

Obstructive Sleep Apnea and Diabetes

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Published Date: November 05, 2016

ABSTRACT

Obstructive sleep apnea is a spectrum of sleep disorders, which is caused by increased airway resistance during sleep, or structural abnormality of the upper airway. It is closely linked to obesity and metabolic syndrome, and may be linked to non-insulin dependent diabetes. Periods of intermittent nocturnal hypoxia may cause increased insulin resistance and glucose intolerance. The presence of diabetic neuropathy may also predispose individuals to obstructive sleep apnea through incomplete paralysis of the respiratory muscles. Though continuous positive airway pressure has demonstrated to aid in reducing the risk of obstructive sleep apnea that may lead to non-insulin dependent diabetes, the reduction of obesity is an optimal way to combat the impact of both these diseases affecting an individual's quality of life.

Keywords: Obstructive Sleep Apnea, Diabetes, CPAP, Metabolic syndrome & OSA, OSA and Diabetes

Running Head: Obstructive Sleep Apnea and Diabetes

INTRODUCTION

Obstructive sleep apnea (**OSA**) and non-insulin dependent diabetes are very prevalent diseases in the general population [1]. They both affect patient's quality of life, and the increasing worldwide burden of these two diseases has led to a significant contribution of health-related spending [2]. Because obesity is the leading cause attributable to these diseases' incidence and severity, and the aforementioned two conditions are often found together in the obese individuals [3]. However, it is not uncommon for individuals to share these two diagnoses independent of diabetes [3-6], with prevalence of diabetes being as high as 15-30% of all patient with OSA [3,4]. In this chapter we will discuss the relationship between OSA and diabetes as well as the risk factors OSA creates for diabetes, and vice versa.

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (**OSA**) is described as a spectrum of sleep disorders which range in severity from increases airway resistance to partial airway collapse during sleep [2]. The disease falls under the umbrella term of sleep disordered breathing (**SDB**) [2]. This spectrum of disorders is categorized based on apnea-hypopnea index (**AHI**), which is the number of average apnea and hypopnea events in one hour (total apneic and hypopneic events divided by hours slept) [7]. Five or more events per hour is considered diagnostic for obstructive sleep apnea [7]. An AHI between 5-14/hour is considered mild sleep apnea, between 15-29 events/hour is considered moderate sleep apnea, and 30 events/hour or more is considered severe sleep apnea [7].

Due to increased airway resistance caused by airway obstruction leads these patients suffer from periods of apnea or hypopnea during sleep, which in turn can lead to increase day-time sleepiness and cardiovascular mortality [2]. Obstructive sleep apnea can cause an increase in sleepiness due to sleep fragmentation during night, leading to decreased productivity, impairment in quality of life, as well as risk of automobile crashes and work related accidental injuries [8]. This syndrome has been historically associated with the obesity, and the term "Pickwickian syndrome", which was inspired from the character Joe from Charles Dicken's novel The Pickwick Papers, was used to refer to the association between obesity and chronic hypoventilation in the 19th century [9].

Despite the historical use of this term, obstructive sleep apnea was not properly identified until the polygraph sleep studies advent in the 1960's, which revealed the existence of recurring apnea during sleep [10]. Although it was typically related to obesity, further sleep studies demonstrated that sleep apnea can also be found among non-obese individuals [11], as well as in individuals with retrognathia, micrognathia, high arched palate, Cushing syndrome and acromegaly patients. Back in 1981, Sullivan and colleagues described five patients with obstructive sleep apnea and their successful treatment with continuous positive airway pressure (**CPAP**), which helped prevent these apneic events during sleep and paved the path for future endeavors in the treatment of OSA [10].

