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Review

Obstructive Sleep Apnea and Type 2 Diabetes

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Abstract
Type 2 diabetes and obstructive sleep apnea (OSA) are diseases with high prevalence and major public health impact. There is evidence that regular snoring and OSA are independently associated with alterations in glucose metabolism. Thus, OSA might be a risk factor for the development of type 2 diabetes. Possible causes might be intermittent hypoxia and sleep fragmentation, which are typical features of OSA. OSA might also be a reason of ineffective treatment of type 2 diabetes. There is further evidence that the treatment of OSA by continuous positive airway pressure (CPAP) therapy might correct metabolic abnormalities in glucose metabolism. It is assumed that this depends on therapy compliance to CPAP. On the other hand, there are also hints in the literature that type 2 diabetes per se might induce sleep apnea, especially in patients with autonomic neuropathy. Pathophysiological considerations open up new insights into that problem. Based on the current scientific data, clinicians have to be aware of the relations between the two diseases, both from the sleep medical and the diabetological point of view. The paper summarizes the most important issues concerning the different associations of OSA and type 2 diabetes.

Key words: obstructive sleep apnea, type 2 diabetes

Introduction

Type 2 diabetes and obstructive sleep apnea (OSA) are both diseases with high prevalence and major public health impact. Obesity is a common feature of both groups of patients. Thus, the metabolic syndrome, which is characterized by obesity, insulin resistance, dyslipidemia and hypertension, often can be found in type 2 diabetes and OSA. In many cases metabolic syndrome seems to be the most important underlying disease both of type 2 diabetes and OSA [1-3]. But how are OSA and type 2 diabetes linked; is there only a coincidental or even a causal relationship between the two diseases? This can be investigated by tackling the following issues:

1) Are regular snoring and OSA risk factors for diabetes?
2) Does CPAP treatment influence glucose metabolism?
3) May diabetes induce OSA?
4) Connections among OSA, hypoxic ventilatory responses, diabetes, and the gluco-sensing by carotid body chemoreceptors.

Are Regular Snoring and Osa Risk Factors for Diabetes?

An increasing number of studies support the hypothesis, that habitual snoring and OSA have an impact on glucose metabolism both in diabetics and non-diabetics [1]. OSA might induce insulin resistance and increase the risk of developing type 2 diabetes. In a 10-years follow-up study in 69852 nurses aged 40-65 years regular snoring was independently associated with a two-fold increased risk of developing a diabetes [4]. Also, in hypertensive men OSA is – besides obesity - a risk factor for diabetes. In the study of Elmasry et al [5] the prevalence of OSA defined by an apnea-hypopnea-index (AHI) of at least 20 per hour was 36.0% in the diabetic group *vs.* 14.5% in non-diabetic hypertensive men. Individuals suffering from OSA in combination with a waist-to-hip-ratio of at least 1 had an odds ratio of 11.8 for development of type 2 diabetes. Our own population-based study in Turkey, which included 1946 individuals, investigated the possible association between OSA syndrome, metabolic syndrome, and insulin resistance. In this study, however, OSA syndrome was associated with metabolic syndrome rather than with insulin resistance, which was estimated by homeostatic model assessment (HOMA) [6]. The reason for this opposite finding could be a high percentage of metabolic syndrome within the female population. In any case, the prevalence of OSA is increased in type 2 diabetes and vice versa. Depending on the definition of OSA and OSA syndrome, the prevalence of diabetes in OSA patients seems to be in a range of 15-30% [7, 8]. Preliminary data of our own working group also show a high prevalence of sleep disordered breathing in type 2 diabetics, with nearly 50% of patients showing a respiratory disturbance index (RDI) of at least 5 per hour and 7.5% of patients with additionally increased daytime sleepiness documented in the Epworth Sleepiness Scale (ESS) score of more than 9 (B. Tautz, personal communication). A recent study went further and investigated whether the severity of OSA is a predictor of glycemic control in type 2 diabetics [9]. In that study, 60 consecutive diabetics were recruited from outpatient clinics and underwent full polysomnography. HbA1c was taken as indicative of the glycemic control. After controlling for age, sex, race, body mass index (BMI), the number of anti-diabetic medications, the level of individual exercise, the years of suffering from diabetes, and the to-

tal sleep time, there was a significant impact of the severity of OSA on the glucose control, expressed in a higher HbA1c in patients with more severe sleep apnea.

