



Review

Continuous positive airway pressure and type 2 diabetes mellitus

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ABSTRACT

Obstructive sleep apnea (OSA) is a sleep disorder, increasingly recognized. It is commonly present in obese persons, treated with continuous positive airway pressure (CPAP), being the gold standard. The disorder has been associated with diabetes mellitus and possibly related to hypoxia per se, increased sympathetic activity, disturbed hypothalamic–pituitary–adrenal axis and increased inflammatory cytokines and leptin, all of which can adversely affect both glucose metabolism and insulin sensitivity. Given this association and the presence of common risk factors, this review assessed the impact of CPAP on diabetes mellitus through various metabolic parameters including HbA1c, nocturnal glucose and insulin resistance, in addition to the effect of CPAP on the prevention of diabetes mellitus. Results have been conflicting; Randomized controlled trials are recommended to allow objective and definite conclusions.

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1. Introduction

Obstructive sleep apnea (OSA) is a sleep disorder, increasingly recognized since 1972, following the first symposium on sleep-related respiratory problems [1]. It is characterized by irregular and abnormal respiratory patterns during sleep, including obstructive apneas or hypopneas and respiratory effort related arousals associated with signs of disturbed sleep, such as snoring, restlessness and resuscitative snorts. This is complicated by diurnal symptoms of sleepiness, fatigue, poor concentration, and maybe also a high cardiovascular and cerebrovascular cost [2]. It is not uncommon, occurring in 4–24% of adult males, with varying

severity [2]. Many risk factors have been identified including age, gender, race, familial and genetic predisposition, smoking, alcohol use, medications [3] and obesity, being the most important, found in 60–90% of patients [3,4]. Nasal continuous positive airway pressure (CPAP), while delivering a constant pressure throughout inspiration and expiration to maintain upper airway patency during sleep, is considered the gold standard of treatment of OSA [5].

On the other hand, diabetes mellitus (DM) type 2 is now recognized as an evolving chronic disease with high morbidity, mortality and economic burden [6]. It is estimated that 8% of American adults have diabetes, 90% of which classified as type 2 diabetes [7], increasing more with the obesity epidemic, a major predisposing factor to insulin resistance [8,9].

2. Mechanisms linking OSA and altered glucose metabolism

Given the common risk factors, the association between OSA and DM has been widely studied. Cross sectional studies have

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found that 20–30% of patients with OSA patients have diabetes [10,11]. Furthermore, in diabetic patients, OSA was found in 23%, independently of Body Mass Index (BMI) [12]. These remarkable associations raise the possibility that OSA may be a novel risk factor for DM type 2 and, conversely, chronic hyperglycemia may promote OSA [13].

Potential mechanisms linking OSA to alterations in glucose metabolism are multiple.

Recurrent arousals and intermittent hypoxia are associated with sympathetic nervous system activation [14,15], which in turn leads to gluconeogenesis and increased glycogen break down thus hyperglycemia [16]. Sleep disruption results in hypothalamic–pituitary–adrenal axis activation with increasing nocturnal cortisol level [17,18]. Furthermore, somatotrophic function is affected with decreased IGF1 levels contributing to dysglycemia [16]. In addition, hypoxia, per se, can adversely affect glucose metabolism and insulin sensitivity, independently of other factors, through increased oxidative stress secondary to repetitive hypoxia-reoxygenation cycles [13]. Inflammatory cytokines, including TNF α and IL-6, elevated in OSA, contribute to insulin resistance [19]. Finally, increased leptin levels in OSA may be associated with disorders of glucose metabolism [16].

On the other hand, diabetes may cause nocturnal breathing abnormalities through autonomic neuropathy that could disturb the control of respiration [20].

Given the data linking OSA and diabetes, the presence of common risk factors and the high morbidity associated with them, we will try in this article to review the studies that addressed the impact of CPAP on DM through various metabolic parameters including HbA1c, insulin sensitivity and nocturnal glucose since it has been suggested that CPAP can ameliorate intermittent hypoxia and sleep sympathetic nervous system overactivity which predicts improvement in glucose metabolism [21,22].

3. CPAP and HbA1c

The effect of CPAP on HbA1c has been assessed in many trials, summarized in Table 1. Some showed improvement in HbA1c but others reported negative results.

