

## Obstructive sleep apnea in Type 2 diabetes and impact of continuous positive airway pressure therapy on glycemic control

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### ABSTRACT

**Background:** Obstructive sleep apnea (OSA) and type 2 diabetes mellitus (T2DM) are two interacting epidemics both with high prevalence and morbidity. Both epidemiologic and clinical studies suggest that the majority of patients with T2DM also have OSA and untreated OSA in these patients results in poor glycemic control leading to acceleration of diabetes-related complications. **Objectives:** To assess the prevalence and severity of OSA in T2DM patients and to assess the impact of OSA treatment on presenting symptoms and hemoglobin A1c (HbA1c). **Methods:** We performed polysomnography (PSG) studies and measured HbA1c in 62 consecutive patients with T2DM that were referred from various subspecialty clinics from July 2011 to August 2013. **Results:** In our 62 diabetic patients, 59 (95.2%) had abnormal PSG. Based on Apnea–Hypopnea Index (AHI) score, 3 (5.1%) patients had mild, 28 (47.5%) had moderate, and 28 (47.5%) had severe OSA. The mean AHI of diabetic patients was significantly more than nondiabetic patients, i.e., 25.7 versus 19.7 ( $P = 0.001$ ). Variables that significantly correlated with the presence of OSA include age, gender, body mass index (BMI), hypertension, diabetes, and cardiovascular disease ( $P < 0.05$ ); however, on logistic regression only BMI, hypertension, and nocturia correlated with OSA. Overall, 59% of diabetic patients showed improvement in their glycemic control as measured by HbA1c with continuous positive airway pressure (CPAP) treatment. Significant, moderate, and mild categories of treatment response were respectively observed in 7%, 20%, and 32% of patients. **Conclusion:** Treatment of OSA with CPAP reduces HbA1c in a significant number of diabetics.

**Key words:** Continuous positive airway pressure, glycemic control, hemoglobin A1c, obstructive sleep apnea, Type 2 diabetes

### INTRODUCTION

Obstructive sleep apnea (OSA) is a respiratory sleep-related disease characterized by sleep-related collapse of the pharynx in the face of persistent ineffective breathing

efforts leading to repetitive interruptions of ventilation during sleep resulting in sleep fragmentation and arterial hypoxemia. OSA is a common disorder that is highly prevalent in patients with T2DM.<sup>[1,2]</sup> OSA, which is characterized by upper airway instability during sleep results in markedly reduced (hypopnea) or absent (apnea) airflow. Intermittent hypoxia and sleep fragmentation, the two major characteristics of OSA, lead to derangements in glucose metabolism mainly by the activation of the sympathetic nervous system and hypothalamic-pituitary axis and changes in the inflammatory pathways. Other

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possible mechanisms include hypoxic injury to pancreas and alterations in hypothalamic pathway for glucose control. Although evidence strongly supports an independent association between OSA and insulin resistance and glucose intolerance, but a causal link remains to be determined.

A substantial proportion of patients with type 2 diabetes mellitus (T2DM) suffer from unrecognized OSA and conversely, T2DM is more prevalent among OSA patients compared to those without OSA. Thus, the role of OSA in the management of T2DM is in urgent need of further rigorous assessment. The question of whether OSA represents an independent risk for the development of prediabetes, and T2DM over time remains to be investigated by large prospective studies. Whether continuous positive airway pressure (CPAP) treatment of OSA improves glucose metabolism is being debated. In addition, the duration of CPAP that is required to improve metabolic outcomes remains to be confirmed. Therefore, large-scale randomized controlled trials of CPAP treatment of OSA with well-validated assessments of insulin sensitivity and glucose tolerance are needed. These trials should focus on identifying those phenotypes of OSA patients who show a better metabolic response to CPAP therapy.