In 1993, Young et al published a study that identified the burden this disease had on general population. He described the disorder as a spectrum of disease, where the increase airway resistance can cause the obstruction or even by an overt partial airway collapse [2]. The study estimated that 2% of women and 4% of men between the ages of 30 to 60 met the minimal diagnostic criteria for obstructive sleep apnea, and also stated that male sex and obesity were strongly associated with obstructive sleep apnea [2]. OSA has been associated with an increased risk of overall mortality, with a prospective study published in 2009 with a hazard ratio of 2.09 [12].

Several studies were published in the year 2000, which linked obstructive sleep apnea as an independent risk factor for hypertension [13-16]. However, the relationship between OSA and diabetes is complex and requires a sound understanding of multiple pathophysiological processes.

DIABETES AND OBESITY

Diabetes is one of the most prevalent chronic degenerative diseases in humans affecting the worldwide population and adds significant burden to the current healthcare spending. In 2014, 21 million patients were affected with diabetes in the United States, accounting for 6.7% of the population, with an additional estimate of 8.1 million individuals with undiagnosed diabetes which, when combined could account for 9.3% of the population [1]. 1.4 million new individuals are diagnosed every year with diabetes, and if growth continues at this rate then diabetes incidence would increase to 18 million new cases by the year 2050 [17]. Diabetes is closely related to obesity, and both of these diseases are part of the metabolic syndrome (central obesity, hypertension, hypercholesterolemia and insulin resistance) [18]. Obesity is estimated to cause approximately 60% of all cases of diabetes [19].

The prevalence of obesity in the US in 2013-2014 was 35% among men and 40.4% among women [20]. The overall prevalence of male obesity has remained stable since 1999, but obesity in the female population has increased from 35.5% in 2007-2008 [21]. Because of this increase in female obesity, overall obesity has increased from 30.4% to 37.7% between the years 1999 and 2014 [22-24].

The prevalence of patients with both obesity and diabetes among US population can be as high as 2.9% and obesity is considered an important risk factor in both OSA and diabetes [25]. The severity of obesity, particularly central obesity [26-28], correlates well with severity of OSA [26,29-35]. Due to obesity being importance risk factor for both diabetes and OSA, it is very common to find the presence of all three disease conditions in one patient [3,36]. Two studies by Hermans et al with large body of participants found that diabetic patients with OSA had higher cardiovascular co-morbidity, altered β -cell function, poorer glycemic control, and hypertension when compared to the diabetic individuals without OSA [37,38]. Another study found that 23% of patients with OSA had diabetes, although after correcting for BMI, only 8% of the patients with OSA were correlated with diabetes directly [39]. Another study found numbers as high as 30.3%

with type 2 diabetics in OSA patients [4]. Several studies have also linked the presence of OSA as a risk factor to diabetes [40-42]. One large study in 2009 by Botros, et al studied 1,233 patients and concluded that sleep apnea was a risk factor for diabetes, independent of other risk factors [40].

Studies that have controlled for obesity have shown an important association between type-2 diabetes and OSA [4,43,44]. Studies have shown that recurrent hypoxia, as found in patients with the OSA (and daytimes sleepiness), may be related to increased insulin resistance and may possibly be an independent risk factor for diabetes [45-50]. Aronsohn et al, in a 2010 study, found that, when controlled for other factors, the severity of OSA was related with increased HbA1C levels in diabetic patients when compared to patients without OSA [51].

Studies have shown that patients with diabetes, as well as patients with metabolic syndrome, have a higher prevalence of habitual snoring and obstructive sleep apnea [4-6]. The association of this relation led the International Diabetes Federation to recommend screening of all patients with diabetes for possible OSA, in an effort to reduce the severity of metabolic changes and cardiovascular mortality in patients with combined OSA and diabetes [52]. Several screening tools have been proposed, such as the STOP-BANG and Berlin questionnaires and NAMES, which hold a high sensitivity and specificity [53-56].

Increase in the severity of sleep apnea and oxygen desaturation have been associated with an increase in insulin resistance [6]. However, while the prevalence of diabetes in patients with OSA is high, the causal relationship between diabetes and OSA is not clearly understood, but many theories have been proposed on interaction between these two disorders as shown in Figure 1.

