Introduction

Sleep is a basic biologic function and is essential for life. It is an active state that is critical for our physical, mental and emotional well being. Defects in sleep quality and quantity can result in metabolic errors and cardiovascular dysfunction. Sleep is an emotional issue and all diseases particularly chronic diseases like diabetes invites emotional reactions which can also affect sleep adversely.

In ancient times sleep was respected and honoured. Modern life style has generated several diseases of which type 2 diabetes mellitus, cardiovascular disorders and sleep disorders occupy prime positions. All 3 disorders are closely related. The mushrooming of call centres cannot be ignored. Parallel to this is the rising prevalence of type 2 diabetes in our country. United Nations General Assembly in 2006 declared type 2 diabetes to be the first non-communicable disease that threatens world health. The mushrooming of call centres cannot be ignored. Parallel to this is the rising prevalence of type 2 diabetes in our country. United Nations General Assembly in 2006 declared type 2 diabetes to be the first non-communicable disease that threatens world health to the same magnitude as communicable diseases such as HIV and tuberculosis.1 South East Asian countries have the highest burden of diabetes.2 Several workers3 have documented this rise which raises the alarm – India is the diabetic capital of the world.

Among the sleep disorders obstructive sleep apnea (OSA), insomnia, sleep deprivation, excessive sleepiness and restless legs syndrome have an impact on the glucose metabolism. OSA appears to have the strongest association with these metabolic disorders.1 In clinical practice detailed sleep history is often not recorded. Detection and treatment of sleep disorders in diabetes is essential since their treatment is highly rewarding.

Sleep and glucose metabolism

Sleep is a metabolic regulator and sleep debt has harmful effects on carbohydrate metabolism. Van Helder4 and colleagues showed that the insulin response to an oral glucose challenge was higher when comparing the total sleep deprivation condition (i.e. 60 hours of continuous waking) to the normal sleep condition, suggesting an insulin resistant state that is induced by acute sleep deprivation.

Subjects deprived of sleep for several days or more become irritable, fatigued, unable to concentrate and usually disoriented. Considerable stress is generated. The secretory rate of ACTH and cortisol are all high in early morning and low in the late evening. These effects result from a 24 hour cyclic alteration in the signals from the hypothalamus that cause cortisol secretion. It has been demonstrated that glucose tolerance is markedly better in the morning than in the evening.5 Spigel et al6 have shown that sleep debt results in impaired glucose tolerance. Acute sleep deprivation whether total or partial is associated with an alteration in hypothalamo-pituitary-renal (HPA) function on the following day consisting of an elevation of evening cortisol concentration.7

Sleep Deprivation (SD)

Chronically reduced sleep times are associated with obesity.8 SD induced stress has a role to play in the development of obesity. Sleep deprived subjects have daytime sleepiness and have a tendency to overeat and eat fast. Intake of food in various forms help the sleep deprived subject to overcome daytime sleepiness. Chewing tobacco, smoking also drive away sleep but are risk factors for type 2 diabetes.3 Chronic sleep restriction coupled with eating contributes separately to the development of obesity. It is not uncommon to find nap pod in commercial organizations where employees can take a power nap to boost their performances.

Sleep deprivation induces or aggravates snoring by increasing muscular hypotonia and delaying contractions of the dilator muscles of the pharynx.9 Chronic partial sleep deprivation is seen in many important groups including doctors, soldiers, shift workers, mothers particularly nursing mothers, cross country

Abstract

Sleep is essential for life. Body systems require sleep of good quantity and quality for their proper functioning. Glucose metabolism can be affected adversely by several sleep disorders. Obstructive sleep apnea (OSA) is one of the most important disorder identified in the last 50 years which has systemic effects including glucose metabolism. Aging process also has its effects on glucose metabolism. There is a close relation between sleep, aging and metabolic syndrome. OSA and Type 2 Diabetes Mellitus (Type 2 DM) share several features in common. There is mounting evidence to show a close association between sleep deprivation, sleep disordered breathing-OSA, excessive sleepiness, insomnia, restless legs syndrome and Type 2 DM. The role of sleep deprivation, particularly REM sleep deprivation, in the genesis of obesity needs to be recognized. The close association of OSA with insulin resistance demands the recognition of OSA in fatty liver and polycystic ovary syndrome. Treatment of OSA by continuous positive airway pressure has been shown to increase insulin sensitivity. It is important for primary care physicians to have a high degree of suspicion of an underlying sleep disorder in patients with diabetes. Management of sleep disorder is highly rewarding.