The majority of patients with T2DM also have OSA, which is a significant risk factor for cardiovascular disease and mortality. Few prospective studies have concluded that even habitual snoring may independently increase the risk of T2DM.<sup>[3,4]</sup> In a 10-year follow-up study in 69852 nurses aged 40–65 years regular snoring was independently associated with a two-fold increased risk of developing diabetes.<sup>[4]</sup> A recent study suggested that mild oxyhemoglobin desaturation of <4% during sleep may predispose to fasting hyperglycemia.<sup>[5]</sup> OSA has been reported as a highly prevalent comorbidity of T2DM by various authors<sup>[1,2,6]</sup> and among obese patients with T2DM, the prevalence has recently been estimated at a staggering 86% in the United States.<sup>[2]</sup> Various clinical and epidemiologic studies have confirmed that nondiabetics with OSA regardless of adiposity show alterations in glucose metabolism, including insulin resistance and impaired glucose tolerance.<sup>[7,8]</sup> Ficker *et al.*<sup>[9]</sup> have shown that OSA is more often prevalent in diabetics with autonomic neuropathy (AN). Six of 23 diabetics with AN (26%) had OSA, whereas there were no OSA patients in the non-AN group. The risk of OSA is particularly increased in obese diabetics with AN because these patients have the most profound oxygen desaturations during sleep.

Given, the high prevalence of OSA in diabetes and independent association between OSA and abnormal glucose metabolism, there is insufficient data on whether

the presence and severity of OSA compromise glycemic control in diabetic patients. The effective treatment of OSA with CPAP could potentially improve glucose control in millions of diabetics with OSA world over and therefore has major clinical implications. Keeping this in mind, in the present study, we evaluated the impact of OSA treatment on hemoglobin A1c (HbA1c), the major clinical indicator of glycemic control, in patients with T2DM.

## METHODS

T2DM patients suspected of OSA who were referred for polysomnography (PSG) from various subspecialty clinics including endocrinology were recruited at Modern Hospital, Rajbagh, Srinagar, between July 2011 and August 2013. Exclusion criteria were (1) Patients on nocturnal oxygen supplementation, (2) failure to meet the criteria for T2DM, (3) unstable cardiopulmonary, neurological, or psychiatric disease, (4) upper airway surgery, (5) using positive airway pressure therapy or oral appliances.

All participants gave written informed consent before PSG. A detailed history of complaints including snoring, witnessed apneas, nocturia, disturbed nocturnal sleep, and morning headaches was taken. Daytime sleepiness was assessed by Epworth Sleepiness Scale (ESS). Height, weight, and neck circumference were measured in all patients. An overnight laboratory PSG was then performed to diagnose the presence and severity of OSA. PSG recordings were started based on the subject's usual domestic sleeping habits, and each patient was recorded for a minimum of 7 hours. HbA1c values were obtained from the patient's records if assessed during the previous 3 months and if that was not available, they were advised to get it checked on the next day. The HbA1c test was repeated at 3, 6, and 12 months after CPAP therapy was initiated.

PSG included the recordings of airflow by a nasal pressure transducer and oronasal thermocouples, chest and abdominal wall motion by piezo electrodes, oxygen saturation by pulse oximeter, electrocardiogram, six electroencephalogram channels, bilateral electrooculogram, chin and tibialis electromyogram. Recordings were scored visually in 30 s in non-rapid eye movement (non-REM) sleep stages 1–4 sleep and REM sleep according to the standard criteria.<sup>[10]</sup> Similarly, respiratory events and microarousals were scored according to established criteria.<sup>[11,12]</sup> Complete cessation of airflow for at least 10 s was defined as apnea (obstructive if respiratory efforts were present and central if respiratory efforts were absent), and hypopnea was identified if there was a discernable reduction in airflow lasting at least 10 s and associated with at least 3% oxygen desaturation. The apnea–hypopnea index (AHI) was defined as the total

number of obstructive apneas and hypopneas per hour of sleep. Oxygen desaturation index (ODI) was defined as the total number of desaturations of at least 3% per total sleep time in hours. We defined OSA severity categories according to commonly used clinical cutoffs, i.e., No OSA (AHI <5), Mild OSA (AHI ≥5 but <15), Moderate OSA (AHI ≥15 but <30), and severe OSA (AHI ≥30).