Obstructive Sleep Apnea and Diabetes

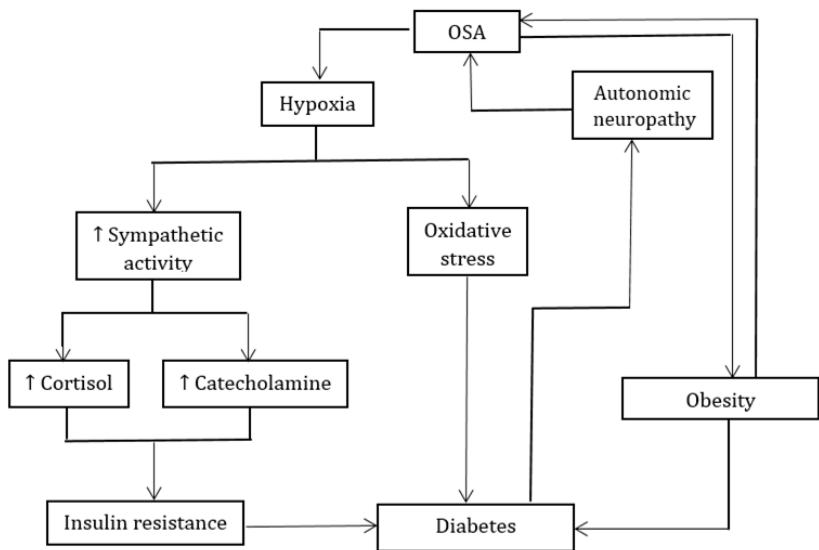


Figure 1: Illustrates de relationship between obstructive sleep apnea and diabetes.

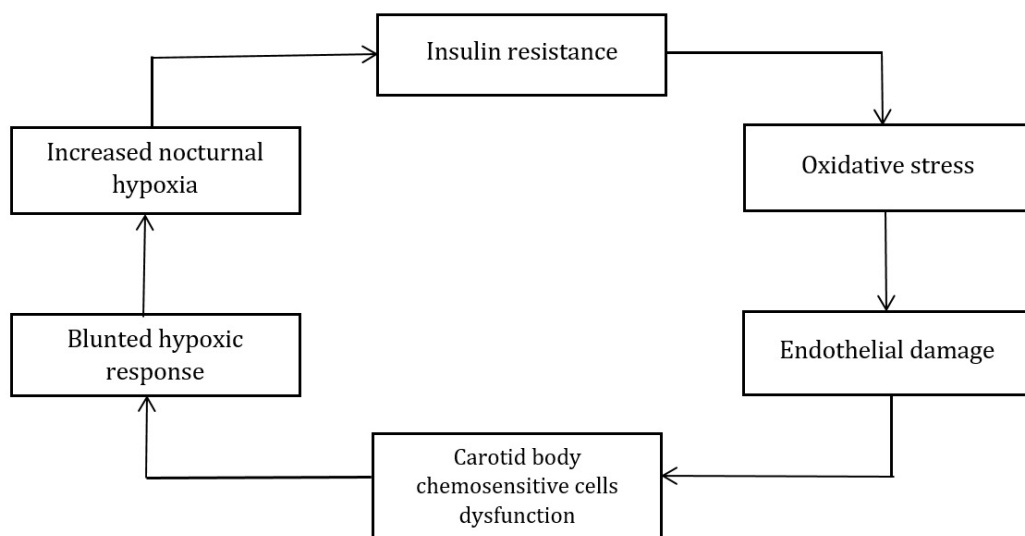


Figure 2: Illustrates the cause and effect diabetes and obstructive sleep apnea have on carotid body dysfunction.

