

# Obstructive Sleep Apnea: A Risk Factor for Type-2 Diabetes Mellitus



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## Abstract

Obstructive sleep apnea (OSA) is a chronic sleep-breathing disorder and a frequent comorbidity in patients with type-2 diabetes mellitus (T2DM). Cardinal features of OSA including arousals from sleep and fragmented sleep pattern have been implicated to cause oxygen desaturations and enhance the nocturnal release of cortisol that sustain during daytime thus providing the stimulus for the development of T2DM. OSA can promote new onset T2DM because intermittent hypoxia decrease insulin sensitivity and sympathetic hyperactivity leads to the release of inflammatory markers that induce insulin resistance. OSA is a common disorder affecting both men and women and it is estimated that 80-90% of people with OSA remain undiagnosed. An ever-growing number of studies support a robust association between OSA and T2DM including glucose intolerance and insulin resistance. Evidences from human and animal models provide an insight into the potential mechanisms that lead to altered glucose metabolism and poor glycemic control in OSA. This review summarizes the overlapping pathophysiology of OSA and T2DM and an overview of various treatment approaches to OSA

**Keywords:** OSA; T2DM; Glucose metabolism; Insulin resistance; Management; Intra-thoracic pressure; Sympathetic activity; Hypoxia; Hypercapnia; Hypertension; Stroke; Depression; Diabetes; High blood sugar; Glucose intolerance

**Abbreviation:** OSA: Obstructive Sleep Apnea; HPA: Hypothalamic-Pituitary-Adrenal; SDB: Sleep Disordered Breathing; PAP: Positive Airway Pressure; CPAP: Continuous Positive Airway Pressure; MMA: Maxillo-Mandibular Advancement; AASM: American Academy of Sleep Medicine; UPPP: Uvulopalatopharyngoplasty

## Introduction

Obstructive sleep apnea (OSA) is a complex sleep disorder characterized by repetitive collapse of upper airway leading to cessation of airflow and greater respiratory effort [1]. The intermittent hypoxia, alternating with periods of normoxia, lead to transient arousals from sleep, restoring the airflow, but causing fragmentation of sleep and marked swings in intra-thoracic pressure [2]. Also, sleep fragmentation associated with hypoxia and hypercapnia increases the sympathetic activity which in turn increases the blood sugar level by decreasing insulin sensitivity [3].

OSA is a common disease which is an independent risk factor for a number of conditions such as hypertension, [4] stroke, [5] depression [6] and diabetes [7]. It affects up to 20% of the population worldwide with approximately 5% experiencing excessive daytime sleepiness [8]. Its prevalence in India is estimated to be 7.5% [9]. On the other hand, T2DM is a growing

challenge and an estimated worldwide prevalence of 6.4% occur among adults (aged 20-79 years) [10]. In India an estimated 8.7% of population suffer from T2DM [11]. It is characterized by presence of hyperglycemia either due to defective insulin secretion or defective insulin action or both [12]. The absence or reduced insulin secretion in turn leads to persistent high blood sugar and glucose intolerance [13]. Given the high prevalence, similar predisposition and overlapping pathophysiology of OSA and T2DM, they can be expected to occur concurrently in the same patient.

## Pathophysiological Link between OSA and Type 2 Diabetes Mellitus

Sleep affects almost every type of tissue in the body from vital organs like brain, heart and lungs to metabolism, immune function, mood, and disease resistance. A chronic lack of sleep or poor quality of sleep is linked to the increased risk of disorders

like high blood pressure, cardiovascular diseases, diabetes, depression and obesity [14]. Under normal conditions glucose homeostasis results from a controlled balance between glucose production and glucose utilization. The association between sleep duration and development of diabetes has been examined in many epidemiological studies. In a prospective study from Germany which followed 8269 non-diabetic men and women for a period of 7.5 years in average observed a significant increased risk of T2DM for those who reported difficulty in maintaining sleep at baseline [15].

