Obstructive sleep apnea and type 2 diabetes mellitus

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Abstract:

Obstructive sleep apnea (OSA) and type 2 diabetes mellitus (T2DM) are both common diseases that present a burden to a remarkable number of individuals worldwide, and their incidence and prevalence are constantly raising. OSA and T2DM coexist very often, they have common independent predisposing factors, and the main of them is obesity. However, they can share many other pathogenetic factors like chronic inflammation, oxidative stress, hormonal changes and autonomic nervous system disbalance, which are discussed in this review. OSA and T2DM, when untreated or undertreated, may lead to the additive or synergistic effect in a patient, leading to accelerated development of atherosclerosis and its cardiovascular complications.

Recently, concomittant presence of OSA and T2DM was linked to possibility of higher incidence of colon cancer. As OSA, obesity and diabetes type 2 presen tindependent increased risk for cardiovascular complications, cardiovascular morbidity and mortality, special focus should be put on the early recognition of OSA simptoms in the patients with T2DM, and vice versa, patients with OSA should be regularly checked for presence of glucose intolerance or insulin resistance, in order to prevent long-term consequences.

Keywords:

sleep apnea, obstructive sleep apnes, sleep apnea syndrome, diabetes mellitus

Sažetak:

Opstruktivna apneja u spavanju i dijabetes melitus tipa 2

Opstruktivna apneja u spavanju (OSA, prema engl. *obstructive sleep apnea*) i dijabetes melitus tipa 2 (T2DM, prema engl. *type 2 diabetes mellitus*) česte su bolesti od kojih pati značajan broj bolesnika širom svijeta, a njihova incidencija i prevalencija su u neprestanom porastu.OSA i T2DM su vrlo često istovremeno prisutne kod istog bolesnika, te imaju zajedničke neovisne čimbenike rizika, od kojih je najvažniji pretilost. Osim toga, OSA i T2DM dijele i više čimbenika patogeneze, kao što su kronična upala, oksidativni stres, hormonalne promjene i poremećena ravnoteža autonomnog živčanog sustava, o kojima se raspravlja u ovom preglednom radu. Ukoliko se kod bolesnika OSA i T2DM ne liječe ili liječe neadekvatno, mogu aditivnim ili sinergističkim učinkom dovesti do ubrzanog razvoja ater-

oskleroze i njezinih kardiovaskularnih i drugih komplikacija. Konkomitantna prisutnost OSA i T2DM je od nedavno povezana i većom incidencijom raka debelog crijeva. Budući da su OSA, pretilost i dijabetes tipa 2 neovisni čimbenici rizika za razvoj kardiovaskularnih komplikacija, kardiovaskularnog morbiditeta i mortaliteta, posebnu pozornost bi trebalo usmjeriti na rano prepoznavanje OSA-e kod bolesnika s T2DM- om, a s druge strane, kod bolesnika s OSA-om bi trebalo redovito kontrolirati eventualne znakove intolerancije glukoze ili inzulinske rezistencije, kako bi se što ranije i učinkovitije spriječile dugoročne posljedice tih bolesti.

Ključne riječi: apneja u spavanju, sindrom apneje, dijabetes

Introduction

Obstructive Sleep apnea (OSA) is a major health problem. Beside that it significantly lowers the quality of life [1], it increases risk for cardiovascular disease, metabolic syndrome and diabetes mellitus, contributing overall morbidity and mortality [1-5]. In the light of new SARS-COV-2 pandemics, available data indicate that it might worsen the outcome and increase the death rate of the COVID-19 infection [6] It is estimated than 936 million individuals aged 30–69 years (men and women included) worldwide have OSA [7]. Among this group, 425 million individuals have moderate to severe obstructive sleep apnea, estimated using criteria based on number of apneic episodes of 15 or more events per hour. The latter group is considered as clinically more important, because the treatment is often required [7].

Diabetes mellitus is another world-wide burden, that decreases quality of life and increases risk for short-term and long-term complications, leading to higher morbidity and mortality [8]. Although type I diabetes mellitus, caused by lack of insulin production, is a severe condition which, when untreated, leads to rapid metabolic impairment and death, type 2 diabetes mellitus in which combination of impaired insulin production and decreased ability of insulin-sensitive tissues to respond to insulin are present, is much more common (>90% of all DM cases) and its incidence is rapidly increasing especially in young population even in adolescents and children [8]. T2DM epidemics is mostly attributed to increase of obesity, caused by high-fat diet and sedentary lifestyle [9,10], and aging of population [11] Early onset of T2DM lowers the age of appearance of microvascular and macrovascular complications and shortens the individual's life-span [9-12].