DIABETIC NEUROPATHY AS A RISK FACTOR FOR SLEEP APNEA

One of the possible links between diabetes and OSA may be due to the development of both central and peripheral neuropathy as a consequence of uncontrolled diabetes [57-60]. This type of neuropathy can be seen in as much as 20 – 30% of diabetic patients and is believed to be a possible cause of sleep disordered breathing [57-60] as well as a factor that increases risk of cardiorespiratory events [61, 62]. Diabetic patients with neuropathy were shown to have a higher prevalence of OSA, when compared with diabetics without neuropathy, independent of obesity [4,43,44]. Another study found that diabetic individuals with neuropathy have higher prevalence of apnea and hypopnea during sleep despite normal breathing patterns during waking hours [44].

Autonomic neuropathy caused by diabetes may predispose an individual to hypoxemic states through poor pharyngeal muscles tone, which may facilitate airway collapse. Somatic neuropathy could interact with the diaphragm and accessory respiratory muscles. This can lead to difficulty in generating the negative airway pressure for proper ventilation, as seen in with patients with Charcot-Marie-Tooth disease and related neuropathy [63-65]. Alterations of the hypoglossal nerve (XII), whether through stroke, denervation, or neuropathy, have been associated with weak pharyngeal muscle tone; similar alterations in the Vagus (X) nerve, which is the link between the diaphragm and autonomous nervous system as well as role in chemoreceptors, have been seen in patients with sleep related breathing disorder [66,67].

Neuropathy is a very common complication of long-standing diabetes. However, strict glucose management in patients has shown to reduce the risk of complications from diabetes. With proper glycemic control, diabetic neuropathy can be prevented in patients with long-standing diabetes [68], and may reduce their risk of developing OSA as a consequence.

ENDOTHELIAL INJURY, CAROTID BODY CELLS, AND HYPOXIC RESPONSE

Diabetes also predisposes to OSA by causing endothelial damage in the carotid body. The carotid body is home to chemosensitive glomus cells, which helps in regulating body's reaction to hypoxia [69,70], and damage to these cells could alter the body's natural response to hypoxia during the apneic portions of sleep related breathing disorder [70]. Studies in mice have shown that denervation of the carotid body leads to a blunted response to hypoxia [71].

This lack of hypoxic response may lead to prolonged hypoxiemia as well as extend the duration of already present hypopneic events. This increase in hypoxemia is strongly related to an increase in insulin resistance, and will be discussed later in the chapter. Figure 2 depicts the cycle of effects of OSA and diabetes and their mechanisms.

To further complicate this relationship, glomus cells in the carotid body have also been found to detect blood glucose levels through a similar mechanism by which blood oxygen levels are sensed [70,72]. In turn, a blunted response by this glucose-sensing mechanism may lead to prolonged glycemic variations, as well as prolonged hypoglycemia and prevents a proper reaction to hyperglycemia. This glycemic variability is related to increased oxidative stress [73], which is related to increased insulin resistance, and worse outcomes among diabetic patients [74].

There is limited evidence that shows that individuals with no diabetes also have a limited response to hypoxia and hypercapnia [75-77]. One study postulated this may be due to an altered dopaminergic pathway in the carotid body [76]. However, other studies have also surfaced, placing this concept into question [78]. Rasche and co-workers have suggested the presence of both OSA and diabetes may overbear the responses of both hypoxia and altered glycemic status in the carotid body, leading to a limitation of signal response resources, reducing the reaction capacity that these mechanisms may offer [79].

INTERMITTENT HYPOXIA AS A RISK FACTOR FOR DIABETES

The disturbances in sleep by OSA can lead to sleep deprivation, which has been associated with metabolic alteration, such as increased insulin resistance and increased cortisol level, both of which can predispose patients to diabetes [80-82]. Habitual snoring was also found to be associated with elevated HbA1C levels, independent of obesity [83]. One prospective study, published in 2002, studied 69,852 healthy female nurses in the US and showed the prevalence of diabetes to be higher in this group after 10 years, in relation to their snoring patterns [84]. The study found that regular snoring was a risk factor to diabetes, and identified a relative risk of

2.03, when adjusted for other risk factors [84]. However, it is believed that the main physiological mechanism through which OSA predisposes diabetes is through intermittent nocturnal hypoxia [45].

