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Review Article

Obstructive Sleep Apnea Syndrome and Type 2 Diabetes

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Abstract

OSA is a chronic treatable sleep disorder and a frequent comorbidity in patients with type 2 diabetes. Intermittent hypoxemia and sleep fragmentation have been linked to abnormal glucose metabolism in laboratory-based experiments. OSA has also been linked to the development of incident type 2 diabetes. The relationship between OSA and type 2 diabetes may be bidirectional. Oxidative stress, sleep fragmentation and sympathetic activation could be the pathophysiological links between the two disorders. CPAP therapy could reduce risk of development diabetes and permit a well control of both diseases.

INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent sleep disorder caused by intermittent partial or complete collapse of the upper airway during sleep resulting in intermittent hypoxemia and hypercapnia, sleep fragmentation, increased oxidative stress, and systemic inflammation [1].

The Hypnolaus Sleep Cohort study [2] is the largest study that has recently assessed the prevalence of sleep-disordered breathing in a population-based sample using the most recent polysomnographic recording techniques and scoring criteria.

It has shown a much higher than previously estimated prevalence: the prevalence of moderate-to-severe sleep disordered breathing (≥15 events per h) is 23·4% (95% CI 20·9– 26·0) in women and 49·7% (46·6–52·8) in men. The study also showed an independent association between the sleep disorders and diabetes, hypertension, metabolic syndrome, and depression, albeit mainly in the highest severity quartile of the apnoea-hypopnoea index (more than 20.6 events per hours of sleep).Diabetes mellitus is a global epidemic disease. There are currently 382 million diabetics worldwide, a figure which is estimated reach 592 million in 2035[3,4].

The prevalence of OSA in patients with type 2 Diabetes ranges between the lowest estimate of 58% in the Sleep Heart Health Study[5] and the highest estimate of 86% that was reported in obese diabetic patients enrolled in the multi-center Sleep AHEAD (Action for Health in Diabetes) study [6]. The variation in OSA prevalence between studies is due to multiple factors including differences in studies populations (e.g. primary care vs secondary care), the methods of diagnosing OSA (polysomnography vs portable devices) and the criteria used to diagnose OSA (apnoea hypopnoea index - AHI). Prevalence of type 2 Diabetes is higher in OSA patients (30-70%) [7] As well as the prevalence of insulin resistance in OSA patients is around 20-67%. Frequency of Type 2 diabetes is higher in OSA patients then in control group and it is well shown in a longitudinal study of Marshall et al, in which they provided the first evidence that moderate–severe OSA is a risk factor for diabetes. After a 4-year follow-up of an Australian population cohort, they found that 20% of patients with moderate–severe OSA had been diagnosed with DM2, showing that OSA is an independent risk factor for incident diabetes [8].

Pathophysiological mechanisms

Obstructive sleep apnea (OSA) is caused by repetitive collapse of the upper airways during sleep. The increased morbidity and mortality of OSA are mainly thought to be the consequence of its adverse effects on cardiovascular (CV) health but insulin resistance and dyslipidemia which may also contribute to the emergence of CV disease. The main triggers of metabolic and cardiovascular consequences of OSA are the intermittent hypoxia with the nocturnal hypoxia-reoxygenation events, the sympathetic activation and arousal with sleep fragmentation. Other OSA-associated stimuli such as hypercapnia, and intrathoracic pressure swings may also play significant roles; however, this has been less extensively studied.

Oxidative stress in OSA

Ota et al shows that intermittent hypoxia reduces pancreatic cell apoptosis and also increased rodent pancreatic cell replication by upregulation of the regenerating gene (Reg) family genes, which encode autocrine and paracrine growth factors for cell replication [9] Cellular studies have demonstrated that intermittent hypoxia significantly decreases the geneexpression

of cluster of differentiation (CD)38 (ADP-ribosyl cyclase/cyclic ADP-ribose [cADPR]), which is an important component involved in glucose-induced insulin secretion through the mobilization of Ca^{2+} in primary cultured rat and mouse pancreatic islets and animal model experiments [10].

