% in the middle aged adults to approximately 24% in community dwelling older adults. [3] In India the prevalence of metabolic syndrome has been reported to be 24.9% (18.4% in men ,30.9% in women – age adjusted).[4]

India is a major contributor to the global cardiovascular mortality. While several risk factors for metabolic syndrome viz heredity, age, sex, sedentary life style, obesity, diet insulin resistance and others have been given attention but sleep apnea as risk factor has been in focus recently.

Obstructive Sleep Apnea

Repetitive pharyngeal collapse in sleep, which is the hallmark of OSA, results in cyclical hypoxemia, sympathetic stimulation and consequent release of stress hormones.

These changes promote development of insulin resistance. Also sleep disruption results in metabolic dysfunction.

Sleep Deprivation and Cardiovascular Events

Chronic sleep deprivation in young healthy volunteers has been reported to increase levels of proinflammatory cytokines decrease parasympathetic and increase sympathetic tone, increase blood pressure, increases cortisol levels as well as elevate insulin and blood glucose levels.[6] Patients of OSA of often REM sleep deprived. REM sleep deprivation may cause anxiety, overeating, loss of memory and hypersexuality.[7] Excessive eating promotes obesity and thereby insulin resistance.

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

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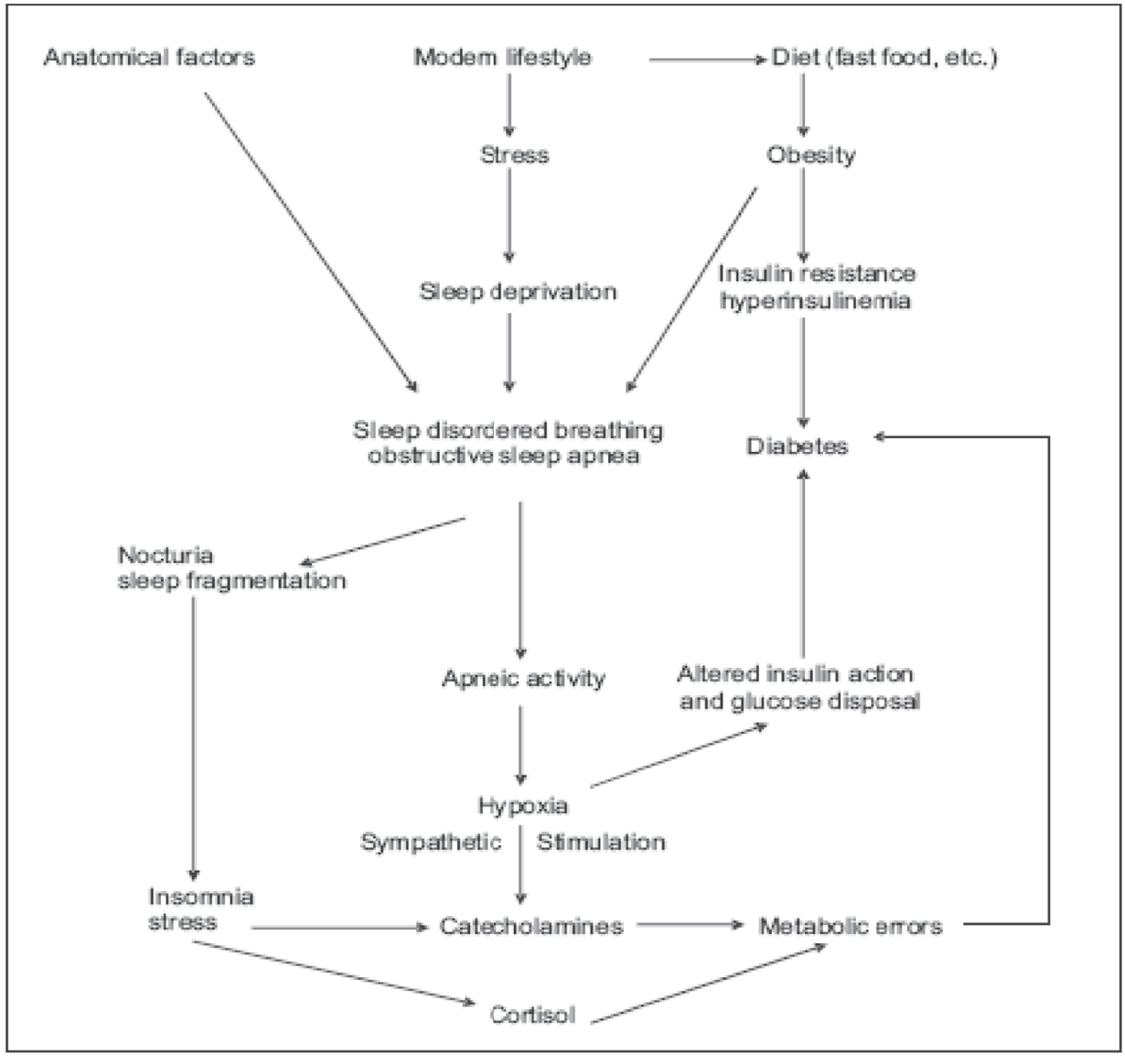