Several studies aiming to closely associate intermittent nocturnal hypoxia with diabetes have been undertaken to clarify this connection [45-50,85,86]. Studies in mice revealed that intermittent hypoxia lead to increased insulin resistance [87,88], as well as impairing beta cell function in the pancreas [88-90] and increased hepatic output of glucose [88]. Studies in altitude related hypoxia with humans showed increased insulin resistance and glucose intolerance that stabilizes after a few days at the higher altitude and as person becomes accustomed to decreased oxygenation [48]. However, studies in rats suggested that reversal of the hypoxic exposure does not fully reverse the affected changes on glucose metabolism [88].

Further studies in humans have also shown that intermittent hypoxia causes an increase in insulin resistance and glucose intolerance [41,86]. The Sleep Heart Health Study in 2004 found that that patients with 5 or more apneic or hypopnea events per hours of sleep were associated with glucose intolerance and insulin resistance [41]. The study included 2,656 patients and is one of the largest studies on the topic; it expressed that sleep-related hypoxemia found in those patients might be a risk factor for type 2-diabetes [41]. A recent study in 2015 showed that patients with intermittent hypoxia had higher median levels of HbA1C than those without, and was related to worse glycemic control even when controlled for other factors [91].

Intermittent hypoxia and improper sleep has also been associated with increased sympathetic activity [92,93], which increases catecholamine levels that can lead to impaired insulin resistance and glucose intolerance [94,95]. This sympathetic activation of catecholamines causes increased glucose output by the liver due to gluconeogenesis and fragmentation of stored glycogen [96]. Intermittent hypoxia has also been associated with alterations in the hypothalamus-pituitary-adrenal axis. High sympathetic discharges, intermittent hypoxia and sleep fragmentation are commonly seen in patients with OSA and these acute adrenergic response can lead to increased levels of cortisol in blood [42, 97,98], which is associated with a pro-hyperglycemic state and reduced insulin sensitivity [99-101]. This can worsen glycemic control among diabetic patient and predispose a non-diabetic patient to type 2- diabetes. It has also been shown that even as little as two nights of sleep deprivation can lead to this neuroendocrine misbalance that can predispose a person to diabetes [102].

OSA patients with intermittent nocturnal hypoxia have shown to cause an increase in levels of inflammatory cytokines, such as IL-6 and TNF- α , with the increase of these cytokines correlating with severity of OSA [103]. This increase of inflammatory cytokines has also been related to increased insulin resistance [104] as well as over-all cardiovascular mortality [103]. This very same pro-inflammatory state predisposes to oxidative stress and may be related to alteration of chemosensitive cells in the carotid body, as discussed previously, although evidence is limited [105,106].

BENEFITS OF CPAP IN DIABETES

The benefits of CPAP in patients with OSA have been clearly established, with CPAP being considered the most effective practical therapy in the management of patients with OSA [107-111]. Taking into account the theoretical benefits of CPAP treatment in the reduction of intermittent hypoxia during sleep, several studies have been performed to evaluate the beneficial effects which CPAP therapy may hold on patients with both OSA and diabetes [40,112-148]. Of the studies performed, the majority of studies seem to agree that CPAP therapy may have benefit by reducing the insulin resistance [113-125] as well as reducing nocturnal hyperglycemia [123,125]. Some studies have shown long term benefits in HbA1C levels with CPAP treatment in patients with both OSA and diabetes [40,116,124,127], and may reduce the risk of diabetes among non-diabetic OSA patients [40,124]. The benefit may even be extended in patients with less severe sleep-disordered breathing, as a study in 1994 revealed that in diabetic patients with heavy snoring and daytime sleepiness that have received treatment with CPAP not only improved symptoms of SDB, but also increased insulin sensitivity [112]. CPAP treatment has also showed benefits in reducing systemic inflammation and oxidative stress, which would reduce endothelial damage and overall cardiovascular risk [122]. The benefit of CPAP treatment can even be seen in as little as two days [149]. Table 1 summarizes the different clinical trials performed on the effects of CPAP on OSA and diabetes.

