

SLEEP APNEA AND TYPE 2 DIABETES: A SHORT REVIEW OF THE LITERATURE

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Abstract

The prevalence of diabetes and obesity has reached epidemic proportions. Even if today it is an accepted fact that diet and reduced physical activity are causes of obesity epidemic, sleep disturbances are seen as risk factors for obesity, insulin resistance, type 2 diabetes and metabolic syndrome. Regardless of the nature of the relation between sleep apnea and diabetes, the observed association have important clinical, epidemiological and public health implications. Clinical studies have shown that the cardiovascular morbidity and mortality is high, both in diabetes and sleep apnea, overcoming the prevalence observed in general population. Thus, understanding the implications of sleep apnea in alteration of glucose metabolism and cardiovascular risk could contribute to the prevention of both micro- and macrovascular complications.

key words: *sleep apnea, diabetes, obesity.*

Introduction

The growing epidemic of obesity in the last decade has drawn the attention on the sleep apnea syndrome as a cardiovascular risk factor. Obstructive sleep apnea (OSA) syndrome represents a frequent pathology, closely related with cardiovascular diseases, especially heart failure and hypertension [1], but it is often unrecognized. The overlap between type 2 diabetes mellitus (T2DM) and sleep apnea was first described few decades ago [2]. A possible explanation of this association is the presence of shared risk

factors such as obesity, visceral adiposity and advancing age. Still, the presence of metabolic or autonomic abnormalities associated with one that could influence the development of the other cannot be excluded [3]. Furthermore, a growing number of studies have suggested that the relationship between T2DM and OSA is independent of the degree of obesity [4-9]. Irrespective of the independence of this relationship, the observed association of sleep apnea syndrome (SAS) with type 2 diabetes has important clinical, epidemiological and public health implications [10]. In 2008 International Diabetes Federation (IDF)

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Taskforce on Epidemiology and Prevention and American Heart Association/American College of Cardiology published almost simultaneously two reports recognizing the burden of sleep disorders breathing and highlighting important evidences regarding the interactions between sleep apnea and cardiovascular diseases and between sleep apnea and T2DM [10, 11]. It is now well established that OSA is associated with increased cardiovascular risk and is increasingly recognized as a potential target for the prevention of cardiovascular disease (CVD) [11]. This is particularly relevant in the context of coexisting T2DM, when patients are already at significant risk of CVD [10]. Thus, understanding the implications of SAS in alteration of glucose metabolism and cardiovascular risk could contribute to the

prevention of both micro- and macrovascular complications.

SAS represents an ensemble of signs and symptoms caused by repetitive episodes of absence (apnea) or reduction (hypopnea) of the airflow at the nose/mouth during the sleep, associated with fall in oxygen saturation, arousals and awakenings [12]. Sleep-disordered breathing is broadly characterized by OSA and central sleep apnea. OSA syndrome is characterized by the repetitive episodes of upper airway obstruction during sleep that results in sleep fragmentation (frequent arousals to reestablish breath), recurrent hypoxemia and hypercapnia. These can lead to neurocognitive decline, cardiovascular complications and eventually death [11].