### Statistical analysis

Standard methods of statistical analysis were used for data analysis. After descriptive statistical analysis of the general characteristics of the study participants, the Kolmogorov–Smirnov test was used to examine the distribution of variables, and the Levene test to study the variance. Qualitative variables were analyzed with the Chi-square test or with Fisher's exact test if at least one cell had an expected count <5. Student's *t*-test was applied to compare the mean values of quantitative variables when the distribution was normal and the Mann–Whitney U-test when it was not. For paired samples, the Student's *t*-test for paired samples and McNemar test were used. Pearson's coefficient was used to test the correlation between quantitative variables;  $P \leq 0.05$  was considered statistically significant. SPSS 11.0 was used for data analyses (SPSS Inc., Chicago, IL, USA).

## RESULTS

Out of 182 patients [Table 1] who underwent PSG, 62 were diabetic with a mean age significantly more ( $P < 0.001$ ) than that of nondiabetic population (60.8 years vs. 51.8 years). Female diabetics were more in number than their male counterparts 37 (59.7%) versus 25 (41.3%). Diabetics had significantly more ( $P < 0.001$ ) comorbidities compared to nondiabetic patients 17 (27.4%) versus 9 (7.5%). Body mass index (BMI) of diabetics was significantly more than that of nondiabetic patients (32.4 kg/m<sup>2</sup> vs. 30.4 kg/m<sup>2</sup> ( $P < 0.005$ ); however, neck circumference was not statistically different in these two groups.

The main presenting symptoms of diabetic patients were snoring 60 (96.8%), daytime sleepiness 55 (88.7%) with a

mean ESS of 15.3, disturbed nocturnal sleep 43 (69.4%), nocturia 42 (67.7%), and witnessed apneas 27 (43.5%). All these symptoms were more common in diabetics compared to nondiabetic patients and among diabetics these were more prevalent in those with OSA than those without OSA [Table 2]. There were few atypical presentations in our diabetic cohort that included nocturnal enuresis and night terrors for 2 years in a 38 year obese male, a 55 year businessman felt asleep while going for a morning walk and slipped into a drain and a near fatal road traffic accident when a retired engineer dozed off while driving his car.

In our 62 diabetic patients, only three (4.8%) had normal PSG, and the remaining 59 (95.2%) had an abnormal test. Based on AHI score, 3 (5.1%) patients had mild, 28 (47.5%) had moderate, and 28 (47.5%) had severe OSA [Table 3]. Compared to nondiabetics, moderate and severe OSA was significantly more in diabetics ( $P < 0.006$ ). There was no significant difference in sleepiness among diabetics and nondiabetics whose mean ESS was 15.2 and 14.7, respectively ( $P > 0.3$ ).

Sleep efficiency was significantly less ( $P < 0.000$ ) in diabetic patients (mean 68.5%) as compared to nondiabetics (mean 74.1%). Mean sleep latency was significantly more in diabetic (25.1 min) as compared to nondiabetic (19.1 min) patients ( $P < 0.000$ ). Like sleep latency, mean REM sleep latency was also significantly more among diabetic patients (78.8 min) as compared to nondiabetic population (72.4 min) ( $P = 0.004$ ). Mean room air awake oxygen saturation (SpO<sub>2</sub>) of diabetic patients (91.7%) was significantly less than nondiabetic patients (93.8) ( $P = 0.001$ ). Like awake oxygen saturation, the average nocturnal oxygen saturation of diabetic patients was significantly less ( $P = 0.004$ ) than that of nondiabetic patients (84% versus 87%). The mean AHI of diabetic patients [Table 4] was significantly more than nondiabetic patients, i.e. 25.7 versus 19.7 ( $P = 0.001$ ). The mean ODI of diabetics was significantly more than nondiabetics, i.e., 25.8 versus 19.5 ( $P = 0.006$ ). Variables that significantly correlated with the presence of OSA include age, gender, BMI, hypertension, diabetes, and