To summarize, regular snoring and OSA are independently associated with alterations in glucose metabolism and metabolic syndrome. They seem to be risk factors for the development and for ineffective treatment of diabetes.

Does CPAP Treatment Influence Glucose Metabolism?

Several studies have investigated the effect of continuous positive airway pressure (CPAP) ventilation on glucose metabolism both in diabetics and non-diabetics. Most of the studies have shown that CPAP has an impact on diabetic metabolism in terms of a better glucose control in both groups. One of the earliest studies was that of Brooks et al [10] 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 [11] 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 non-obese non-diabetics [12]. Obesity seems to be the most important cofactor which influences the CPAP effect on glucose metabolism. In a recent placebo-controlled CPAP intervention study in OSA patients without diabetes, insulin sensitivity is immediately enhanced by CPAP, but the improvement holds out after 12 weeks of treatment only in the patients with moderate obesity [13]. In contrast to those findings, a randomized, double blind placebo-controlled study does not find any significant improvement of glycemic control or insulin resistance in male type 2 diabetics after a CPAP treatment period of 3 months [14]. A limitation of the study, however, is that the daily average usage of CPAP was just about 3.5 h, which would be regarded as non-compliance of therapy according to the international guidelines of sleep medicine.

To summarize, CPAP - at least in case of good adherence to therapy - may improve insulin sensitivity in diabetic OSA patients. In case of accompanying obesity, the CPAP effect can only be seen after several months of treatment.

May Diabetes Induce OSA?

According to a small number of papers autonomic neuropathy (AN), which is present in diabetics in 20-30% of the cases, seems to play a role in the development of sleep disordered breathing [15-18]. Diabetics with AN, in general, have an increased mortality. If AN is present, central hypercapnic respiratory drive is increased and peripheral chemical drive is decreased. If AN is located in central and peripheral chemoreceptors and in the glossopharyngeal (IX), vagal (X), or proprioceptive nerves, that may have an impact on the chemical control of breathing and, by means of a reduced muscle tone, also on the dilation of the pharynx, all of which may result in sleep disordered breathing. According to these pathophysiological considerations, Ficker et al [19] have shown that OSA is more often prevalent in diabetics with AN. Six of 23 diabetics with AN (26%) had an AHI of at least 10 per h, whereas there were no OSA patients in the non-AN group. Two other studies by Bottini et al [20, 21] have confirmed these results. These authors also show that the prevalence of increased AHI (≥10 per h) in diabetics is increased for up to 28%. The risk of OSA is particularly increased in obese diabetics with AN, and these patients have the most profound oxygen desaturations during sleep. The authors, however, do not find central posthyperventilatory sleep apneas or periodic breathing in diabetics with AN [20]. They ascribe the lack of central apneas to reduced peripheral CO_2 chemosensitivity, which is a major determinant of such apneas, even though central CO_2 drive increases. In our previous study in 198 OSA patients with diabetes, we have investigated the question of whether diabetics with AN and OSA suffer from a reduced perception of clinical symptoms of OSA, notably from excessive daytime sleepiness [22]. We found that the prevalence of AN in diabetics with OSA is high (35%), but it is also present in non-diabetic OSA patients (13%). Perception of clinical symptoms, however, does not differ significantly between diabetic OSA patients with and without AN. What makes a difference is that diabetic OSA patients with AN suffer from the most profound oxygen desaturations during sleep, which also have been demonstrated by Bottini et al [20].

To summarize, the prevalence of sleep disordered breathing is increased in diabetics with AN. Most of the respiratory events are obstructive apneas. Diabetic OSA patients with AN suffer from the most profound oxygen desaturations during sleep, but typical clinical symptoms of OSA do not differ between diabetics with and without AN. Hence, diabetic AN may, to an extent, contribute to the high prevalence of OSA in diabetics in general.

