Review Article:

Diabetes mellitus and obstructive sleep apnoea: implications for clinicians

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ABSTRACT

Diabetes mellitus (DM) is a major public health problem globally. Current estimates suggest a significant increase in the global burden of DM in the years to come. Sleep disordered breathing (SDB) is an emerging health concern world over. Evidence is available suggesting that obstructive sleep apnoea (OSA) is considered to be both the cause and consequence of DM. Due to lack of awareness regarding the condition and non-availability of diagnostic facilities, OSA remains an underdiagnosed problem in patients with DM, in developing countries like India. Early detection of OSA in patients with DM and assessment for DM in those with OSA can potentially reduce cardiovascular disease risk and improve the quality of life in these patients.

Key words: *Obstructive sleep apnoea, Diabetes mellitus,Epidemiology, Continous positive airway pressure, India*

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INTRODUCTION

As per the International Diabetes Federation (IDF) Diabetes Atlas 7thedition, Update for 2015,[1] globally, 1 in 11 adults (415 millions) are estimated to be suffering with diabetes mellitus (DM); 46.5% of these remain undiagnosed and every five seconds one person dies with DM. Nearly one-fifth of the world's people with diabetes mellitus live in South-East Asia region. The year 2015 estimates suggest that there are 78.3 million persons with DM in South-East Asia of whom 69.2 million are in India.The number of people with DM in India is expected to increase to 123.5 million by 2040.[1]

The term "sleep disordered breathing (SDB)" includes obstructive sleep apnoea (OSA), central sleep apnoea, and sleep-related hypoventilation/hypoxia syndrome. Published data from the West suggest that the prevalence of obstructive sleep apnoea syndrome (OSAS) has ranged from 0.3% to 5%, affecting 2%-4% of middle-aged men and 1%-2% of middle-aged women; the majority of affected individuals remain undiagnosed.[2-6]Sparse epidemiological data are available from India on the epidemiology of OSA (Table 1).[7-11] If these figures are extrapolated to India's population, SDB seems to be an under-diagnosed health problem in India.

Recognizing the importance of OSA, recently, the consensus and evidence-based Indian Obstructive Sleep Apnoea (INOSA) guidelines have been brought out.[12] Further, recent research has brought out several important clinical, epidemiological and public health implications of the association between OSA, the most common form of SDB and type 2 diabetes mellitus (T2DM) which is the most common type of DM.[13-21] Some of these key issues regarding the complex relationship between OSA and T2DM are described in this review.

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Table 1: Prevalence of adult obstructive sleep apnoea in some studies from India

Study (year) (reference)	Type of study	OSA (%)	OSAS (%)
Udwadia et al (2004) (6)	Hospital based*	19.5	7.5
Sharma et al (2006) (7)	Community based	13.7	3.6
Vijayan et al (2006)(8)	Community based	3.5	1.7
Reddy et al (2009) (9)	Community based	9.3	2.8

* fully supervised PSG in laboratory was not done

OSA = obstructive sleep apnea; OSAS = obstructive sleep apnea syndrome; PSG = polysomnography

OBSTRUCTIVE SLEEP APNOEA

The clinical syndrome of OSA is characterized by the presence of abnormal breathing in sleep along with excessive daytime sleepiness. OSA is characterized by repeated episodes of upper airway collapse resulting in apnoeas or hypopnoeas. Of the several demographic variables and risk factors associated with OSA, DM is considered to be a high risk factor for OSA.[22,23] Presently, in-hospital, in-laboratory, technician-attended, overnight polysomnography (PSG) is considered to be the "gold standard" for evaluation of SDB.[24-26]Apnoea is defined as *cessation* of airflow for 10 seconds or more. Hypopnoea is defined as a decrease in the amplitude of airflow (quantitative or semi-quantitative) of >30% from baseline during sleep; or a clear amplitude reduction of a valid measure of breathing during sleep that does not reach the above criterion, but is associated with either an oxygen desaturation of greater than 3% or an arousal and the event lasts 10 seconds or longer. OSA is the occurrence of an average five or more episodes of obstructive respiratory events per hour of sleep with either sleep related symptoms or co-morbidities or ≥ 15 such episodes without any sleep related symptoms or co-morbidities. OSAS is defined as OSA associated with daytime symptoms, most often excessive sleepiness.[24-26]The classical clinical manifestations of OSA are listed in Table 2.[14-18,22,23]