**Table 1: Baseline characteristics of the study population**

	Total (n=182)	Nondiabetic (n=120)	Diabetic (n=62)	P
Age (years)				
Mean±SD	54.89±12.89	51.83±12.61	60.82±11.34	<0.001 (S)
Range	22–90	22–82	38–90	
BMI				
Mean±SD	31.09±4.61	30.40±4.57	32.41±4.43	<0.005 (S)
Range	21–49	21–49	25–45	
Neck circumference (cm)				
Mean±SD	40.27±3.38	40.20±3.38	40.40±3.41	0.702 (NS)
Range	33–50	33–50	33–47	

BMI: Body mass index, SD: Standard deviation, S: Significant, NS: Not significant

**Table 2: Patient presentation in diabetic patients-with and without obstructive sleep apnea**

	OSA (n=59) (%)	No OSA (n=3) (%)	Total (n=62) (%)
Snoring*			
Yes	58 (98.3)	2 (66.7)	60 (96.8)
No	1 (1.7)	1 (33.3)	2 (3.2)
Witnessed apneas*			
Yes	27 (45.8)	0 (0.0)	27 (43.5)
No	32 (54.2)	3 (100.0)	35 (56.5)
Disturbed sleep*			
Yes	42 (71.2)	1 (33.3)	43 (69.4)
No	17 (28.8)	2 (66.7)	19 (30.6)
Daytime sleepiness*			
Yes	53 (89.8)	2 (66.7)	55 (88.7)
No	6 (10.2)	1 (33.3)	7 (11.3)
Nocturia*			
Yes	40 (67.8)	2 (66.7)	42 (67.7)
No	19 (32.2)	1 (33.3)	20 (32.3)

\*P>0.05. OSA: Obstructive sleep apnea

**Table 3: Severity of obstructive sleep apnea based on apnea-hypopnea index**

	All patients (n=157) (%)	Diabetic patients (n=59) (%)	Nondiabetic patients (n=98) (%)
Mild	27 (17.2)	03 (5.1)	24 (24.5)
Moderate	69 (43.9)	28 (47.5)	41 (41.8)
Severe	61 (38.9)	28 (47.5)	33 (33.7)

P=0.006 (diabetic vs. nondiabetic patients)

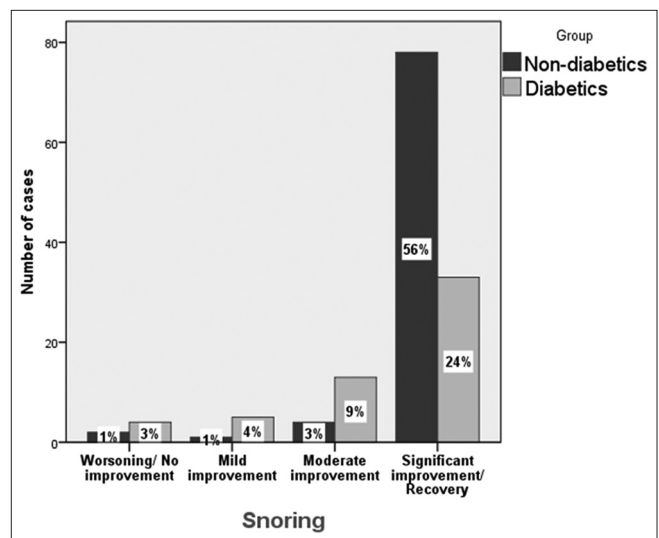
**Table 4: Polysomnography observations in diabetic patients versus those without diabetes**

	All patients	Nondiabetics	Diabetics	P
AHI				
Mean±SD	21.79±12.03	19.74±12.80	25.74±9.28	0.001*
Range	1-54	1-54	2-43	
ODI				
Mean±SD	21.68±14.97	19.52±15.51	25.85±13.01	0.006*
Range	0-61	0-61	2-61	

\*Significant (non-diabetic vs. diabetic patients). AHI: Apnea-hypopnea index, SD: Standard deviation, ODI: Oxygen desaturation index

cardiovascular disease ( $P < 0.05$ ); however, on logistic regression only BMI, hypertension, and nocturia correlated with OSA. Correlation between AHI and BMI was better in nondiabetic patients than in diabetics.