Figure 1: Flow Chart highlighting the path taken by nocturnal events to culminate in the development of diabetes in a subject with OSA

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 it has been reported that the age distribution of metabolic syndrome is similar to the age distribution of symptomatic sleep apnea.[8]

Vgontzas et al[9] 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 OSA. The study comprised of 3 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.

Patients of OSA have a higher incidence of cardiovascular morbidity and mortality.[10] However recent data suggest that OSA may also be associated with a number of cardiovascular risk factors independently of obesity such as hypertension,[11] insulin resistance, impaired glucose tolerance [9] and dyslipidemia.[12] To know whether sleep apnea is independent risk factor for metabolic syndrome, several studies were conducted.

Coughlin et al[13] recruited 61 male subjects with OSA and 43 controls..Glucose, insulin, lipids and blood pressure were measured following an overnight fast.Insulin resistance was estimated using homeostasis model assessment (HOMA). Metabolic syndrome was diagnosed according to National Cholesterol Education Programme(NCEP) criteria. Subjects with OSA were more obese,had higher BP and fasting insulin, were more insulin resistant ,had lower HDL cholesterol and an increased incidence of metabolic syndrome.(87% verusus35%,p<0.0001) . In order to determine whether these associations were independent of obesity and other known covariates, a regression analysis adjusted for age ,BMI, smoking and alcohol consumption was performed. This demonstrated that OSA was independently associated with increased systolic and diastolic blood pressure ,higher fasting insulin and triglyceride concentrations, decreased HDL cholesterol, increased cholesterol:HDL ratio, and a trend towards higher HOMA values. Metabolic syndrome was 9.1(95% confidence interval 2.6, 31.2:p<0.0001) times more likely to be present in subjects with OSA. Based on these observations the workers concluded that OSA is independently associated with an increase in the cardiovascular risk factors that comprise the metabolic syndrome and its overall prevalence.

Earlier Mary et al [14] investigated the relationship between sleep disordered breathing and insulin resistance. The study included 270 consecutive subjects (197 males) who were referred for polysomnography and who did not have known diabetes mellitus were included . 185 subjects were documented to have OSA. These subjects were more insulin resistant as indicated by higher levels of fasting serum insulin.Also they were older and more obese.

Stepwise multiple linear regression analysis showed that obesity was the major determinant of insulin resistance but sleep disordered breathing parameters (AHI and minimum oxygen saturation) were also independent determinants of insulin resisitance(fasting insulin :AHI,p=0.02,minimum oxygen,p=0.041; HOMA IR:AHI,p=0.044,minimum oxygen,p=0.022); this association between OSA and insulin resistance was seen in both obese and non obese subjects. Each additional apnea or hypopnea per sleep hour increased the fasting insulin and HOMA-IR by about 0.5%.

Further analysis of the relationship of insulin resistance and hypertension confirmed that insulin resistance was a significant factor for hypertension in this cohort.The authors concluded that OSA is independently associated with insulin resistance. Also this association between OSA and insulin resistance was seen in both obese and non-obese subjects . In India type 2 diabetes is frequently observed in low body weight or normal body weight subjects making room for the suggestion that possibly SDB can be present in these subjects which can act as a risk factor for the development of type 2 diabetes.[15] Punjabi et al [16] reported insulin resistance even in mild forms of sleep apnea. Strohl et al[17] demonstrated a modest correlation between severity of sleep apnea and indices of insulin resistance. It is also interesting to observe that Asian Indians are more insulin resistant than their European counterparts. [18] Snoring predicts the onset of diabetes.[19] Reichmuth etal [20] study had 2 objectives (a)to investigate the prevalence of and incidence of type II diabetes in subjects with sleep disordered breathing and (b)whether an independent relation exists between them. The study comprised of 1,387 participants who underwent full PSG to characterize SDB. Diabetes was defined in 2 ways (physician diagnosis alone or (b)for those with glucose measurements, either fasting glucose $\geq$ 126mg/dl or physician diagnosis. The authors concluded that diabetes is more prevalent in SDB and this relationship is independent of other risk factors. However, it was not clear whether SDB is causal in the development of diabetes.