In a retrospective analysis of 38 patients (23 men and 14 women), known to have severe OSA (Apnea Hypopnea Index (AHI) of 53 events per hour) and diabetes, with a mean age of 53 years, mean BMI 42 kg/m², Epworth Sleepiness Score (ESS) of 16, treatment with CPAP for 4 h \pm 3 h per day for a mean duration of 134 days led to a significant drop in HbA1c (pre-CPAP HbA1c was 7.8 \pm 1.4% and decreased to post-CPAP HbA1c = 7.3 \pm 1.3%

($P < 0.001$)). However, in this study, there was no assessment or control for changes in exercise and level of activity, treatment of concomitant disease, change in diet, smoking and alcohol consumption that might have interfered with the results. In addition, it was not powered enough to assess the effect of adherence to CPAP on HbA1c level [23].

In a small prospective study of 25 obese patients, whose BMI was 42.7 kg/m², 64% of which were men, with a mean age of 50 years, known to have DM for 8 years (with baseline HbA1c level of 8.3%) and OSA (AHI of 56 events per hour, mean ESS of 14), CPAP was used for a mean duration of 4.2 h per day for a period of 83 days. For the entire population, the improvement in HbA1c level before and after CPAP treatment was not significant. However, in a subgroup analysis of 17 patients with an initial higher baseline HbA1c level of 9.2%, there was a significant drop in HbA1c to 8.6% after CPAP treatment ($P = 0.02$). In addition, in the high compliance group (CPAP use > 4 h, $n = 12$), there was a significant correlation between HbA1c improvement and number of days of CPAP use [24].

However, a double blind randomized placebo controlled trial included 40 men known diabetic for more than 5 years and newly diagnosed with OSA (> 10 dips/h in oxygen saturation of $> 4\%$), with same baseline characteristics (age, BMI, diabetes control) who were randomized to receive therapeutic ($n = 20$) or placebo CPAP ($n = 22$) 3 h a day, for 3 months. Glycemic control and HbA1c did not significantly change in neither the therapeutic nor the placebo groups, even when poor compliers were excluded, despite a significant improvement in the sleep apnea and sleepiness quality of life score, possibly explained by the short duration of CPAP use (< 4 h) [25].

Similarly, a pilot crossover study included 13 diabetic patients, with mean HbA1c 5.8%, known to have OSA (mean AHI of 27.9 events per hour) but minimally symptomatic (mean ESS of 6.8), mean age of 55.5 years, mean BMI of 31.1 kg/m², who were initially randomized to either CPAP (mean use of CPAP for 5.53 h per night) or no therapy for 4 weeks followed by a washout of 4 weeks, and then a crossover to the other intervention. There was no significant improvement in HbA1c in the CPAP group compared to no therapy. The lack of effect was probably related to the small number of patients, short duration (< 3 months not enough to allow significant changes in glycosylated hemoglobin), good glycemic control at baseline, less severe obesity and less severe OSA compared to other studies [26].

Furthermore, in 9 obese patients with severe OSA (mean AHI of 43.1 events per hour, ESS of 11.4), obese (mean BMI 37.3 \pm 5.6 kg/m²) and diabetic on oral antidiabetic or on diet alone with good

Table 1
Studies assessing the effect of CPAP on HbA1c.

Author	Sample size (number of patients)	Mean age (years)	Mean BMI (kg/m ²)	Mean AHI events per hour	CPAP use (h/night)	CPAP use duration	HbA1c changes	Results
Brooks et al. [29]	10	50.8 \pm 9.6	42.7 \pm 4.3	47 \pm 31.6	Not available	4 months	No significant change	Improved insulin responsiveness
Harsch et al. [27]	9	56.3 \pm 8.2	37.3 \pm 5.6	43 \pm 21	5.8 \pm 1.2	3 months	No significant change	Improved insulin responsiveness
Hassaballa et al. [23]	38	53 \pm 10	42.9 \pm 9.5	53 \pm 36	4 \pm 3	4 months	Significant decrease	Improved post meal glucose
Babu et al. [24]	25	50.7 \pm 9	42.7 \pm 8.7	56 \pm 37	4.2 \pm 2.9	3 months	Significant decrease only when HbA1c > 7 and high compliance	
West et al. [25]	42	57.8 \pm 10.4	36.6 \pm 4.9	33 \pm 21.6	3.6 \pm 2.8	3 months	No significant change	No significant improvement in insulin resistance
Dawson et al. [28]	20	59.8 \pm 10.2	39.6 \pm 8	63 \pm 30	5.8 \pm 1	1 month	No significant change	Less nocturnal glucose variability
Comondore et al. [26]	13	55.5 \pm 7.07	31.1	27.9	5.53	1 month	No significant change	Improved cardiovascular markers