CPAP therapy improved snoring in both diabetics as well as nondiabetics [Figure 1]; however, the improvement in significant category was more in nondiabetic group compared to diabetic group (56% vs. 24%) but in the categories of mild and moderate improvement diabetics showed a better response than nondiabetic patients (4% vs. 1% and 9% vs. 3%, respectively). CPAP therapy improved nocturia in 90% of our patients both diabetics as well as nondiabetics; however, the overall improvement was more in nondiabetics compared to diabetic patients (27% vs. 5%, 24% vs. 17% and 4% vs. 12%, respectively, in significant, moderate, and mild categories of response to treatment). Nocturnal sleep improved with CPAP therapy in 84% of our patients [Figure 2], however, the overall improvement was more in nondiabetic patients compared to



**Figure 1: Effect of continuous positive airway pressure on snoring**

diabetic patients (25% vs. 5%, 22% vs. 11%, and 5% vs. 17%, respectively in significant, moderate and mild categories of treatment response). Both diabetic and nondiabetic patients showed improvement in daytime sleepiness with CPAP treatment, i.e., 38% versus 8%, 17% versus 18%, and 4% versus 7%, respectively, in significant, moderate, and mild categories of the treatment response. Overall, 59% of our diabetic patients showed improvement with CPAP treatment in their blood sugars as measured by HbA1c [Figure 3]. Significant, moderate, and mild categories of treatment response were respectively observed in 7%, 20%, and 32% of our diabetic patients.