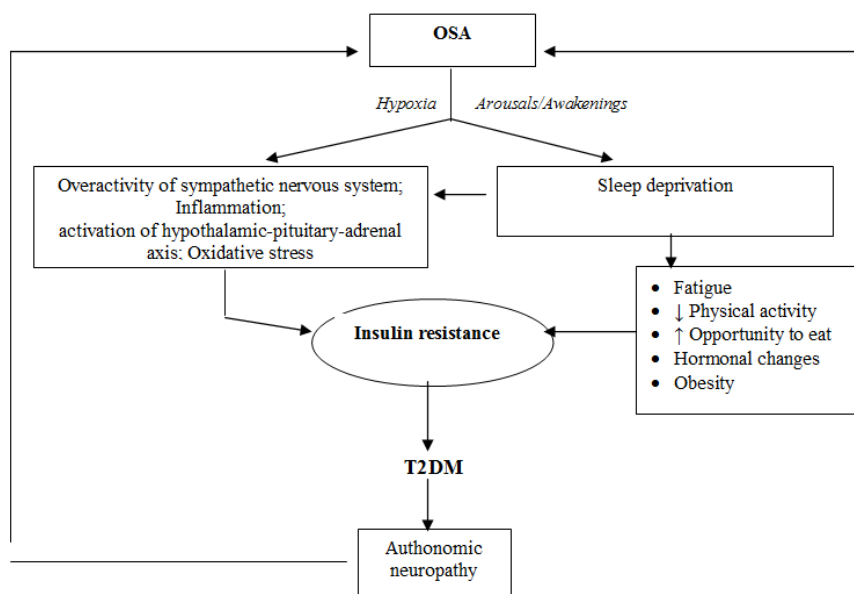


Figure 1. Proposed mechanisms of the interaction between OSA and T2DM (addapted from [10]).

Type 2 diabetes and OSA – pathogenetic mechanisms

Several mechanisms have been proposed to explain the interaction between OSA and T2DM (Figure 1). Sleep respiratory breathing disturbances can alter glucose metabolism

through both intermittent hypoxia and recurrent episodes of upper-way obstruction [13]. The repetitive episodes of upper way obstruction cause alterations in sleep architecture, recurrent arousals from sleep and finally sleep deprivation. Intermittent hypoxemia and frequent arousals trigger:

1) sympathetic overactivity, 2) activation of hypothalamic-pituitary-adrenal axis and consecutive alteration of hormone secretion, 3) increased circulating levels of inflammatory cytokines and 4) leptin resistance and higher ghrelin levels [13, 14].

Moreover, the causal relationship seems to be bidirectional: currently, a number of researches confirmed that hyperglycemia and T2DM increase the risk for sleep apnea [15]. Data from Sleep Heart Health Study showed that patients with T2DM had a higher prevalence of sleep disordered breathing and presented more severe hypoxemia compared with participants without diabetes [16]. In 2009, Lecube and collaborators confirmed these results showing that at the same apnea-hypopnea index (AHI), diabetic patients experienced significantly more episodes of desaturation < 90% compared with non-diabetics [15]. Involved mechanisms are not fully understood. Altered reflexes of the upper airways due to involvement of the autonomic nervous fibers are suspected [15].

Prevalence of OSA in patients with type 2 diabetes

If in general population, the prevalence of SAS is 3-7% in men and 2-5% in women [1], in patients with T2DM it varies from 23 to 80% [17-20]. These discrepancies in the reported prevalence of OSA in patients with T2DM are attributable to both screening methods used in epidemiological studies and inclusion of highly selected population (only males or patients with a BMI > 35 kg/m²). The screening methods used were heterogeneous, including questionnaires (Epworth Sleepiness Scale [19], questionnaires about snoring or day time sleepiness derived from Berlin Questionnaire [17], polygraphy (cardio-

respiratory studies) [20] or polysomnography [18].

The first major study designed to determine the prevalence of OSA in patients with diabetes was published in 2006 by West, Nicoll and Stradling [17]. Symptoms of daytime sleepiness, snoring, neck circumference and hypertension were assessed using Berlin questionnaire in 1676 men with T2DM. The response to this questionnaire was used to classify participants as having a low or a high risk for sleep apnea. In a second stage, a percent of patients from both groups were evaluated by overnight oxymetry and the results were verified by detailed sleep studies. This study reported a prevalence of OSA of 23%. Also, the authors identified BMI as significant independent predictor of OSA in this population [17].

Other 4 studies that included a total of 1300 patients with T2DM reported a prevalence of SAS between 53.9 and 86%. In all above mentioned researches the screening and diagnosis of SAS was based on overnight polysomnography, which is considered the “gold standard” for the diagnosis of sleep apnea [16, 18, 21, 22]. The highest prevalence (86%) was reported by Foster et al among diabetic patients enrolled in the Sleep AHEAD Study, a sub-study of the trial Look AHEAD [18].