SLEEP DISORDERED BREATHING AND DISORDERS OF GLUCOSE METABOLISM

Pathophysiological basis

The interaction between sleep and endocrine system is postulated to be *bi-directional*. It is well known that several hormones can affect sleep. More recent work has shown sleep to be a key factor in physiological restitution and consequent systemic implications. Sleep debt affects peripheral function and if this persists chronically, it may adversely impact carbohydrate metabolism and endocrine function resulting in decreased glucose

Table 2: Obstructive sleep apnoea: common clinical manifestations

Cardinal manifestations	Salient associated features
A history of habitual snoring	Fatigue, loss of energy
A record of witnessed apnoeas	Irritability
Excessive daytime sleepiness	Poor memory
	Depression,
	Mood changes
	Morning headaches
	Sexual dysfunction
	Nocturia

Source: references 22,23

tolerance and insulin sensitivity.[27-29] Some workers have postulated that sleep debt increases the severity of age-related chronic disorders such as T2DM.[30] Published data also suggest that long-term sleep loss may represent an important risk factor for weight gain, insulin resistance, and T2DM. Evidence is also available linking long duration of sleep to the subsequent development of T2DM. In a study[31](n=1139 men), subjects reporting short sleep duration (d" 5 -6 hours of sleep per night) were twice as likely to develop T2DM than those with a sleep duration of 6 to 8 hours; and subjects reporting a long sleep duration (≥ 8 hours sleep per night) were more than three times as likely to develop T2DM over a period of 15 years. A systematic review and meta-analysis[32] evaluating the quantity and quality of sleep and incidence of T2DM included 10 prospective studies (n=107,756 median follow-up 9.5 years); sleep duration and sleep disturbances were self-reported in all these studies. This[30] meta-analysis revealed that the risk of developing T2DM was 28% higher with short sleepduration (defined as ≤ 5 or < 6 hours), 48% higher with long sleep duration (defined as > 8 hours), 57% higher with difficulty in going to sleep, and 84% higher with difficulty staying asleep.

The physiologic stress imposed by intermittent hypoxia and/or sleep fragmentation is considered to result in insulin resistance, pancreatic β-cell dysfunction and T2DM through several mechanisms. In subjects with OSA increased sympathetic activity (elevated catecholamine levels) due to hypoxaemia and hypercapnia has been observed not only during sleep, but also in the awake state. Nocturnal hypoxia and repeated arousals from sleep following obstructive breathing event are thought to be responsible for this. Recent human data also suggest that sleep disruption and intermittent hypoxia can each decrease insulin sensitivity and worsen glucose tolerance. Sleep fragmentation and hypoxia tend to result in hypothalamo-pituitary-adrenal (HPA) axis dysfunction, elevated cortisol levels and reduction in insulin sensitivity and secretion. The HPA axis hyperactivity is also implicated in sleep disorders, such as, insomnia, sleep fragmentation and shortened sleep time. Intermittent hypoxia, and possibly sympathetic activation result in increased monocyte and lymphocyte activation and systemic inflammation as evidenced by increased tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Alterations in adipokine levels (elevated leptin levels and lower adiponectin levels), sleep architecture are also thought to contribute to reduced insulin sensitivity and animpairment of glucose tolerance.[14-18]

The metabolic syndrome (MetS) is a constellation of abnormalities, namely, central obesity, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol, hyperglycaemia, and hypertension that confers an increased risk of coronary artery disease (CAD) and T2DM.[31,32] For a long time it was thought that OSA and T2DM were linked by obesity. However, recent data reveal that OSA was independently associated with other neuro-endocrine-metabolic changes that might favour the development of T2DM suggesting that OSA and T2DM may be also associated independent of obesity.[35,36]

Impaired appetite regulation, consequent decreased satiety and increased caloric intake is thought to result from short sleep duration due to leptin and insulin resistance and these may be exacerbated by OSA. Some evidence is available linking autonomic dysfunction in T2DM to the causation of OSA, but this area merits further detailed study. Evidence is also available suggesting that excitatory neuropeptides orexin A and orexin that are found in lateral hypothalamus and perifornical area stimulated by ghrelin, promote

wakefulness, increase appetite and sympathetic activity.[14-18] Thus, individuals with short sleep duration are likely to gain weight and have an increased risk of developing T2DM and OSA. Furthermore, patients with OSA are less physically active due to fatigue and somnolence and this may contribute to the causation of T2DM as well.