Table 1: Effect of continuous positive airway pressure on blood glucose control. Modified with permission from Surani et al in the paper “Effect of continuous positive airway pressure therapy on glucose control” published in *World Journal of Diabetes* in April 15, 2012.

Study	Study Design/ Cohort	Sample Size	Control Group	Outcome/Measurements	Study Duration	Conclusions	+/-
Stoohset al[129]	OSA patients	5	None	Fasting glucose and insulin	2 months	No change in either fasting or nocturnal insulin level. Increase in nocturnal and fasting glucose	—
Saini et al[130]	OSA patients BMI 32.7 ± 2.3 Kg/m2	8	None	Glucose and insulin every 10 min interval during sleep	1 night	Mean insulin and glucose did not differ between pre-treatment and treatment night	-
Davies et al[131]	OSA patients	10	Matched control	Fasting insulin, lipid profile	3 months	No change in insulin level with CPAP	-
Dorkova et al[122]	OSA patients with metabolic syndrome	32	None	HOMA-IR	8 weeks	Reduction of HOMA-IR	+
Cooper et al[113]	OSA patients	6	None	Insulin and c-peptide sample every hour and glucose sample every 30 min during sleep	1 night	No changes in glucose, insulin and C-peptide with CPAP treatment	-
Saarelainen et al[114]	OSA patients	7	None	Hyperinsulinemic euglycemic clamp	3 months	No change in insulin responsiveness	—

Pierzchala <i>et al</i> [132] (article in Polish)	Type 1 and type 2 diabetes patients with OSA	30	None	Blood glucose	6 months	Better blood glucose control	+
Chin <i>et al</i> [133]	OSA patients	22	OSA patients	Oral glucose tolerance test with insulin measurement	6 months	No change in glucose and insulin level except in patients who have lost weight	—
Ipet <i>et al</i> [134]	OSA patients	30	Matched 30 non-OSA control	Fasting glucose and insulin	6 months	No change in fasting glucose and insulin seen (decrease in Leptin and triglyceride was seen)	—
Smurra <i>et al</i> [135]	16 OSA patients; 10 from endocrine clinic and 6 other OSA patients	16	None	Oral glucose tolerance test in 10 patients and hyperinsulinemic euglycemic clamp in 6 patients	2 months	No change in mean glycemia, insulin level or insulin responsiveness was seen	—
Harschet <i>et al</i> [115]	OSA patients	40	None	Hyperinsulinemic euglycemic clamp	3 months	Improvement in insulin sensitivity at day 2 and 3 mo, in patient with BMI < 30, than in patients with BMI > 30	+
Harschet <i>et al</i> [145]	Type 2 diabetes patients with OSA	9	None	Hyperinsulinemic euglycemic clamp	3 months	Insulin sensitivity was unchanged after 2 days, but significantly improved after 3 mo; glycemic control was unaffected after 3 mo	+/-
Babuet <i>et al</i> [118]	Type 2 diabetes patients with OSA	25	None	HBA1c and post prandial blood glucose	3 months	Decrease in HBA1c and postprandial am glucose level	+
Czupryniak <i>et al</i> [117]	Non diabetic OSA patients	9	None	Continuous glucose monitoring, plasma insulin, HOMA-IR	1 night	Mean blood glucose, fasting insulin and HOMA-IR were significantly higher with CPAP treatment	-
Hassaballa <i>et al</i> [116]	Type 2 diabetes and OSA (retrospective)	38	None	HBA1c	Approx. 3 months	Decrease in HBA1c was seen with CPAP therapy	+
Lindberg <i>et al</i> [136]	OSA patients	28	Matched control without OSA	HOMA and fasting insulin	6 months	Decrease in insulin resistance and fasting insulin	+
West <i>et al</i> [121]	Type 2 diabetes and OSA	42	Randomized, double blind	HOMA, hyperinsulinemic euglycemic clamp, HBA1c, highly sensitive C-reactive protein	3 months	No change in glycemic control or insulin resistance	—
Coughlin <i>et al</i> [120]	OSA patients	34	Randomized placebo-controlled blinded crossover trial	Insulin, fasting glucose, HOMA-IR	6 weeks	No change in glucose or insulin resistance	—
Pallayova <i>et al</i> [123]	Type 2 diabetes with OSA	14	None	Continuous glucose monitoring	Several days	Reduction in nocturnal glucose variability and improved overnight glucose control	+
Wang <i>et al</i> [137]	Type 2 diabetes and OSA	30	None	HOMA	7 days	Improve ISI	+