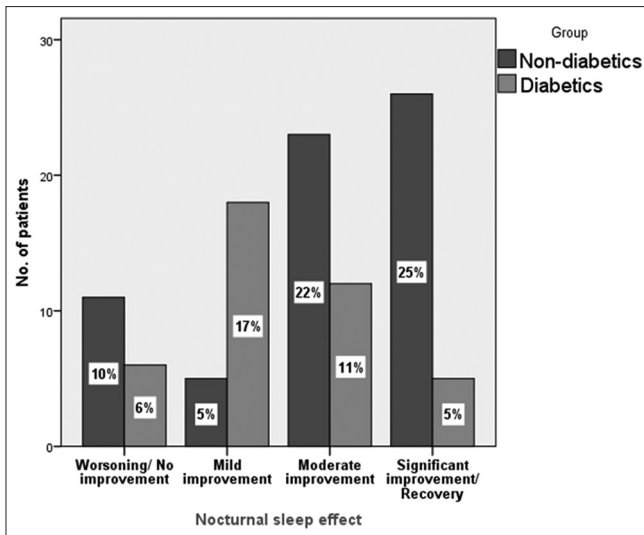


Figure 2: Effect of continuous positive airway pressure on nocturnal sleep

## DISCUSSION

Worldwide, there is a relentless increase in T2DM and to prevent or delay the development of life-threatening complications, a very good control of blood glucose levels is needed. Multiple drugs are required for most patients; substantial proportion requires insulin injections, and this antidiabetic pharmacotherapy may promote further weight gain and compound OSA severity. Although once thought to be independent diseases, the high prevalence of OSA among patients with T2DM<sup>[1,2]</sup> and vice versa<sup>[13]</sup> has raised interesting questions as to how OSA and DM interact. OSA is characterized by recurrent upper airway occlusions during sleep that results in specific physiologic disturbances, including sleep fragmentation, and chronic intermittent hypoxia. These disturbances lead to a cascade of events related to the activation of the sympathoadrenal system, oxidative stress, systemic inflammation, and changes in adipokines— all of which are important in increasing the risk of hypertension, cardiovascular disease, metabolic syndrome, and T2DM.<sup>[14-16]</sup> Multiple prospective epidemiologic studies have indicated that poor sleep quality and short sleep which is typical of OSA, is associated with an increased incidence of diabetes over time.<sup>[17,18]</sup> Enough evidence has been found that supports the hypothesis that OSA and the resultant intermittent hypoxia, elevated sympathetic nervous activity, sleep fragmentation, less amount of slow wave sleep, and cumulative sleep loss has adverse effects on glucose tolerance.<sup>[19,20]</sup> Moderate to severe OSA has been reported to be a significant risk factor for incident diabetes during a 4-year follow-up period in a prospective population study.<sup>[21]</sup> There is an association between OSA and insulin resistance and glucose intolerance even after statistical adjustments for shared risk factors.

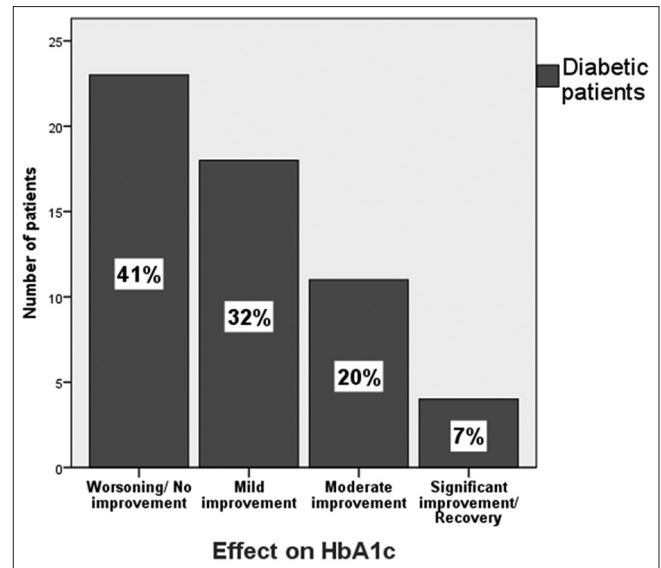


Figure 3: Effect of continuous positive airway pressure on hemoglobin A1c

OSA is associated with increased risk of T2DM, and the mechanisms that contribute to this association include intermittent hypoxia, sleep fragmentation, and immune activation.<sup>[8,22,23]</sup> Chronic sleep loss, a consequence of OSA, is associated with decreased glucose tolerance, decreased leptin, and an increase in evening cortisol levels. Both adipose tissue and diabetes are associated with immune activation and subsequent increase in the circulating pro-inflammatory cytokines, which in turn play a role in the pathogenesis of OSA.<sup>[24]</sup>

In the present study, more than 95% of patients with T2DM had OSA indicating that OSA is highly prevalent comorbidity in our diabetic population. In addition, an important observation of our study was that compared to nondiabetics, severe and moderate OSA was significantly more in diabetics. Regarding the prevalence of OSA in patients with T2DM our findings are consistent with those of the most recent and largest study, the sleep AHEAD (Action for Health in Diabetes) study, which included 306 obese patients with diabetes, and reported OSA prevalence of 86% in diabetics.<sup>[2]</sup> The SHHS (Sleep Heart Health Study) an earlier study that estimated the prevalence of OSA in patients with T2DM involved older individuals (about 50% >65 year of age), found an OSA prevalence of 58%.<sup>[6]</sup> In this study, the definition of hypopneas was based on at least 4% desaturation, whereas we used a cutoff of 3% desaturation, which could explain the difference in prevalence estimations.<sup>[25]</sup> In a recent study, ~90% of subjects with type 2 DM were diagnosed with OSA<sup>[2]</sup> which is very close to our observation.