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The usual cause of sleep deprivation is lack of time to sleep. Subjects travelling long distances for work are plagued with late night sleeps and early awakenings. Also late night television viewing exposes the retina to bright light which can inhibit the release of melatonin and delay the sleep onset further.

I have observed rebound sleep deprivation in elderly subjects who wait for their children and loved ones to return from place of work. The glycemic status of the elderly subject is thus affected adversely.

Shift work and diabetes

Shift work concept is good for the industry but it comes with a human cost. Shift workers are at heightened risk to a spectrum of illnesses. Shift work results in circadian rhythm disruption. Shift work can have deleterious effects on metabolic equilibrium and can precipitate diabetes particularly in genetically prone subjects due to chronic SD. 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.

Data from Sleep Heart Health Study indicate that people sleeping <6 hours or less and those sleeping >9 hours or more per night have a higher prevalence of type 2 diabetes and impaired glucose tolerance than people sleeping 7-8 hours per night even after those with insomnia symptoms are excluded, suggesting that voluntary sleep restriction may account for some of the public health burden associated with type 2 diabetes.

Sleep disordered breathing

Sleep disordered breathing (SDB) is a spectrum of disorders consisting of snoring, upper airway resistance syndrome and sleep apnea. Sleep apnea can be obstructive, central or mixed. Snoring is a common symptom and is evident when a group of subjects sleep together for eg in sleeper coaches of railway trains. In India Udwadia et al reported habitual snoring in 26% of the study population (middle aged urban Indian men) and the estimated prevalence of SDB was 19.5% and that of obstructive sleep apnea hypopnea syndrome (SDB with daytime hypersomnolence) was 7.5%.

It must be appreciated that obstructive sleep apnea (OSA) is a risk factor for the development of hypertension, ischemic heart disease, stroke. Habitual snoring predicts the onset of diabetes. Joq et al have reported that frequent snoring is associated with reduced glucose tolerance, as assessed by abnormal oral glucose tolerance tests (OGTT) results and higher levels of HbA1c.

Habitual snorers have inflamed palates. Grimble has reported that chronic inflammation is known to act as a trigger for chronic insulin insensitivity.

Sleep Complaints in Diabetic Patients

Gislason et al reported that diabetes was associated with near frequent complaints of difficulty in initiating sleep (21.1%), difficulty in maintaining sleep (21.9%) and excessive daytime sleepiness (12.2%). The sleep complaints are often related to the presence of underlying SDB, nocturia, physical complications of disease and underlying depression. Polysomnography done in diabetic subjects revealed more wakefulness, a high number of awakenings and fragmented sleep.

In 1985 Mondini and Guillemena24 reported an increased frequency of abnormal breathing in lean and obese individuals. Ip and associates observed an association between OSA and insulin resistance, even in non obese subjects. It has been observed that majority of diabetic subjects in India are low body weight or normal body weight. Anatomical factors in the face and neck is conducive for the development of sleep disordered breathing. However sleep disordered breathing can be observed in both lean and obese individuals. In lean subjects anatomical features which promote SDB include macroglossia, short neck, retruded chin, retruded maxilla and neck circumference of more than (17 inches) 43 cms. This raises an important issue whether sleep disordered breathing which occurs in normal weight or low body weight subjects poses a risk for the development of type 2 diabetes mellitus?

Sleep and insulin resistance

Insulin resistance denotes the inability of insulin to produce usual biological effects at circulating concentrations that are effective in normal subjects. The consequences of insulin resistance are well known.

Visceral adiposity is associated with several metabolic abnormalities including insulin resistance, dyslipidemia, type 2 diabetes mellitus, hypertension and cardiovascular problems.

It has been suggested that visceral adiposity appears to play a strong role in the pathogenesis of sleep apnea and manifestations that frequently accompany the disorder namely hypertension and its sequela.

Recent studies indicate that visceral fat is more important than generalised obesity that predisposes obese subjects to sleep apnea. Vgontzas et al in a well controlled study included 3 groups of subjects (i) obese patients with sleep apnea (ii) obese patients without sleep apnea (iii) normal weight controls. The first 2 groups were matched for weight whereas all 3 groups were matched for age and sex. None of the patients with sleep apnea or the obese controls had developed overt diabetes. Those with sleep apnea had significantly higher levels of fasting plasma insulin and glucose levels than their obese controls. Also the group with sleep apnea demonstrated a higher degree of visceral but not subcutaneous fat compared to their obese controls. Based on these observations Vgontzas et al in an extensive review commented that there is perrnious association between sleep apnea and insulin resistance primarily in obese patients.