Intermittent hypoxemia and sleep fragmentation are cardinal features of OSA and are likely in the causal pathway leading to metabolic dysfunction [16]. Short-term laboratory-based experiments in healthy human subjects have demonstrated that sleep restriction, sleep fragmentation and intermittent hypoxemia can lead to glucose metabolism dysregulation [17]. In healthy volunteers, exposure to 5 hours of intermittent hypoxia during wakefulness inducing an average of 24 desaturation events per hour, led to a 17% reduction in insulin sensitivity without a simultaneous increase in insulin secretion [18]. In another experiment, however, exposure to three hours of intermittent hypoxia (leading to 25 desaturations/hour) resulted in an increase in plasma glucose without changes in insulin secretion [19].

Therefore, there may be a threshold with regard to the intensity of hypoxemia or duration of exposure that may lead to an adverse impact on insulin sensitivity [20]. The role of sleep fragmentation on glucose metabolism has been demonstrated in multiple human experiments. Although the exact pathophysiologic and causal links between OSA and glucose metabolism dysregulation are not fully understood, multiple mechanistic pathways are likely to be causally involved. Direct recordings of muscle sympathetic nerve have demonstrated increased sympathetic activity in patients with OSA [21]. This sympatho-excitation persists during the daytime in untreated patients with OSA and is significantly reduced by effective CPAP therapy [22]. Most endocrine organ releasing hormones involved in glucose regulation are inhibited by elevations of sympathetic tone. Well-documented examples relevant to metabolic risk are pancreatic insulin secretion, hepatic glucose production, and adipocyte regulation of energy balance [23]. In addition, peptidergic factors originating from the intestine (glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide) augment the insulin response induced by nutrients.

The secretion of these incretin hormones is intimately linked to autonomic nervous system activity [24]. Thus, the sympathetic hyperactivity and parasympathetic withdrawal associated with OSA are likely mediators of its adverse effects on glucose tolerance. The ability of OSA to activate the sympathetic nervous system is well characterized [25]. Increased sympathetic nerve activity is implicated as a primary mechanism in the

development of sustained hypertension in OSA patients. Since activating the sympathetic nervous system can also potentially impact insulin sensitivity, it has been proposed that increased sympathetic nerve activity may lead to insulin resistance in OSA patients.

However, the possibility remains that hypoxic activation of the sympathetic nervous system or an increase in circulating catecholamines contribute to the long-term progression of insulin resistance and metabolic function that may occur over decades in patients exhibiting OSA and obesity [26]. The hypoxic stress of OSA likely activates the hypothalamic-pituitary-adrenal (HPA) axis, elevates cortisol levels and putatively contributes to insulin resistance. The downstream sequelae of OSA impact a vast array of organ systems and cellular processes [25]. It is suggested that OSA is an independent risk factor for the development of T2DM and that as many as 15–30% of patients with OSA have this comorbidity. Also, as the severity of OSA increases, incidence of T2DM also increases [26]. The association between OSA and T2DM further compounds or aggravates the effect of OSA on cardiovascular health. Screening for cardiovascular disease and T2DM is part of routine healthcare. However, despite the fact that OSA is common and affecting 24% and 9 % of men and women respectively, it is estimated that 80-90% of people with OSA remain undiagnosed [27]. It is very difficult to ignore the public health costs of undiagnosed OSA especially given its association with cardiovascular disease and diabetes [28].

There are several possible mechanisms by which OSA could be associated with glucose intolerance and T2DM. Severe OSA results in an increased neurogenic sympathetic activity and circulating levels of nor-epinephrine, which could result in increased glycogenolysis, lipolysis, and insulin resistance. It is also possible that sleep disordered breathing (SDB) leads to release of cortisol resulting in higher glucose concentration and excessive insulin secretion. Yet another possibility is that adipocyte-derived inflammatory mediators, such as IL-6, TNF- $\alpha$ , and leptin, which are released as a result of cyclic hypoxia, contribute to insulin resistance and hyperglycemia. Sleep loss and poor sleep quality have been associated with the risk of T2DM [29]. The association of obstructive sleep apnea (OSA) syndrome with obesity, hypertension and cardiovascular disease has highlighted the broad public health importance of this condition.