OSA AND TYPE 2 DIABETES MELLITUS: EPIDEMIOLOGY

Methodological issues

The association between T2DM and SDB has been recognized since long. Several studies have addressed the issues related to: prevalence of T2DM in patients with OSA; the burden of OSA in patients with T2DM; and sleep deprivation as a risk factor for impaired glucose tolerance (IGT), T2DM among others. However, several methodological issues listed below should be kept in mind while interpreting these data, making comparisons across studies. From a OSA point-of-view, these include: a small sample size, highly selective denominator studied, inadequate adjustment for confounders; use of surrogate measures (e.g., snoring, difficulty falling asleep, the need for sedatives to fall asleep, and difficulty in maintaining sleep), use of limited ambulatory PSG with only respiratory monitoring, rather than the gold standard PSG as described above. Some studies have defined T2DM based on self-report or medication use, others have used validated T2DM based on fasting glucose and/ or 2-hour post-challenge glucose levels.

Prevalence and incidence of T2DM in patients with OSA

Data from studies using self-reported subjective measures, considered to be surrogate parameters for the presence of OSA, and those using objective measurement with PSG have indicated a possible causal association between the presence of OSA and development of T2DM and OSA has been shown to be an independent risk factor for the development and progression of T2DM.[37]Cross sectional data[38-45]have demonstrated a significantly higher prevalence of diabetes in patients with OSA as compared to those without OSA. In some studies[40,42,43]a significant dose-response relationship between the severity of OSA and the prevalence of T2DM. In one study,[40] patients with severe OSA had a significantly higher adjusted odds for self-reported diabetes following adjustment for weight and neck circumference [odds ratio (OR) 2.18; 95% confidence intervals (CI) 1.22 to 3.89; $p<0.01$]. On stratified analysis, this relationship was observed exclusively in patients with excessive daytime sleepiness (Epworth Sleepiness Scale score ≥ 10) compared to patients without sleepiness [OR 2.59; (95% CI 1.35 to 4.97) Vs 1.16 (95% CI 0.31 to 4.37)]. Men with OSA and an AHI greater than 10 have been observed to be more likely to have IGT and diabetes compared to those without OSA.[38] Data from the Sleep Heart Health Study[44] has documented a significant association between oxygen desaturation during sleep and elevated fasting and 2-hour plasma glucose concentrations during an oral glucose tolerance test (OGTT). In the Wisconsin Sleep Study,[42] a significant cross-sectional association was noted between OSA and T2DM for all degrees of OSA severity. In this study,[42]among patients with moderate-severe OSA, this association persisted even after adjustment for obesity.

However, longitudinal data over 4 years from Wisconsin Sleep Study,[42]did not indicate that presence of OSA at the baseline was not a significant predictor of the development of T2DM after adjusting for obesity. The Busselton Health Study[45] reported a significant independent association between moderate to severe OSA and incident diabetes over a 4-year follow-up period. The sample size in this study was small and there were only few incident cases of diabetes. In another study[41] over a mean

follow-up period of 2.7 years, an independent association was observed between OSA and incident diabetes, that was significant after adjusting for various confounders as well as the weight change.

Prevalence of OSA in patients with T2DM

Prevalence of OSA in patients with T2DM has been found to be variable in different studies ranging from 48% to 86%.[46-49] The prevalence of OSA in patients with T2DM 58% in the Sleep Heart Study[46] that included older individuals, used self reported diabetes, and an oxygen desaturation threshold of at least 4% for defining hypopnoeas. In the Sleep Action for Health in Diabetes (Sleep AHEAD) study, a multicentre ancillary study of the Look AHEAD trial[47]the prevalence of OSA among obese subjects with diabetes was reported to be 86%. In another study[48] the prevalence of OSA in patients with T2DM was found to be 77% using a cut-off of 3% for oxygen desaturations, and when the dataset was re-analyzed using a stricter 4% criteria this figure decreased to 58%. Similarly, a high prevalence of OSA was observed in adults with T2DM, ranging from 48% (AHI ≥10) to 29% (AHI ≥20) in another study (49).The INOSA guidelines[50] observed that the prevalence of OSA in diabetic and pre-diabetic obese patients is higher than those with normal glucose tolerance. Further, the risk of developing type 2 DM increases with the severity of OSA.[50] In another recent study,[51] at least one third of people with T2DM referred to a diabetes clinic in Denmark were found to have symptomatic OSA.