OSA and type 2 diabetes mellitus

Obstructive sleep apnea (OSA) is a common disorder which is usually not suspected in clinical practice. There is repetitive pharyngeal collapse in sleep resulting in cyclical hypoxemia, cyclical hypertension and release of stress hormones and catecholamines. Habitual snoring and excessive daytime sleepiness are two prominent symptoms of obstructive sleep apnea. Daytime sleepiness is usually overcome by consuming tea, coffee and tobacco singly or in combination. The other nocturnal symptoms include witnessed apneas, choking, dyspnea, restlessness, diaphoresis, acid reflux, drooling, somniloquy, frequent change of posture in sleep, unable to sleep supine and bruxism. The daytime symptoms apart from sleepiness include fatigue, morning headache, poor concentration, decreased libido or impotence, decreased attention, depression, decreased dexterity and personality changes. Mood swings and angry behavior is often present which may force the subject to seek psychiatric advice. In diabetic subjects there is often postprandial drowsiness, poor concentration, fatigue and depression. Therefore symptoms can be confusing and misleading. In OSA there is intermittent hypoxia, recurrent arousals from sleep.
and sleep fragmentation causing sympathetic stimulation. Sympathetic stimulation results in the release of stress hormones and catecholamines. Both these effects are known to decrease insulin sensitivity and worsen glucose tolerance. Also altered corticotropic and somatotropic function increase circulating adipocytokines which alter glucose metabolism. There is strong possibility that changes in sympathetic nervous system activity, corticotropic function and systemic inflammation are associated with subjects with short sleep duration and insomnia, thereby causing metabolic dysfunctions.

Nocturia results in arousals. Nocturia is often due to (a) secretion of atrial natriuretic peptide from right atrium in patients with OSA and (b) hyperglycemia (c) Urinary tract infection.

Polysomnographically there is destruction of sleep architecture with cyclical hypoxia. REM sleep may be deficient. REM sleep deprivation may cause anxiety, increased appetite and hypersexuality. Patients who are sleep deprived often exhibit fast eating and binge eating which adversely affects glycemic status and digestion. Figure 1 flow chart shows the close association of sleep deprivation, obstructive sleep apnea and type 2 diabetes mellitus and also the path taken by nocturnal events in a patient of obstructive sleep apnea leading to the development of type 2 diabetes mellitus.

The prevalence of SDB increases with age. In elderly subjects polysomnography shows predominance of obstructive events over central or mixed events. Therefore several elderly subjects suffer from obstructive sleep apnea.

Also with advancing age there is reduction of lean tissue and increase in fat content. Central obesity is a common feature of ageing process. The fat of this central obesity is also metabolically active. It is also observed that blood glucose increases as age advances. People over the age of 65 years constitute more than 40% of cases of diagnosed diabetes. The potential age dependent risk factors for development of sleep apnea in the elderly are increase in body weight, decreased lung capacity, increased upper airway collapsibility, increased sleep fragmentation, decreased slow wave sleep, decreased muscular endurance, decreased ventilatory control and decreased thyroid function.

**Table 1: Comparison of Type 2 Diabetes Mellitus and Obstructive Sleep Apnea**

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Type 2 Diabetes Mellitus</th>
<th>Obstructive Sleep Apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing prevalence with advancing age</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Family History</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Obesity</td>
<td>Often</td>
<td>Often</td>
</tr>
<tr>
<td>Lean subjects</td>
<td>Affected</td>
<td>Affected</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>Often insomnia, Excessive daytime sleepiness, early awakenings,</td>
<td>Snoring + EDS, Sleep architecture disrupted. May have associated DM (OSA risk factor for DM)</td>
</tr>
<tr>
<td>Post Prandial drowsiness</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Yes (Glycosuria)</td>
<td>Yes (Atrial natriuretic peptide release)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Part of metabolic syndrome</td>
<td>?A manifestation of metabolic syndrome. If associated with Syndrome X then it is labelled Syndrome Z.</td>
</tr>
<tr>
<td>Polysomnography</td>
<td>Necessary to rule out OSA</td>
<td>Essential</td>
</tr>
<tr>
<td>Management of OSA</td>
<td>Rewarding for metabolic control</td>
<td>Rewarding and may prevent development of DM in IGT subjects</td>
</tr>
</tbody>
</table>

The potential age dependent outcomes can be cardiovascular, metabolic and neurobehavioural morbidity.