Intermittent hypoxia has been shown to cause damage of hepatocytes and the levels of serum liver enzymes. In animal studies using mouse models, intermittent hypoxia exposure caused hepatic steatosis, necrosis of hepatocytes, and inflammation of the liver with neutrophil accumulation and collagen deposit. The mechanisms involve increases ~~in~~ proinflammatory cytokines. Another study observed increases in NF-kB activation and liver proinflammatory cytokines such as IL-1, IL-6, and CXCL2 in lean mice exposed to longer periods of intermittent hypoxia. Liver damage is significantly involved in the pathogenesis of Non-Alcoholic Fatty Liver disease (NAFLD). NAFLD is strongly associated with obesity, diabetes, and metabolic syndrome (obesity, hyperlipidemia, type 2 DM, and high blood pressure). Intermittent hypoxia upregulates hepatokines such as selenoprotein P to increase insulin resistance to proliferate such hepatocytes via downregulation of microRNA-203, resulting in insulin resistance, fat accumulation, and arteriosclerosis [11].

In cellular studies using human and rat hepatocytes, intermittent hypoxia exposure cause upregulation of mRNAs in selenoprotein P. These upregulates levels of selenoprotein P in human hepatocytes accelerate insulin resistance and the levels mRNAs to proliferate. NAFLD patients usually have hepatic insulin resistance, that is the key cause of impaired fasting glucose, which contributes substantially to the development of type 2 DM. Intermittent hypoxia exposure in mice increases hepatic lipogenic enzymes such as stearoyl-coenzyme A desaturase-1 via the upregulation of sterol regulatory element–binding protein-1 and high- density lipoprotein receptor [12], leading to the development of NAFLD and metabolic syndrome.

There is also an involvement of adipose tissue. Intermittent hypoxia stress upregulates adipokines such as tumor necrosis factor-alfa (TNF-alfa), C-C motif chemokine ligand 2 (CCL2), and resistin via downregulation of microRNA-452 in adipocytes to increase insulin resistance [13] but also growing the releasing of fatty acid, with a upregulation of lipolysis. Free fatty acids accelerate insulin resistance in muscle, liver and adipose tissue.

In conclusion intermittent hypoxia in OSA patients induces a number of cellular responses, most of which worsen insulin sensitivity and glucose tolerance (e.g., reduction of glucose-induced insulin secretion, upregulation of selenoprotein P, upregulation of adipokines such as CCL2, TNF-alfa, and resistin, and upregulation of myokines such as IL-8, osteonectin, and myonectin), leading to type 2 DM.

Sympathetic activation in OSA

The sympathetic nervous system plays an important role in the metabolic regulation of glucose and fat. Obstructive events are responsible of a higher sympathetic activation both day and night with an increase in circulating catecholamines. Adrenaline stimulates the production of glucose and alters the production of insulin which leads to insulin resistance. Catecholamines are known to reduce insulin sensitivity, insulin-mediated glucose uptake, promote pancreatic cell apoptosis, and reduce insulin secretion. They can also inhibit insulin- mediated glycogenesis and increase glycolysis. Activation of the sympathetic nervous system appears to have an impact on insulin sensitivity, it has been suggested that this plays a major role in the development of insulin resistance in patients with OSA [14]. Experimental evidence supports the suggestion that increased basal sympathetic tone plays an essential role in the relationship between OSA and Diabetes. Glucose intolerance caused in healthy volunteers by exposure to periods of acute hypoxia is associated with an increase in plasma catecholamines. Hypoxic activation of the sympathetic nervous system contributes to long-term progression of insulin resistance, which may occur for decades in patients with OSA.

Arousal and sleep fragmentation in OSA

There is a strong association between glucose metabolism and sleep, in particular short sleep is linked with increased risk of becoming overweight and/or obese; while poor sleep quality with an increased risk of both mellitus and gestational diabetes [15].