Currently, the available data in Romania are derived from two small studies conducted in the Clinical Center of Diabetes, Nutrition and Metabolic Diseases Cluj-Napoca [23, 24]. The first research included 100 consecutive patients with T2DM that underwent in a hospital cardio-respiratory study performed with a portable device: ApneaLink™ (ResMed Corporation, Poway, Calif) [25]. It is a three-channel sleep diagnostic tool

previously validated for the screening of sleep apnea [26]. The reported prevalence of SAS in this population was 64%. The other research was conducted as a pilot study aimed to evaluate the feasibility of a sleep apnea screening program in Romanian patients with T2DM and obesity. For the screening of OSA a two stage approach was used: first, every patient completed Epworth Sleepiness Scale [27]. Patients with a score >10 at this scale were referred to polysomnography for a sleep study. Overall, 20% of these patients had excessive daytime sleepiness (Epworth Sleepiness Scale >10) and in all of these cases obstructive sleep apnea was confirmed. Of these patients, 33.3% had moderate OSA (AHI=15-30 events/hour of sleep) and 58.3% had severe OSA (AHI \geq 30 events/hour of sleep) [23].

Prevalence and incidence of T2DM in OSA

A growing number of observational and experimental studies from different geographical regions and involving various populations suggests the existence of a relationship between impaired glucose metabolism and OSA. Although, there have been two decades since researchers studied metabolic consequences of OSA, the results were contradictory [28]. We will present below the most important results regarding this aspect.

In 2003 Meslier and collaborators published the results of a cross-sectional study that aimed to evaluate the prevalence of T2DM and impaired glucose tolerance (IGT) in a large clinic-based male population (n=595) presenting various degrees of obstructive sleep apnea syndrome and to analyse the relationship between OSA and

glucose-insulin metabolism [29]. Prevalence of T2DM was significantly higher in patients with OSA compared with non-apnoeic patients (30.1% vs. 13.9%). Additionally, authors concluded that in this clinical-based sample fasting and postload blood glucose increased and insulin sensitivity decreased with severity of sleep apnea, and the observed relationship between sleep-disordered breathing and impaired glucose-insulin metabolism was independent of obesity and age [29].

The most valuable evidence regarding the association between sleep apnea and diabetes is provided by Sleep Heart Health Study, a landmark trial in somnology. In a subset of participants (2656 persons) OSA diagnosis was based on an unattended polysomnography conducted in each participant's home. Fasting and 2-hour glucose levels measured during an oral glucose tolerance test were used to assess glycemic status [30]. Increased severity of OSA (as assessed by respiratory disturbance index – RDI) was associated with higher odds of impaired fasting glucose and impaired glucose tolerance after adjustment for several confounding covariates, including age, gender, smoking status, body mass index, waist circumference, and self-reported sleep duration (HR: 1.46; 95% CI: 1.09-1.97) [30]. The severity of sleep-disordered breathing, as assessed by the RDI, was also found to be independently associated with degree of insulin resistance [30].

The Wisconsin Sleep Study is the largest prospective trial that evaluated the prevalence and the incidence of T2DM in 1387 patients with sleep apnea followed for 4 years [31]. In the cross-sectional analysis of baseline data there was a greater prevalence of diabetes with increasing severity of OSA independent of

age, sex and waist circumference (14.7% of subjects with an AHI of 15 or more had a diagnosis of diabetes compared with 2.8% of subjects with an AHI of less than 5). However, these results were not confirmed by the longitudinal analysis: after adjusting for shared risk factors, incidence of diabetes over a 4 years follow-up period was not significantly related to the severity of SDB at the time of initial enrollment in the cohort (OR:1.62; 95% CI, 0.67-3.65; p = 0.24) [31].

Impact of OSA on glycemic control in patients with type 2 diabetes

Aronsohn and collaborators have recently published a research that evaluated the effect of OSA on HbA1c (as a measure of glycemic control) in 60 patients with type 2 diabetes [21]. The authors demonstrated that increasing severity of OSA was associated with poorer glycemic control, after adjusting for age, sex, race, BMI, number of diabetes medications, level of exercise, years of diabetes and total sleep time. Compared to patients without OSA, the adjusted mean HbA1c was increased by 1.49% in patients with mild OSA (p=0.002), 1.93% in patients with moderate OSA (p=0.003), and 3.69% in patients with severe OSA (p<0.0001).