There are several similarities between type 2 diabetes mellitus and OSA (Table 1).

**Sleep and Metabolic Syndrome**

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)

**Metabolic syndrome suggested hypothesis**

Based on observations, two types of metabolic syndrome can thus be recognized. One is the obese type – metabolically obese and the other metabolically non obese. I would like to coin the term Lean metabolic syndrome to these subset of patients who are metabolically non obese.

**OSA and Fatty Liver**

Fatty liver is a seat of insulin resistance. Its role in the pathogenesis of diabetes and metabolic syndrome is well recognized. There are multiple etiologic factors and the exact cause of non alcoholic fatty liver disease still unknown. Insulin resistance and obesity occupy the center stage but the factors responsible for the progress and transformation from one stage to another is matter of research and debate.

Recent reports suggest that hepatic dysfunction has also been associated with irregular breathing during sleep. Non-alcohol drinking subjects with apnea and hypopneas during sleep were
found to raised liver enzymes and more steatosis and fibrosis on liver biopsy, independent of body weight. Cyclic hypoxemia, sympathetic stimulation, cyclical release of stress hormones in patients of OSA can pave the path for liver insults and injury. Patients of OSA who consume alcohol run the double risk of developing fatty liver. It must also be appreciated that alcohol worsens OSA. Experimental evidence suggests OSA impairs lipid homeostasis and could therefore worsen non-alcoholic fatty liver disease. In a recent prospective series of adults presenting to a sleep clinic, a threefold increase in the likelihood of elevated liver enzymes was found in subjects with newly diagnosed severe OSA. Liver biopsy, performed only on subjects with abnormal liver enzymes in this same study identified NASH in the vast majority of subjects with severe OSA whereas a minority of subjects with mild or no OSA had biopsy proven NASH. Patients of fatty liver need to be screened for SDB.

Sex hormones, insulin resistance and SDB

Evidence suggests that testosterone promotes upper airway collapsibility in patients with sleep apnea. However testosterone levels appear to be low in men with sleep apnea, possibly because of hypoxia and sleep fragmentation. Sexual dysfunction is a known consequence of OSA. However OSA patients may exhibit hypersexual behavior due to REM sleep deprivation. REM sleep deprivation is common in OSA. Patients of sleep apnea with sexual dysfunction may be advised to take testosterone injections which can aggravate OSA.

Nocturnal Penile Tumescence and Nocturnal Clitoral Tumescence occurs during REM sleep. There is increased blood flow to erectile tissues which possibly prevents excessive collagen formation in these tissues. Increased fibre formation in the erectile tissues could lead to tissue cell death and eventual loss of erectile function. In situations of chronic sleep deprivation particularly REM sleep deprivation as occurs in OSA these nocturnal mechanisms may be affected causing erectile dysfunction (ED). ED is known complication of diabetes mellitus.

Female sex hormones appear to be protective against OSA. Sleep apnea is rather infrequent in premenopausal women whereas prevalence reaches almost the prevalence in men, matched for age and BMI after menopause.

Polycystic ovary syndrome and SDB

PCOS is the most common endocrine disorder of premenopausal women. Chronic hyperandrogenic oligoovulation and oligomenorrhea are key features of PCOS. Vgontzas et al have demonstrated that premenopausal women with diagnoses of PCOS are at much higher risk for development of sleep apnea and daytime sleepiness. Metformin is used to treat insulin resistance in PCOS. As reported insulin resistance in OSA can be treated with Continuous Positive Airway Pressure (CPAP) (see below.) Therefore it is desirable to screen patients of PCOS for SDB. Usage of CPAP in these patients is expected to give favourable results. Studies are being conducted on this issue.

Continuous positive airway pressure (CPAP) and insulin resistance

CPAP is an established mode of treatment for OSA. In a well designed study improvement in insulin sensitivity by CPAP therapy in patients with OSA has been demonstrated by Harsch et al. Forty patients of OSA were taken up in this study. We have also reported beneficial effects of CPAP in 4 patients with type 2 diabetes. Lindberg et al demonstrated reductions in fasting insulin levels and insulin resistance (estimated by HOMA) after 3 weeks of CPAP treatment in 28 men with OSA compared with matched controls. This has important implications since patients with impaired glucose tolerance and mild diabetes can look forward to reversal of diabetes with treatment of associated OSA.