Connections among OSA, Hypoxic Ventilatory Responses, Diabetes, and the Gluco-sensing by Carotid Body Chemoreceptors

The mutual connections between diabetes and sleep apnea are still an area of limited understanding. Diabetes may hamper breathing by virtue of accompanying central and peripheral neuropathy. Dysfunctioning central motor output to pharyngeal muscles fosters the collapsibility of upper airways; the effect that cannot be sufficiently counteracted for by deficient, for the same reason, respiratory muscle pump. On the other side, diabetes causes malfunction of the carotid body, at both morphological and functional levels. Glomus cells in diabetic rats assume apoptotic appearance, neovascularization, and are subject to general degeneration [23]; the events likely underlain by endothelial microvascular damage, which also underlies atherosclerotic changes in diabetic humans [24]. The hypoxic ventilatory responses are decreased in diabetes in both humans [25] and animals [26]. We also found a sub-

stantial decrease in the profile of the acute hypoxic ventilatory responses in conscious unrestrained rats with streptozotocin-induced diabetes compared with the responses in the healthy condition (Fig. 1) [27]. Notably, the peak hypoxic hyperventilation decreased by ~35% in diabetic rats (Fig. 1, inset). With regard to humans, a decrease in hypoxic reactivity in diabetes is bound to delay hypoxic arousals, which is likely to result in deepened desaturation dips if OSA develops.

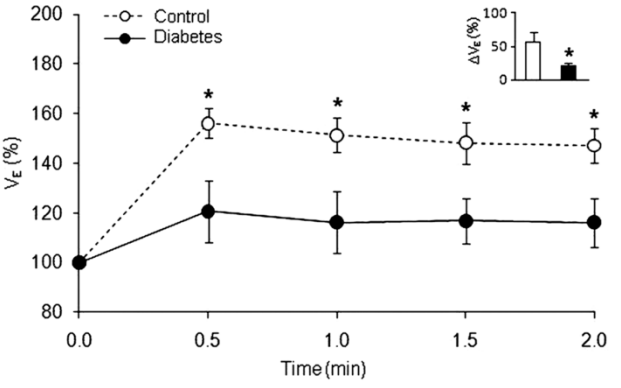

Fig. 1. Minute ventilation (V_E) responses to acute hypoxia (11% O_2 in N_2) in diabetic (streptozotocin-induced) and healthy adult Wistar rats (n = 6 in both groups). Symbols are means ±SE of percentage increases in ventilation at sequential 30 s time points of hypoxic tests from the baseline level taken as 100% in each animal. Inset: difference in mean percentage increases from baseline to peak hypoxic hyperventilation between diabetic and healthy rats. *P<0.03 for all (Mann-Whitney U test).

The reverse, the influence of OSA uncomplicated by diabetes on the carotid body-mediated control of ventilation is more difficult to conceive and the information is meager and contentious. In humans, there seems to be a consistent impression that in the long-lasting apnea/hypopnea syndrome the hypoxic chemoreflex is dampened [28-30]. A possible mechanism of the decline, which worsens hypoxic episodes during sleep, could be dysfunctioning dopaminergic pathway in the carotid body [29]. Others, however, report no significant alterations in the hypoxic ventilatory responses (31, 32), or evidently higher responses (33). The mechanisms underlying the influence of sleep related breathing disorders on the hypoxic chemoreflex are not readily explainable. In humans, these mechanisms are usually ascribed to metabolic and circulatory sequelae of the syndrome, such as obesity and atherosclerosis (24). However, the carotid body is definitely affected by episodes of intermittent hypoxia. Intermittent hypoxia is known to activate Ca^{2+}/calmodulin (CaM)-dependent protein kinase II (CaMKII) signaling pathway which, in turn, induces HIF-1α transcriptional activity aimed at recruiting adaptable processes in response to intermittent hypoxia [34]. CaMKII is a memory consolidating enzyme which has to do with neural plasticity and long-term potentiation; a feature characteristic of carotid body function in intermittent hypoxia. Long-term potentiation is indeed noted in the ventilatory responses to hypoxia in humans in whom intermittent hypoxia is modeled, but it is a feature of short rather than long-lasting disorders [35, 36]. The CaMKII pathway has no major bearing on the HIF-1α induction in sustained hypoxia [37] in which the lack of oxygen, by itself, decreases the rate of O_2-dependent proline hydroxylation and degradation of HIF-1α [38]. The carotid body is bound to be exposed to sustained hypoxia in diabetes due to the proliferation of connective tissue and parenchymal degeneration [23]. Therefore, the sleep apnea syndrome complicated by diabetes gives rise to a complex and as yet poorly understood interaction between two synergistic molecular mechanism leading to the activation of HIF-1α and a spate of homeostatic processes.