Dawson <i>et al</i> [125]	Type 2 diabetes with OSA	20	None	Continuous glucose monitoring	Average 41 dayd (26-96 days)	Decrease in sleeping blood glucose seen	+
Steiropoulos <i>et al</i> [138]	Diabetes with OSA	56	None	HBA1c, fasting glucose, insulin level, HOMA-IR	6 months	Only patients with CPAP use > 4 h/night showed decrease in HBA1c	+/-
Wei <i>et al</i> [139]	OSA patients	11	None	Fasting blood glucose, plasma insulin, HOMA-IR	4 days	Decrease in blood glucose and increase in insulin sensitivity seen	+
Oktay <i>et al</i> [140]	OSA and metabolic syndrome	20	None	Fasting blood glucose	1 year	No difference in blood glucose seen	–
Lam <i>et al</i> [141]	OSA patients	61 (30 control and 31 study group)	Sham CPAP	Short insulin tolerance test	12 weeks	Improvement in insulin sensitivity seen only in subjects with BMI ≥ 25	+/-
Garcia <i>et al</i> [142]	Obese OSA patients	20	None	OGTT, insulin level, Gherlin, adiponectin, leptin	6 months	Increase insulin and IR; gherlin decrease, whereas leptin and adiponectin remains unchanged	-
Shpirer <i>et al</i> [143]	OSA patients	30	None	HBA1c	3-5 months	Decrease in HBA1c in severe OSA patients	+
Brooks <i>et al</i> [112]	Obese diabetics with heavy snoring or excessive sleepiness	10	12	Glucose disposal as measurement by hyperinsulinemic euglycemic clamps.	4 months	Improved insulin responsiveness	+
Trenel <i>et al</i> [119]	Obese OSA patients	29	none	Abdominal adipose tissue, HOMA-IR, fasting venous and arterial blood.	12 weeks	Visceral adipose tissue volume was reduced with regular, but not irregular CPAP use. No change in insulin sensitivity scores	-
Schahin <i>et al</i> [124]	OSA patients	16	none	Mean insulin sensitivity index	Mean 2.9 years (963 ± 98 days)	Mean insulin sensitivity index was higher than baseline with regular and effective use	+
Guo <i>et al</i> [144]	Diabetic OSA patients	40	none	Continuous glucose monitoring system, HOMA-IR, HbA1c	30 days	Reduced 24h and night time mean blood glucose, reduced glycemic variability, reduced nighttime hyperglycemia, reduced HbA1c, lower HOMA-IR	+
Vgontzas <i>et al</i> [128]	Obese OSA patients	16	13 non-apneic obese controls, 15 non-obese controls	Fasting blood glucose and insulin.	3 months	Did not affect fasting glucose or insulin	-
Weinstock <i>et al</i> [147]	Patients with sleep apnea and glucose intolerance	50	Randomized to sham CPAP	Oral glucose tolerance test and measurements of indices of glucose control.	8 weeks	Insulin sensitivity improved in patients with severe OSA, but not moderate sleep apnea.	+
Cuhadaroglu <i>et al</i> [148]	Patients with OSA	31 patients	none	HOMA-IR, HOMA-S, and HOMA-beta	8 weeks	Lowered insulin resistance and higher insulin secretion.	+