glycemic control (HbA1c = $6.4 \pm 0.7\%$), after CPAP use for 5.8 h per night for 3 months, there was no significant change in HbA1c despite an improvement in insulin sensitivity. In fact, the effect of CPAP on insulin sensitivity is not necessarily associated with a reduction of serum HbA1c [27].

Dawson et al. in a group of 20 patients, newly diagnosed with OSA (AHI of 63 events per hour), diabetic, obese (mean BMI 39.6 kg/m^2), assessed the effect of CPAP on glycemic control, when applied for 41 days, for 5.8 h per day. No significant change in HbA1c was detected, probably related to the short duration of CPAP therapy which was not enough to allow changes in HbA1c [28].

In addition, Brooks et al., in a subgroup analysis of 10 patients (7 males and 3 females) with moderate to severe sleep apnea (mean AHI 47 events per hour) and uncontrolled DM (HbA1c > 7%) found no significant change in HbA1c after 4 months of CPAP treatment in a study to investigate the effect of OSA treatment with nasal CPAP, although a significant improvement in insulin responsiveness was detected. The authors concluded that the increase in insulin responsiveness was modest in the context of severe insulin resistance and morbid obesity precluding any benefit on the metabolic profile [29].

When comparing these studies, we can conclude that OSA patients may improve HbA1c after CPAP use, only if applied for 4 h or more during sleep, for at least 3 months, enough duration to detect changes in glycosylated hemoglobin.

4. CPAP and nocturnal glucose level

CPAP therapy, while decreasing upper airway obstruction, improving oxygen saturation and decreasing arousals, can improve nocturnal glucose; this has been explored in two studies.

In the first study, in order to assess short-term changes in glycemic control during sleep while using CPAP, continuous glucose-monitoring system to measure interstitial glucose every 5 min during polysomnography (using a sensor that was inserted subcutaneously in the lower abdomen) was used. Twenty patients with type 2 diabetes and newly diagnosed OSA (AHI > 15 events per hour) were studied, initially without CPAP and repeated measurements were done after an average of 1.5 months of CPAP, applied for at least 4 h per night. The mean sleeping glucose decreased significantly before ($122 \pm 61.7 \text{ mg/dl}$) and after CPAP ($102.9 \pm 39.4 \text{ mg/dl}$). Furthermore, the sleeping glucose level was more stable, with a significant decrease in the mean difference between maximum and minimum values [28].

Similarly, in the second study, CPAP was applied to 14 diabetic, OSA men in order to assess CPAP effect on nocturnal glucose. Nocturnal glucose monitoring (for 150.5 h/patient) while on CPAP showed significant reduction and less variability as compared to nocturnal glucose readings without CPAP [30].

5. CPAP effect on glucose metabolism and insulin sensitivity

Studies assessing the effect of CPAP on insulin sensitivity showed conflicting results.

Brooks et al., in his small study, found a significant improvement in insulin responsiveness – also measured by hyperinsulinemic euglycemic – during CPAP treatment. However, the study had many limitations. Patients had different treatment modes for diabetes including insulin, oral antidiabetic drugs or diet alone, without sufficient glycemic control. There was no information about changes in lifestyle during the treatment period (e.g. sports, alcohol, and nicotine consumption), concomitant diseases such as hypertension, the duration of diabetes and the presence or absence of autonomous diabetic neuropathy [29].

In a population based study, complete 3-week data were obtained from 28 treated men with CPAP (of whom 5 patients were diabetic, age of 64 years, BMI 29.4 kg/m^2 , ESS = 8.4) and 28 controls (of whom 8 were diabetic, age of 65 years, BMI 26.9 kg/m^2 , ESS = 6). Compared with controls, the CPAP group displayed a greater reduction of fasting serum insulin ($P=0.02$) and a significant decrease in insulin resistance ($P=0.01$), partly due to an increase in serum insulin and HOMA-IR in the control group but there was no significant changes in fasting blood glucose or HbA1c [31].