In laboratory conditions, complete sleep deprivation has been found to reduce glucose tolerance. Various observational studies in the general population have also shown a relationship between sleep deprivation and altered glucose metabolism. The Sleep Heart Health Study confirmed that less than 6 h of sleep per night are associated with a higher prevalence of diabetes or glucose intolerance. An analysis of the First National Health and Nutrition Examination Survey [16] showed that fewer than 5 hours sleep per night resulted in a 1.47-fold increase in the risk of developing diabetes. In more than 1000 men enrolled in the Massachusetts Male Aging Study, the risk of developing diabetes in subjects reporting a shorter average sleep time was double that of those sleeping for 7–8 h [17]. Although there is as yet little information on this aspect, the effect of sleep restriction on the risk of developing diabetes appears to be sex-dependent [18]. In more than 70,000 non-diabetic adult women included in the Nurses Health study, sleeping less than 5 h was found to increase the risk of developing diabetes in 10 years by 1.57-fold, although significance was reduced when adjusted for BMI and other confounding factors. Therefore, sleep restriction appears to be an independent risk factor for diabetes, primarily in men.

In addition to studies in general population, several authors have evaluated the duration and quality of sleep in patients with diabetes. Most of them found that poor sleep quality was more prevalent in patients with diabetes, and that this negatively affected blood glucose control. The potential contribution of sleep fragmentation to the OSA–diabetes relationship is evidenced by the importance of sleepiness, as demonstrated by Barceló et al., [19] who found that patients with OSA and excessive daytime

sleepiness have a higher HOMA index than non-sleepy patients with OSAS or healthy controls.

Human sleep is composed of rapid-eye-movement (REM) sleep and stages 1, 2 and 3 also called non-REM (NREM) sleep. The deeper stages of NREM sleep is the stage 3, also known as slow-wave sleep (SWS), and is considered the most ''restorative'' sleep stage. There is indeed evidence that SWS plays a role in waking neurobehavioral function and particularly in memory consolidation, but whether SWS is also important for peripheral physiological function is not so well known. The initiation of SWS is temporally associated with transient metabolic and hormonal changes that they could potentially affect glucose homeostasis. Some authors hypothesized that SWS plays a role in glucose regulation and that suppression of SWS may adversely affect glucose homeostasis. In an experimental study of young healthy adults, conducted by Tasali et al, [20] all-night suppression of SWS (without awakening the subjects, changing sleep duration or REM sleep) was achieved via acoustic stimuli of varying intensity for three nights. This resulted in a reduction in insulin sensitivity, based of intra venous glucose tolerance testing at the end of each experimental condition, without a compensatory increase in insulin release. This decrease in SWS is similar to what occurs over the course of 4 decades of normal aging, because normal young adults spend 80–100 min per night in SWS, whereas individuals 60 years of age generally have 20 min of SWS. This study suggests that reduction of SWS has an adverse impact on daytime glucose tolerance with a clear increase in a well validated marker of diabetes risk.

The loss of REM sleep, due to sleep fragmentation, may also contribute to the development of diabetes. REM sleep has high energy requirements due to sustained neuronal activity, and is accompanied by an increase in cerebral glucose uptake as well as reduced insulin and glucagon levels [21]. REM sleep is found to be associated not only with insulin resistance and diabetes, but it also results in hypoxaemia due to sympathetic hyperactivity as well as a variable blood pressure which eventually increases the severity of diabetes and its risks. The study by Surani et al [22]. showed a very high prevalence of diabetes in an unselected cohort of Hispanic patients with obstructive sleep apnea compared to Caucasian. A REM apnea-hypopnea index of >20 was significantly associated with an increase prevalence of diabetes in Hispanic population. The higher prevalence of diabetes in OSA patients with a greater clustering of respiratory events during REM sleep could be related with fragmentation of this sleep phase.

Nonetheless, the number of cortical arousals is associated with fasting insulin levels and insulin resistance (IR) even when adjusted for age and obesity.

A study of Barceló et al. [19], shows that Excessive Daytime Sleepiness (EDS) is a marker of IR in patients, independent of obesity. It also shows that in patients with OSAS and EDS, CPAP therapy improves both EDS and IR. These findings suggest that EDS is a potentially useful clinical marker to identify patients with OSAS at risk of metabolic syndrome. EDS and IR in OSAS may share common pathogenic mechanisms, such as tissue hypoxia. The fact that patients with EDS had lower mean and minimal nocturnal oxygenation saturation than patients without EDS, despite similar BMI and AHI values, supports this hypothesis. Furthermore, this study showed a significant correlation between insulin levels and HOMA values and indices of nocturnal hypoxemia and arousal index, suggesting that nocturnal hypoxemia may influence both EDS and IR in OSAS. This study support the idea that EDS could contribute by itself to IR and that patients with EDS represent a particular OSAS phenotype [19].