It seems even more difficult to conceive the role of OSA in the development of diabetes. The carotid body glomus cell is a polymodal receptor neuron that detects low blood glucose which increases afferent discharge rate emanating from the organ. The gluco-sensing process utilizes the same neurotransmitter signaling pathways as does hypoxic stimulation [39]. It may thus be so that in the hypoxia of the sleep apnea combined with diabetes all signal responsive resources in the carotid body are used up and carotid glucosensor malfunction cannot initiate counter regulatory processes to prevent an increase in blood glucose. We put forward this hypothesis as a plausible mechanism by which sleep apnea may increase propensity for the development of diabetes, independent of other metabolic-related issues. Hyperglycemia, in turn, acutely attenuates carotid body discharge rate [40], and in the longer term causes degeneration of carotid body parenchyma [23], which would explain dampened carotid body hypoxic reactivity in both sleep apnea and diabetes. The entwined interrelationships between sleep apnea, diabetes, and carotid body chemo- and gluco-sensing are open to further exploration.

Clinical Consequences

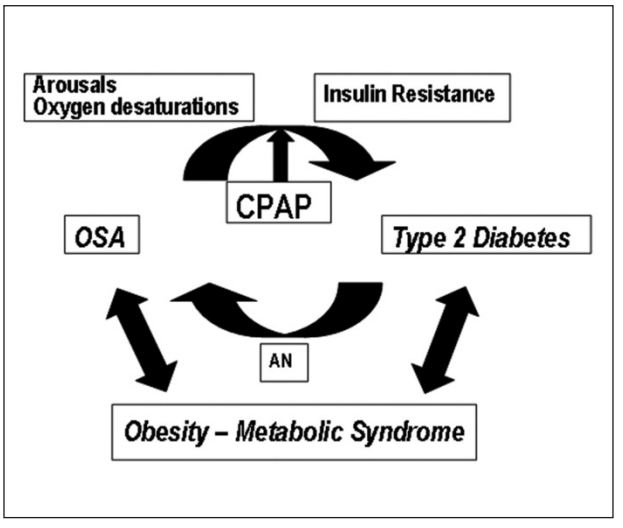

Fig. 2. Possible interactions between obstructive sleep apnea and Type 2 diabetes. OSA - obstructive sleep apnea, CPAP - continuous positive airway pressure, AN - autonomic neuropathy [adopted from Tasali and Ip 2008].

There are mutual interactions between the two diseases OSA and type 2 diabetes, which are schematically depicted in Fig. 2. The basis for the interactions are obesity and the metabolic syndrome, since both patient groups very often suffer from these disorders. Particularly, visceral adiposity seems to be an important confounding factor in the relationship between OSA and diabetes. OSA itself may induce insulin resistance by arousals, oxygen desaturations, and other unknown factors. To a certain amount, by means of CPAP treatment this effect can be reduced. On the other side, diabetic AN itself may play a role in the development of OSA and may also contribute to the high prevalence of OSA in diabetics and vice versa. Hence, based on the current scientific data, clinicians have to be aware of the relations between OSA and diabetes. In OSA patients, one has to pay attention to the possible presence of diabetes, and diabetics with ineffective treatment should be examined for the presence of OSA.

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Conflicts of interest: The authors declare no conflicts of interest in relation to this article.

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