Salordet <i>al</i> [146]	Obese OSA patients	42	38	HOMA-IRF, glucose tolereance	12 weeks	Impaired glucose tolerance reversed in 9 patients and developed in none in CPAP group compared to reversal of impaired glucose tolerance in 5 and development in 5 in non CPAP group.	+
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Five meta-analysis on the subject concluded that there was a reduction of insulin resistance that could benefit diabetic patients with OSA [150-154], although two of those studies revealed no benefit in HbA1C levels or BMI [150,151]. Another analysis concluded that with long-term use of CPAP, the benefits on glucose metabolism can help prevent diabetes in patients with OSA [127]. Another study found an increase in HbA1C levels in untreated OSA, correlated to disease severity [51].

On the contrary, another study concluded that the use of CPAP in patients with abnormal apnea-hypopnea index but no daytime sleepiness showed no benefit [50]. Some other studies similarly concluded that CPAP offers no benefits in glycemic control and insulin resistance [121,126,128]. As far as non-diabetic OSA patients are concerned, a study in 2005 found that CPAP treatment in non-diabetic obese patients may increase glucose levels throughout the night, generating more controversy to this challenging area [117].

A few more studies suggested that, while there exists theoretical value in CPAP treatment towards glycemic control, it may not hold any importance in real-world glycemic control. One study found that although CPAP was beneficial in reducing insulin resistance, but the benefit was greater among non-obese patients [115]. It is postulated that the negative effects that obesity has on glucose control can be so overbearing that the correction of OSA may not hold much benefit in reducing insulin resistance when compared to a focus on weight reduction and exercise [115,119]. Other studies noted that positive changes in insulin resistance found in their studies trying to relate CPAP to glucose control were more due to changes in weight rather than from the CPAP treatment itself [142,155]. It should be noted, however, that CPAP therapy, may be beneficial in reducing visceral fat accumulation in patients with OSA [119,133], which can lead to a reduction in insulin resistance by reducing both central obesity and the effects of intermittent nocturnal hypoxia.

CONCLUSION

Both OSA and diabetes are very prevalent diseases and poses a significant challenge to the global health care burden and are one of the major causes of compromised quality of life. They are both very closely linked to each other by obesity, which is a key portion of metabolic syndrome. However, some evidence has been found, which may link OSA and diabetes independent of their association with obesity.

Diabetic neuropathy has been related to increased prevalence of OSA. Proper glycemic control can reduce the risk of diabetic neuropathy and reduce risk of OSA. Diabetes may also predispose OSA through endothelial damage of the carotid body, blunting the body's natural response to hypoxia by its chemosensitive cells, as well as possibly altering its glucose sensing capacity. OSA, in turn, may also alter the carotid body's function, creating a perpetually worsening status of both diseases.

Intermittent nocturnal hypoxia caused by OSA can lead to increase an insulin resistance and glucose intolerance. This intermittent hypoxia has been associated with increased sympathetic activity that leads to increased catecholamine and cortisol levels in blood, both which predispose to diabetes and inadequate glucose management.

The use of CPAP can help combat the negative effects which intermittent nocturnal hypoxia may have on glycemic control, and studies have confirmed that treatment with CPAP may be beneficial by reducing insulin resistance in patients with both diabetes and OSA, as well as helping reduce central obesity, which can also assist in the reduction of insulin resistance. However, there is some evidence that the benefits of CPAP may be dwarfed in comparison to the benefits of weight loss and exercise in the reduction of obesity. Further randomized control and longitudinal studies should be done to address this important public health challenge.

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