Effects of CPAP on risk of diabetes

Research over the last decade suggests that in type 2 diabetes, increasing OSA severity is associated with worsening glycemic control as determined by hemoglobin A1c (HbA1c). Randomized control trials, however, have not shown improvements in HbA1c with positive airway pressure (PAP) treatment in adults with type 2 diabetes and OSA [23].

OSA also is associated with the elevated risk of incident type 2 diabetes and observational study suggests that regular CPAP treatment may reduce the risk [24]. Nevertheless randomized trial didn't show the same results.

In particular Loffler et al. [25], report their findings in a sub study of 888 participants from the Sleep Apnea Cardiovascular Endpoints (SAVE) trial, a randomized clinical trial in which 2687 participants aged 45-75 years with OSA and stable cardiovascular disease were randomized to CPAP treatment plus usual care versus usual care alone. The aim was to investigate the long-term effect of CPAP on glycemic control and type 2 diabetes risk with a median follow up of 4.3 years. After a median follow up of 4.3 years, there was no difference between CPAP and usual care in serum glucose, HbA1c, or antidiabetic medication use in those with known type 2 diabetes. Moreover, no significant differences were found in those with prediabetes or in new diabetes diagnosis. However, CPAP adherence was low (3.5±2.3 h/night), the study lacked enough statistical power, adjustment for antidiabetic medications was perhaps not be able to capture fully the effects of glucose lowering agents on HbA1c, confounding the effects of CPAP in subjects with known type 2 diabetes. Nonetheless this study excluded subjects with excessive daytime sleepiness (EDS) as well as those with severe nocturnal hypoxemia, and we have already mentioned the study from Barcelò et al [19] in which they shows that EDS is a marker of Insulin Resistance (IR) and CPAP therapy improves both EDS and IR.

West et al. [26], 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, the 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. [27], found that in patients who used CPAP for more than 4 h per night (average nightly use of 6.6h/night), there was a reduction in HbA1c levels.

In well-controlled laboratory experiments, there is evidence that short-term CPAP use with ensured compliance of 8 h nightly for 1-2 weeks results in improved glucose metabolism both in adults with type 2 diabetes both in those with prediabetes. This night-long use of CPAP could be a significant factor [1].

Malik et al. [28], in their study have shown a positive impact of CPAP in the management of blood glucose control as reflected by decline in HbA1c levels in 59% of diabetic patients.

Short term study [29] demonstrated a improvements of glucose levels after begin CPAP or negative change after withdrawal in patients with diabetes , in the medium term studies [30] the results are mixed, but in long term studies the beneficial effect of CPAP in glucose levels have not been demonstrated.

The difference between observational study and longitudinal could be explain for some confounding factors in the observational studies as for example coexistence of obesity oralso introduction of other therapies. Also, in longitudinal and clinical trials studies, people sometimes change their lifestyle.

While several limitations could explain the discordance between observational and interventional studies (e.g., poor adherence to PAP therapy), an important consideration in the available randomized trials is that glycemic status was characterized with measures such as HbA1c, fasting glucose, or fasting insulin. While these metrics have been important in establishing the potential association between OSA and altered glucose metabolism, they do not provide information on whether OSA influences the degree of meal-related excursions in glucose levels in type 2 diabetes. In one of the earliest studies examining the effects of PAP therapy on glycemic control in obese patients with type 2 diabetes, postprandial glucose values on continuous glucose monitoring pre- and post-CPAP use in small sample of 24 subjects varied with PAP therapy [27]. Adherence with PAP (i.e., average use of > 4 hours per night over a period of three months), was associated with a reduction in postprandial glucose values after breakfast, lunch, and dinner. In particular, PAP treatment reduced the total number of glucose values above 200 mg/ dl.

COMPLIANCE WITH ETHICAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This study is a review so isn't necessary that the study was approved by the referral Ethics Committee of Azienda Sanitaria Universitaria Giuliano Isontina.

Work was performed in the Pulmonology Department Hospital of Trieste (Italy) All authors haveseen and approved the manuscript

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