CPAP a nonpharmacological intervention which is the gold-standard treatment of OSA is highly effective

in relieving the symptoms of OSA. Our study also demonstrated the positive impact of CPAP in the management of blood glucose control as reflected by decline in HbA1c levels in 59% of diabetic patients. In addition to improvement in blood glucose, CPAP therapy also resulted in improvement in blood pressure of as many as 75% of our diabetic patients. This dual benefit of positive impact on blood sugar and blood pressure by CPAP treatment may potentially help globally millions of diabetics with undiagnosed OSA. A reduction in HbA1c level has been shown to be associated with a reduction in the risk of macrovascular and microvascular complications associated with T2DM.<sup>[26,27]</sup> Like our study, some earlier studies have also shown that CPAP results in improved glucose control in diabetics with OSA. One of the earliest studies was that of Brooks *et al.*,<sup>[28]</sup> who investigated the insulin responsiveness before and during CPAP in 10 very obese OSA patients. CPAP significantly improved insulin responsiveness in those patients within 4 months of treatment. In a comparable study, Harsch *et al.*<sup>[29]</sup> also have reported improvement in insulin sensitivity in obese diabetics. The effect, however, was seen after 3 months of CPAP and not immediately like that in nonobese nondiabetics.<sup>[30]</sup> Babu *et al.*<sup>[31]</sup> examined the impact of CPAP treatment on the measures of glucose tolerance in 25 obese diabetic patients and showed beneficial effects of 3 months of CPAP treatment on HbA1c and postprandial glucose levels. Likewise, two other studies<sup>[32,33]</sup> reported earlier have also demonstrated improvements in nocturnal glucose levels in diabetics after CPAP treatment of their OSA. In contrast, two earlier studies<sup>[28,29]</sup> showed no change in HbA1c levels but reported improvements in insulin sensitivity after 3–4 months of CPAP therapy. However, both these studies were small and included only a total of ten patients. West *et al.*,<sup>[34]</sup> who conducted a randomized controlled study, and allotted 20 obese diabetic patients to the active CPAP arm, found no effect of active CPAP on HbA1c levels or insulin sensitivity but reported significant improvements in sleepiness measures. However, these authors have used CPAP on the average only for 3.3 h per night over a 3-month period. By contrast, a study by Babu *et al.*<sup>[31]</sup> found that in patients who used CPAP for more than 4 h per night (average nightly use of 6.6 h/night), demonstrated a reduction in HbA1c levels. These findings highlight the importance of not only obtaining PSG recordings and subsequent CPAP therapy for longer than the commonly used minimum of 4 h but also to examine associations between OSA severity and metabolic variables. These variable results may be related to differences in study population characteristics, methods of assessment of insulin sensitivity, and adherence to the duration of CPAP therapy. Although CPAP adherence is fundamental to OSA therapy, we should not ignore that the benefits of

CPAP may not be the same for cognitive and metabolic outcomes. Our study demonstrates that CPAP treatment not only reduces HbA1c levels in a significant number of diabetic OSA patients but it also improves their cognitive function.

Our study also revealed that the majority of patients with diabetes have undiagnosed OSA and are referred for PSG nearly a decade late compared to nondiabetics. Untreated OSA in diabetics is associated with poor glycemic control resulting in an intensification of pharmacotherapy that promotes weight gain and further exacerbates the severity of existing OSA and elevates cardiovascular risk.

## CONCLUSION

The findings of our study suggest that OSA is highly prevalent in diabetes and is largely unrecognized in the primary care setting. Most of the clinicians do not suspect this important comorbidity of diabetes in the beginning resulting in delayed diagnosis. The present study also demonstrates that treatment of OSA with CPAP reduces HbA1c in a significant number of diabetics. Thus, the role of OSA in the management of T2DM is in urgent need of further assessment, and current practice approaches should be modified to include systematic evaluation and treatment of OSA. In future, randomized-controlled trials with robust assessments of insulin sensitivity and glucose tolerance will be required to comprehensively assess the effects of CPAP on metabolic parameters in diabetic OSA patients.

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## Conflicts of interest

There are no conflicts of interest.

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