In the only double-blind randomized controlled trial of therapeutic and placebo CPAP for 3 months in men, West et al. has not shown any significant improvement in insulin resistance measured by euglycaemic clamp and HOMA. To note that the mean use of CPAP was less than 4 h per night and this has been suggested to be responsible of the negative results of the study [25].

In another study of 25 middle-aged patients, obese with uncontrolled diabetes, who had concomitant OSA, subgroup analysis demonstrated significant postmeal glucose reduction for all 3 mealtimes in subjects using CPAP greater than 4 h per day. In patients using CPAP for a shorter duration, postmeal glucose decreased significantly only after the breakfast time. This shows again that the duration of CPAP use significantly affects results [24].

Conversely, Harsch et al. did not detect early but late improvement in insulin sensitivity, after 3 months of CPAP use, for a mean of 5 h per night, mostly in patients with lower BMI compared to more obese patients [27].

The various results of these studies can be related to the small number of patients, which sometimes may not be enough to allow a statistical significance. Also, many confounding factors including BMI, fat distribution, smoking and medications can interfere with the results since they can change during the study period.

6. CPAP and prevention of diabetes

In an observational cohort study, after a follow up of 2.7 years, incident diabetes was significantly more common in the OSA patients group compared to control. These findings persisted even after adjustment for possible confounding factors that were more common in the OSA group including older age, higher BMI, higher baseline fasting glucose (adjusted HR per quartile 1.43; 95% CI, 1.10–1.86; $P=0.008$). Importantly, among patients with moderate to severe sleep apnea, compliance with regular CPAP use increased, and this treatment was independently associated with a significantly attenuated risk of incident diabetes [32].

7. Conclusion

OSA and diabetes are tightly associated [10–12], given the presence of many shared risk factors [33], including obesity, hypertension, disorders of metabolism [34] and common complications, specially cardiovascular [35,36]. The impact of OSA treatment with CPAP on diabetes has been evaluated in many studies, but results were conflicting. These findings can be related to differences in sample size, treatment duration, population recruited, adherence to CPAP and the primary endpoints assessed. Additionally, diet and lifestyle changes that could be interfering with the results were not always mentioned. Randomized controlled trials are recommended to allow objective and definite conclusions after adjustment for all variables that might affect outcome.

Conflict of interest

The authors declare that they have no conflict of interest.