Harsch et al[21] investigated whether OSA itself is an independent risk factor for increased insulin resistance and whether continuous positive pressure (CPAP) treatment improves insulin sensitivity.Forty patients (AHI

index of>20) were treated with CPAP. Before,2days after, and after 3 months of effective CPAP treatment hyperinsulinemic euglycemic clamp studies were performed.Insulin sensitivity significantly increased after 2 days(5.75± 4.20 baseline versus 6.79 ± 4.91 umol/kg min;p=0.003) and remained stable after 3 months of treatment.The improvement in insulin sensitivity after 2 days was much greater in patients with body mass index less than 30 kg/m^2 than in more obese patients. The improved insulin sensitivity after 2 nights of treatment may reflect a decreasing sympathetic activity, indicating that sleep apnea is an independent risk factor for increased insulin resistance. The effect of CPAP on insulin sensitivity is smaller in obese patients than in nonobese patients, suggesting that in obese individuals insulin sensitivity is mainly determined by obesity and to a smaller extent by sleep apnea.

However I would propose that sleep apnea patients who are treated become active during daytime helping them to lose weight.Therefore continued use of CPAP would make them more insulin sensitive.

Brooks et al [22]demonstrated a tendency to improved insulin sensitivity after 4 months of CPAP treatment measured by hyperinsulinemic euglycemic clamp. However such results were not confirmed by Saarelainen et al[23] and Smurra etal.[24] One reason for these conflicting findings could be the lack of statistical power due to low patient numbers. The large sample size in the study by Harsch and his coworkers concluded that sleep apnea is an independent and causal risk factor for metabolic dysfunction /syndrome is convincing. We have reported the beneficial effects of CPAP in subjects of type 2 diabetes.[25]

Offshoots

Sleep Apnea and Diabetes

SDB is common in subjects of type 2 diabetes and sleep apnea is a risk factor for type 2 diabetes. Insulin resistance is the key for progression of metabolic errors in metabolic syndrome.It is interesting to note that there are several features which are common to both type 2 diabetes and OSA.[5] A comparison is as follows:

Chronic Inflammation and Insulin Resistance

There appears to be close link between chronic inflammation and insulin sensitivity.Chronic inflammation is known to act as a trigger for chronic insulin insensitivity.[26] Disorders of insulin insensitivity eg. obesity, type 2 diabetes, atherosclerosis also show increased cytokine production and markers of inflammation.. Habitual snorers have inflamed palate and are also prone to repeated respiratory infections. We have proposed that chronic inflammation in these subjects possibly triggers insulin insensitivity. [27]

Sleep, Ageing and Metabolic Syndrome

Sleep and ageing have close interactions. Sleep apnea is common in the elderly population. Cardiovascular disorders like hypertension, coronary heart disease , type 2 diabetes are also common in the elderly.We have reported that blood glucose levels increase with advancing age.[28] Since sleep apnea itself is an independent risk factor for insulin resistance it is important that sleep apnea is

Table 1

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

closely looked for in elderly population so that treatment of this disorder can provide better quality of life. Also insomnia is often complained by elderly subjects making recognition of sleep apnea difficult.

SDB and Pregnancy

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)[29]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.[30] A story from the womb to the tomb!

Sleep Apnea and Diabetic Retinopathy

Retina is the highest consuming part of the body and cyclical hypoxemia can have deleterious effects on the retina. This hypothesis was proposed by us in 2004.[15] Recenlty Merritt et al [31] have reported that sleep disordered breathing in type 2 diabetic subjects may play an aetiological role in the development and /or progression of diabetic retinopathy.

Conclusions

OSA induces insulin resistance by more that one mechanism. Studies done point to the understanding that OSA is an independent risk factor for metabolic syndrome. It has been said that India has several modern epidemics like hypertension, coronary heart disease, diabetes. To this list we must add snoring and OSA-mother of these epidemics? Opening the pharynx in sleep, correcting cyclical hypoxia will probably close the gateway to these modern epidemics.

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