Sleep, eye and diabetic retinopathy

I had suggested in 2003 (possibly for the first time) that since retina is the highest oxygen consuming part of the body, it is likely that cyclical hypoxemia in sleep in subjects suffering from OSA will have deleterious effects on the retina. This should be considered especially in patients of diabetic retinopathy since type 2 diabetes mellitus and OSA are usually associated. Hypoxemia and angiogenesis need recognition. Merritt et al 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.

Recently McNabb has reported association of OSA with several eye disorders, viz. floppy eyelid syndrome, anterior ischemic optic neuropathy, optic neuropathy, glaucoma, papilloedema, secondary to raised intracranial pressure. Treatment of OSA/SD with CPAP is highly rewarding and correction of hypoxemia should have beneficial effects on retina also.

Restless legs syndrome, narcolepsy and glucose metabolism

There is a high prevalence of RLS in diabetic subjects. Cuellar and Ratcliffe showed that in type 2 diabetes and with and without RLS, poor glycemic control (determined by haemoglobin A1c levels) was directly correlated with sleepiness regardless of underlying RLS. Narcolepsy has also been shown to be associated with type 2 diabetes.

OSA, cortisol, thyroid, REM sleep and diabetes mellitus

It is known that cortisol can cause moderate degree of fatty acid mobilization from adipose tissue. A peculiar moon facies and buffalo like torso occurs in patients who have excessive cortisol secretions. In OSA there is excessive release of stress hormones viz catecholamines, cortisol in sleep causing a Cushing like disease. The nocturnal excessive cortisol and catecholamine secretion can also spill over in the day (spill over effect) resulting in fasting hyperglycemia. In such cases 2 hour OGTT is essential if post prandial blood glucose levels are normal. In fact fasting hyperglycemia must raise the suspicion of SDB-OSA. The daytime sleepiness in OSA is reflected in development of obesity due to lack of exercise and physical activity. Patients are too tired and sleepy to do activities. Exercise against a background of hypoxemia and elevated catecholamines can precipitate cardiovascular events.

Hypothyroidism can be associated with OSA. Daytime tiredness and sleepiness can be confused with hypothyroidism. Administration of thyroxine without treating OSA can precipitate cardiovascular events in sleep due to cyclical hypoxemia particularly in REM sleep.

The unique neuroendocrine aspects of REM sleep coupled with sleep disruption in OSA patients is conducive for the development of insulin resistance and diabetes. REM sleep deprivation is common in OSA subjects, which may cause increased appetite. Increased appetite forces the subject to consume large quantities of food. Binge eating is often observed. However fast eating may not occur in subjects who have dentures or in patients with associated hypothyroidism. It would be wise to record sleep history in subjects who exhibit these eating habits. All these habits only promote obesity, insulin resistance and OSA. It must be appreciated that children with Type I diabetes run the risk of developing OSA with advancing age which can worsen the metabolic status.
Conclusions

Evidence points to a possible role of sleep disorders as risk factors for metabolic abnormalities. There is a close relation between sleep, circadian rhythm, obesity, insulin resistance, hypertension and cardiovascular disorders which needs to be dissected and managed. There is evidence to show sleep disorders such as OSA, insomnia, short or long-term sleep duration and restless legs syndrome are potential risk factors for insulin resistance, glucose intolerance, type 2 diabetes mellitus and metabolic syndrome.

In a given patient of type 2 diabetes though the question remains whether these associations are causal, it would be worthwhile to rule out the presence of sleep disorders viz SDB, clinically and polysomnographically. The treatment of SDB particularly OSA by CPAP will help the patient in varying degrees by reducing insulin resistance and preserving beta cell function. It is well known that beta cell protection is of utmost importance. Also the correction of hypoxemia in sleep will have beneficial effects in various system dysfunctions like cardiovascular, neurological and the eye. It must appreciated that OSA is no longer a respiratory tract disease but a systemic one. It is wise to open the pharynx in sleep and close the gates which lead to systemic diseases.

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References

3. Iyer SR. Type 2 Diabetes Express Highway, where is the ‘U’ turn? J Assoc Physicians India 2003;51:495-500.