References

- [1] Guilleminault C, Tilkian A, Dement W. The sleep apnea syndromes. *Annual Review of Medicine* 1976;27:465–84.
- [2] Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *American Journal of Respiratory and Critical Care Medicine* 2002;165:1217–39.
- [3] Strohl K, Redline S. Recognition of obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine* 1996;154:279–89.
- [4] Young T, Shahar E, Nieto FJ. Predictors of sleep disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Archives of Internal Medicine* 2002;162:893–900.
- [5] Malhotra A, Ayas NT, Epstein LJ. The art and science of continuous positive airway pressure therapy in obstructive sleep apnea. *Current Opinion in Pulmonary Medicine* 2000;6:490–5.
- [6] Engelgau MM, Geiss LS, Saaddine JB. The evolving diabetes burden in the United States. *Annals of Internal Medicine* 2004;140:945–50.
- [7] Harris MI, Flegal KM, Cowie CC. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 1998;21:518–24.
- [8] Mokdad A, Ford E, Bowman B. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003;289(1):76–9.
- [9] Mykkanen L, Laakso M, Uusitupa M. Prevalence of diabetes and impaired glucose tolerance in elderly subjects and their association with obesity and family history of diabetes. *Diabetes Care* 1990;13:1099–105.
- [10] Meslier N, Gagnadoux F, Giraud P, Person C, Oukel H, Urban T, et al. Impaired glucose–insulin metabolism in males with obstructive sleep apnoea syndrome. *European Respiratory Journal* 2003;22:156–60.
- [11] Elmasry A, Lindberg E, Berne C. Sleep-disordered breathing and glucose metabolism in hypertensive men: a population-based study. *Journal of Internal Medicine* 2001;249:153–61.
- [12] West S, Nicoll D, Stradling J. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax* 2006;61:945–50.
- [13] Tasali E, Mokhlesi B, Van Cauter E. Obstructive sleep apnea and type 2 diabetes interacting epidemics. *Chest* 2008;133:496–506.
- [14] Luenberger U, Jacob E, Sweer L. Surges of muscle sympathetic nerve activity during obstructive apnea are linked to hypoxemia. *Journal of Applied Physiology* 1995;79:581–8.
- [15] Smith ML, Niedermaier ON, Hardy SM. Role of hypoxemia in sleep apnea-induced sympathoexcitation. *Journal of the Autonomic Nervous System* 1996;56:184–90.
- [16] Punjabi N, Polotsky V. Disorders of glucose metabolism in sleep apnea. *Journal of Applied Physiology* 2005;99:1998–2007.
- [17] Follenius M, Brandenberger G, Badesapt JJ. Nocturnal cortisol release in relation to sleep structure. *Sleep* 1992;15(1):21–7.
- [18] Spath-Swalbe E, Geofferje M, kern W, Bern J, Fehm HL. Sleep disruption alters nocturnal ACTH and cortisol secretory patterns. *Biological Psychiatry* 1991;29:575–84.
- [19] Pickup JC, Chusney GD, Thomas SM, Burt D. Plasma interleukin-6, tumour necrosis factor α and blood cytokine production in type 2 diabetes. *Life Sciences* 2000;67:291–300.
- [20] Mondini S, Guilleminault C. Abnormal breathing patterns during sleep in diabetes. *Annals of Neurology* 1985;17:391–5.
- [21] Ziegler M, Mills P, Lored J. Effect of continuous positive airway pressure and placebo treatment on sympathetic nervous activity in patients with obstructive sleep apnea. *Chest* 2001;120:887–93.
- [22] Coy TV, Dimsdale JE, Ancoli-Israel S, Clausen J. Sleep apnoea and sympathetic nervous system activity: a review. *Journal of Sleep Research* 1996;5:42–50.
- [23] Hassaballa H, Tulaimat A, Herdegen J, Mokhlesi B. The effect of continuous positive airway pressure on glucose control in diabetic patients with severe obstructive sleep apnea. *Sleep & Breathing* 2005;9:176–80.
- [24] Babu A, Herdegen J, Fogelfeld L, Shott S, Mazzone T. Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. *Archives of Internal Medicine* 2005;165:447–52.
- [25] West S, Nicoll D, Wallace T, Matthews D, Stradling J. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. *Thorax* 2007;62:969–74.
- [26] Comondore V, Cheema R, Fox J. The impact of CPAP on cardiovascular biomarkers in minimally symptomatic patients with obstructive sleep apnea: a pilot feasibility randomized crossover trial. *Lung* 2009;187:17–22.
- [27] Harsch I, Schahin SP, Brückner K. The effect of continuous positive airway pressure treatment on insulin sensitivity in patients with obstructive sleep apnoea syndrome and type 2 diabetes. *Respiration* 2004;71:252–9.
- [28] Dawson A, Abel SL, Loving RT, Dailey G, Shadan FF, Cronin JW, et al. CPAP therapy of obstructive sleep apnea in type 2 diabetics improves glycemic control during sleep. *Journal of Clinical Sleep Medicine (JCSM) Official Publication of the American Academy of Sleep Medicine* 2008;4:538–42.
- [29] Brooks B, Cistulli P, Borkman M. Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: effect of continuous positive airway pressure treatment on insulin responsiveness. *JCEM* 1994;79:1681–5.
- [30] Pallayova M, Donic V, Tomori Z. Beneficial effects of severe sleep apnea therapy on nocturnal glucose control in persons with type 2 diabetes mellitus. *Diabetes Research and Clinical Practice* 2008;81:e8–11.
- [31] Lindberg E, Berne C, Elmasry A, Hedner J, Janson C. CPAP treatment of a population-based sample—what are the benefits and the treatment compliance? *Sleep Medicine* 2006;7:553–60.
- [32] Botros N, Concato J, Mohsenin V. Obstructive sleep apnea as a risk factor for type 2 diabetes. *American Journal of Medicine* 2009;122:1122–7.
- [33] Boyer S, Kapur V. Obstructive sleep apnea: its relevance in the care of diabetic patients. *Clinical Diabetes* 2002;20:126–32.
- [34] Strohl KP. Diabetes and sleep apnea. *Sleep* 1996;19(Suppl. 10):S225–8.
- [35] Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea–hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046–53.
- [36] Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *New England Journal of Medicine* 2005;353:2034–41.