### Prevalence of OSA in Patients with Type 2 Diabetes Mellitus

A number of studies have explored the prevalence of OSA in patients with T2DM. As illustrated in Table 1, the prevalence of OSA is alarmingly elevated in patients with T2DM. Among patients with OSA, the prevalence of T2DM has been estimated to be 15-30%, with higher prevalence in those with severe OSA [30].

**Table 1:** Prevalence of OSA in Patients with Type 2 Diabetes.

Reference	N	Setting	Mean Age (yrs)	Mean BMI kg/m <sup>2</sup>	Male%	Sleep Assessment	Follow Up (yrs)	Results
[31]	318	Australia	53.1	26.6	41.3	RDI>5 from 4a-channel home monitoring device (heart rate, oxygen saturation, snoring and body position)	4	Moderate to severe OSA (RDI ≥15) was associated with diabetes, OR 13.45 (95% CI 1.59–114.11)
[32]	43,98	Japan	57.6	23.5	34.7	3% ODI ≥5 events/h using pulse oximetry	3	Moderate OSA (ODI ≥15) was associated with diabetes, HR 1.69 (95% CI 1.04–2.76)
[33]	47093	U.S.	36.7	26.3	25.3	Report of a physician diagnosis of OSA	6	OSA was associated with diabetes, OR 1.78 (95% CI 1.39–2.28)
[34]	8,678	Canada	48	28.4	62	AHI ≥5 by polysomnography	5	AHI >30 was associated with diabetes, HR 1.31 (95% CI 1.07–1.61)

### OSA and Nocturnal Blood Glucose

The increased blood glucose levels and insulin resistance may lead to nocturnal hyperglycemia which occurs as a result of increased insulin secretion from beta cells. Nocturnal hypoxemia triggers hyperglycemia in patients who have both OSA and diabetes. The obstructive events which occur during sleep result in drop in blood oxygen levels which return to base level when the person’s breathing resumes. As a result of this airway obstruction and multiple arousals that occur during the night, people have sleep fragmentation and often experience daytime sleepiness. In healthy subjects, sleep restriction is associated with insulin resistance, increased appetite and carbohydrate craving and even in the absence of breathing disorders sleep fragmentation and sleep deprivation can affect glucose tolerance.

Nocturnal awakening and arousal are associated with altered levels of leptin, leptin resistance, pulsatile cortisol release and autonomic activation. Repeated arousal and subsequent cortisol release can lead to dysregulation of the hypothalamic-pituitary adrenal axis, which results in glucose impairment [35]. In 10 years follow up study by Al-Delaimy, et al. [36] 69852 nurses aged 40-65 years, it was found that regular snoring was independently associated with a two-fold increased risk of developing diabetes.

However, because of the lack of awareness by the public and healthcare professionals, the vast majority remains undiagnosed and untreated. It’s estimated that about 70% of those with OSA are obese. The prevalence of OSA in obese men and women is about 40% [25]. Interestingly there is evidence to suggest that T2DM independently increases the likelihood of sleep disordered breathing possibly through the effects of diabetes on the autonomic and central nervous system [26].

### Screening of OSA in Patients with Type-2 Diabetes Mellitus

Since there are evidences of high prevalence of OSA in patients with T2DM, there is need of increasing awareness

of OSA amongst diabetes societies. In 2008 and 2017 the International Diabetes Federation’s Taskforce on Epidemiology and Prevention and American Diabetes Association respectively strongly recommended that health professionals working in both T2DM and sleep-disordered breathing must consider screening a patient presenting with one condition for the other [37]. Therefore, given the high prevalence of OSA in patients with T2DM and the suboptimal performance of screening questionnaires, clinicians must consider exploring the diagnosis of OSA using home sleep monitoring devices if clinically appropriate.

### Management of OSA

Treatment to control the signs and symptoms of OSA includes behavioral approaches to improving sleep habits and weight control. Both medical and surgical weight loss significantly reduce the severity of OSA. More recently, weight loss related to lifestyle interventions in people with type 2 diabetes has been shown to significantly improve OSA severity. Along with lifestyle modifications, there are also some mechanical as well as pharmacological options of OSA [38].