The results published by Aronshon et al are in contradiction with those from an earlier study that involved 279 patients and did not report any association between OSA and HbA1c [32]. The negative results could be explained by the duration of sleep recording (ranging from 4 hours) and could be also due to the fact that only 22% in the population performed a full polysomnography. In contrast, Aronsohn et al included in analysis only patients with sleep recording duration over 7 hours and performed an additional

analysis which showed that if in analysis would be used only the first 4 hours of polysomnography the association between OSA and HbA1c was no longer visible [21].

CPAP treatment and glucose metabolism

If we think about the mechanism involved in the association OSA- glucose metabolism, it can be hypothesised that treatment of sleep apnea could impact insulin resistance and improve glucose metabolism. Studies with OSA patients, with or without diabetes, which have investigated the impact of CPAP therapy regarding insulin-sensitivity and glucose metabolism have shown heterogeneous results. These contradictory results could be explained by the absence of the control group, low statistical power, difference in length of follow up or the absence of data regarding CPAP compliance [14].

Several *uncontrolled interventional studies* evaluated the impact of CPAP therapy on insulin resistance or glucose metabolism in patients with or without T2DM. The largest uncontrolled interventional study that documents the beneficial effect of CPAP therapy on insulin sensitivity (evaluated by hyperinsulinemic, euglycemic clamp) included 40 non-diabetic patients [33]. Insulin sensitivity significantly increased after 2 days of CPAP therapy (5.75±4.20 baseline versus 6.79±4.91 $\mu\text{mol/kg} \cdot \text{min}$; p=0.003) and remained stable after 3 months of treatment. The improvement in insulin sensitivity after 2 days was much greater in patients with a BMI <30kg/m² compared with patients with BMI \geq 30kg/m² [33].

Recently a small number of trials that included diabetic patients with OSA evaluated the effect of CPAP therapy on glycemic

control assessed by HbA1c and continuous glucose monitoring (Table 1). The earlier two studies included a total of 19 patients and reported improvement in insulin sensitivity after 3-4 months of treatment, but with no effect on HbA1c levels [33, 34]. Babu et al demonstrated beneficial effects of 3 months of

CPAP use on HbA1c and post-prandial glucose levels in 25 diabetic [35]. Other trials reported improvement in glucose variability of 24 h [33] and improvement in nighttime glucose levels during just one night of CPAP therapy [36] or after several weeks [37].

Table 1. Uncontrolled trials examining the effects of CPAP therapy on measures of glucose control in patients with T2DM.

Authors (publication year)	No of participants	Measures of glycemic control/metabolism	Duration	Results
Brooks et al (1994) [34]	10	Hyperinsulinemic euglycemic clamp; HbA1c	4 months	No change in HbA1c Improvement in insulin sensitivity
Harsch et al (2004) [33]	9	Hyperinsulinemic euglycemic clamp, HbA1c	3 months	No change in HbA1c Improvement in insulin sensitivity
Babu et al (2005) [35]	25	CGMS, HbA1c	83 ± 50 days	Improvements in HbA1c and postprandial glucose levels
Pallayova et al. (2008) [36]	14	CGMS	1 night	Improvement in nocturnal glucose levels
Dawson et al (2008) [37]	20	CGMS, HbA1c	26-96 days	Improvement in glucose levels during sleep No change in HbA1c
Wei et al (2009) [38]	11	CGMS, HOMA-IR	4 days	Improvement in glucose levels during sleep Improvement in insulin sensitivity

The only **randomized controlled trial** was published by West et al [39]. In this study were included 42 diabetic patients with OSA, randomly assigned to active CPAP therapy or placebo CPAP. The authors reported that after 3 months of treatment, there was no significant effect of CPAP therapy on HbA1c or insulin resistance. These negative results could be explained by the mean duration of CPAP usage of 3.3 hours/night in the active group of this trial. By contrast, the positive study by Babu et al, found that the correlation between the reduction in HbA1c levels and CPAP usage was present in patients

compliant to OSA therapy (defined as CPAP usage >4h/night) [35].

In summary, existing evidences support a potential role of OSA in the development of insulin resistance, increased diabetes risk and altered glycemic control in patients with T2DM. Regardless of the nature of the relation between sleep apnea and diabetes, the observed association have important clinical, epidemiological and public health implications. Thus, understanding the implications of sleep apnea in alteration of glucose metabolism and cardiovascular risk could contribute to the prevention of both micro- and macrovascular complications.

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