More recently, evidence is available suggesting that that among patients with DM OSA may be a strong risk factor for the development of diabetic nephropathy.[52,53]

OSA and prediabetes conditions

A number of population and clinic-based cross-sectional studies[38,54-56]have consistently demonstrated a consistent independent association between the presence and severity of OSA, insulin resistance and glucose intolerance. From a methodological point of view, majority of these studies were conducted in men and few women were studied. These studies most frequently used AHI and the frequency and the degree of intermittent hypoxia as measures of severity of OSA; fasting blood glucose and oral glucose tolerance test (OGTT) to define glucose tolerance and fasting insulin levels and/or homeostatic model assessment (HOMA) index to assess insulin sensitivity. The prevalence of prediabetes (range 20%-37%), as defined by the presence of either IFG and/or IGT was found to be significantly higher in patients with OSA compared to those without OSA.[38,54-56]It was also observed that OSA was found to be associated with insulin resistance and higher fasting glucose levels after adjusting for the confounding effect of visceral adiposity.[54] In a later study,[57] patients with mild, moderate, and severe OSA showed a 26.7%, 36.5% and 43.7% decrease in insulin sensitivity, respectively, after adjusting for age, sex, race and percent body fat compared to normal subjects.

Effects of CPAP treatment of OSA

Several studies have been conducted to assess if treatment of OSA with CPAP improves insulin resistance, glucose metabolism and glycaemic control. However, the results have been conflicting. These studies have been limited by a small sample size, lack of adequate control subjects and many of these studies showed no significant effects.[14-18]Further, the current evidence suggests that the degree of obesity and the amount of CPAP used may be important predictors of metabolic response to CPAP.[14-18]A recent systematic review and meta-analysis did not support the view that OSA independently influenced glucose metabolism and revealed that CPAP did not influence plasma insulin levels, HOMA-index, adiponectin levels or HbA1c. [58] Another

systematic review and meta-analysis[59] also suggested that CPAP does not reduce HbA1c levels when used in the short term in patients with diabetes mellitus.

OSA IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

Though a large body of evidence is available addressing OSA and T2DM, relatively sparse data are available regarding the burden of OSA in patients with type 1 diabetes mellitus (T1DM). While sleep disorders seem to trigger T2DM, presently available evidence does not indicate that they influence T1DM. In T1DM glycaemic variations, poor glycaemic control might lead to poor quality and/or length of night time sleep resulting in daytime sleepiness but also exacerbate diabetes control by increasing pro-inflammatory cytokines that inhibit glucose uptake into fat and muscle and increase the secretion of counter-regulatory hormones. This results in insulin resistance and glucose intolerance, further exacerbating the glycaemic control.[60-62]

SCREENING

Screening patients with OSA for diabetes mellitus

Current evidence strongly favours screening and monitoring all patients strongly suspected or diagnosed to have OSA to be screened for diabetes mellitus and metabolic syndrome.[14-18] The tests that are required for this, such as, waist measurement, blood pressure measurement and fasting lipids and glucose followed with a glucose tolerance test (OGTT), where appropriate are easily available and inexpensive as well.[14-18]

Screening patients with diabetes mellitus for OSA

The uncertainty regarding the metabolic benefits of CPAP therapyin patients with diabetes and the lack of a clear understanding regarding the latent or early asymptomatic stages of OSA, currently raises questions regarding routine testing for OSA amongpatients with diabetes.[14-18]Current evidence favours screening patients with diabetes manifesting classical symptoms, such as witnessed apnoeas, heavy snoring or daytime sleepiness, and those with refractory hypertension. As DM is considerd to be a high risk condition for OSA, the INOSA guidelines[50] advocate that persons with DM should have comprehensive sleep evaluation.

Ideally, in-hospital, in-laboratory, technician-attended, overnight PSG should be used to diagnose OSA. However, such facilities are not widely available or accessible. So, a two-stage screening strategy, such as the strategy advocated by the IDF[63] can be used for screening. In this approach, a structured questionnaire e.g., the Epworth Sleepiness Scale[64] or the Berlin questionnaire[65] is used in the first stage to assess the level of EDS and the pre-test probability of OSA. In patients who score as a low risk but have other risk factors for OSA may undergo second stage evaluation, with an overnight evaluation at home with pulse oximetry or portable respiratory monitoring. Persons with evidence of OSA on second stage evaluation, patients with a high pre-test probability of OSA but a negative second stage testing may require further investigation including PSG by a sleep specialist.

The relationship between diabetes and OSA is complex and has profound clinical implications. Our present understanding suggests that sleep exerts marked modulatory effects on glucose metabolism. Sleep debt, OSA, obesity and T2DM appear to be the part of a vicious circle where one influences, provokes, or impairs the others. However, the mechanisms through which these interactions occur need to be understood further. In patients with diabetes, adopting a healthier lifestyle, dietary modifications, ensuring adequate physical activity, judicious use of oral hypoglycaemic agents/

insulin as appropriate along with adequate sleep quality and duration can help in diminishing the sympathetic activation, regulating the secretion of counter-regulatory hormones, insulin, leptin and ghrelin, and lowering the pro-inflammatory cytokines, there by help in achieving adequate metabolic control.

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