### Positive airway pressure (PAP)

The elimination of nocturnal apneic events and intermittent hypoxia are the key goals to control OSA effectively. PAP devices function as a pneumatic support that allows one to maintain upper airway patency by increasing the upper airway pressure above a ‘critical’ value (pressure value below which the airways collapse). The device is applied to the patient, through a nasal or oronasal mask, overnight or during sleep hours at a set positive pressure. The pressure to apply can vary with the severity of OSA and higher pressures are needed to abolish those apnea’s occurring during rapid eye movement sleep, in the supine position or in the presence of severe obesity. For each patient, the effective pressure is obtained after one or more nights of PAP titration. PAP therapy is indicated in all patients with an AHI greater than 15, independently from the presence of comorbidities, type of work and severity of symptoms [39].

### Continuous positive airway pressure (CPAP)

For moderate to severe sleep apnea, the use of a continuous positive airway pressure (CPAP) is the first line therapy. CPAP uses continuous pressurized air flow to keep the individual's airway open during sleep. The amount of pressure used is initially titrated during the PSG (split test) based on the patient's comfort and lowest pressure required to decrease apneic and hypo apneic episodes. CPAP therapy is the most effective treatment option in reducing apneas in OSA. It has been shown to improve AHI, RDI, sleep architecture, EDS, neurobehavioral performance and cardiovascular morbidity (hypertension) [40].

### Dental appliances

Dentists specializing in sleep dentistry make a custom-made mouthpiece that shifts the lower jaw forward, thereby maintaining an open airway. In a study comparing CPAP to dental appliance in mild to moderate OSA, dental appliances decreased AHI from 21 (baseline) to 14, compared to decreased AHI of 5 in patients using CPAP [41].

### Surgical interventions

Surgical treatment for OSA needs to be individualized in order to address all anatomical areas of obstruction. The most frequently utilized surgery treatment is the uvulopalatopharyngoplasty (UPPP or UP3). These surgeries aim to address pharyngeal obstruction by removing tissue in the back of the throat, including part of the uvula, the soft palate, the tonsils, the adenoids and pharynx [42].

### Maxillo-mandibular advancement (MMA)

MMA is another type of surgery that has been used to treat OSA. This procedure aims to advance the maxilla and mandible, thereby pulling forward the anterior pharyngeal tissues attached to the maxilla, mandible and hyoid to structurally enlarge the retro lingual and retropalatal spaces. It is considered the most effective surgery for OSA patients, because it increases the posterior airway space. In a study in 2008, it was noted that MMA surgery led to a significant increase in general productivity, social outcome, activity level and sex [43].

### Pharmacological management of OSA

Medications are generally not a part of the primary treatment of OSA. Modafinil is approved by the FDA for use in patients with OSA who have residual daytime sleepiness. Armodafinil, the R-enantiomer of modafinil, is now FDA approved for use as well. The American Academy of Sleep Medicine (AASM), in a clinical review of medical therapies for OSA, recommended Modafinil as a standard treatment of residual excessive daytime sleepiness in patients with OSA despite maximal management of CPAP [44].

### Conclusion

OSA, via sympathetic activation, oxidative stress, inflammation, and neuroendocrine dysregulation, alters glucose homeostasis, including in-patients with type 2 diabetes. Early recogni-

tion and interventions for OSA are expected to improve insulin sensitivity and control hyperglycemia in many patients. Both disorders are associated with adverse cardiovascular morbidity and mortality. Since there are evidences of high prevalence of OSA in patients with diabetes, there is need of increasing awareness of OSA amongst diabetes societies as is recommended by the American Diabetes Association. Clinicians need to be vigilant in screening and treating diabetic patients for OSA. Therefore, given the high prevalence of OSA in patients with type 2 diabetes, clinicians must consider exploring the diagnosis of OSA along with treatment options for both the diseases.

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