OSA and T2DM often overlap in the same patient, and share common comorbidities and risks, which can increase the mortality risk and demands for treatment [13-15]. The aim of this review is to focus on some common aspects between OSA and T2DM, with special attention to metabolic factors in pathogenesis of these two conditions.

Clinical aspects

Sleep apnea is a common sleep disorder characterized by absence of inspiratory airflow for periods for ≥10 seconds. Hypopnea is defined as reduction in airflow to ≥ 50% for periods for ≥10 seconds. Both apnea and hypopnea usually may lead to intermittent drop of oxygen saturation, hypercapnia and decreased quality of sleep [5,15]. Typical symptoms in a patient with sleep apnea include snoring in most of the sleep period, and, when awake, patients often complain about tiredness despite sleeping all night, with lack of concentration, morning headache or behavioural changes. Sleep apnea can be caused by 1. abnormal impulses transmission from central nervous system to respiratory muscles (central sleep apnea, CSA), and 2. collapsed airways or increased airway resistance that prevent airflow (obstructive sleep apnea, OSA). A distinct form of sleep apnea is complex sleep apnea syndrome (CompSAS), where CSA develops in patients with preexisting OSA, previously treated with a continuous positive airway pressure (CPAP) device [16,17]. The latter combination of both obstructive and central mechanisms, is considered as severe emergency condition. Obstructive sleep apnea (OSA) is the most common type of sleep apnea defined as temporary cessation or reduction of airflow caused by intermittent increase of upper airway resistance during respiratory effort in association with sleep fragmentation [18,19]. Although all OSA patients have certain level of impaired upper airway anatomy, since last 7 years four subphenotypes of OSA have been recognized, taking into account additional non-anatomical factors: ineffective upper-airway dilator muscles influencing pharyngeal critical closing pressure (Pcrit), respiratory control instability (high loop gain), and upper airway recruitment and low repiratory arousal threshold [20, 21]. This subdivision is important for finding the best treatment approach [21] Increase of airway resistance may be caused by anatomic abnormalities (enlarged tonsils), decreased muscle tone in oropharyngeal or nasopharyngeal muscles, or, in most cases, accumulation of fat in the neck or pharyngeal tissue [19]. Polysomnography (PSG) is a standard method for estimation of sleep apnea, and determining of sum of apneas or hypopneas per hour of sleep, known as apnea-hypopnea index (AHI) is required for diagnosis and assesment of OSA grade. AHI ≥ 5 per hour of sleep is considered abnormal, and increased daytime sleepines associated with abnormal AHI is typical for OSA. [22] OSA can be classified as mild, when AHI is 5-14 events/hour of sleep, moderate (AHI 15-29), and severe (AHI ≥ 30 per hour of sleep [23].

Best and the first-line method for OSA treatment is an application of continous positive airway pressure (CPAP) [8,9]. The alternatives are oral appliances, surgical procedures and electrical stimulation [9] These methods can be combined with lifestyle changes and obesity reduction [24, 25].

Epidemiology of sleep apnea and association with type 2 diabetes mellitus

OSA prevalence is increasing rapidly worldwide [7,26,27], which can be attributed mostly to increasing epidemics of obesity [28]. In earlier investigations, it was estimated that in people with body mass index (BMI) 25-28, every 1 in 5 adults have at least mild OSA, while 1 of 15 adults have moderate or severe OSA [29]. Newer studies that are based on different diagnostic criteria indicate that in general population, prevalence of moderate to severe OSA ranges 49,7 % in men and 23,4 % in women [30] However, in obese adults OSA prevalence can reach 70%, and in adults with diabetes mellitus type 2 (T2DM) is 58-86% [26]. As reported in Sleep AHEAD Study, the highest prevalence of OSA (86,6%) is found among individuals with T2DM with severe obesity and BMI ≥ 36,5 ± 5,8 kg/m^2, while 30,5% obese T2DM had moderate OSA and 22,6 % had severe OSA [31]. The prevalence of OSA in patients with T2DM is higher in White Europeans than in South Asia. [32] Moderate to severe sleep apnea is present in 46,3 % of patients with long-standing type I diabetes mellitus (DMT1) [33]. This strongly suggests that association exists between sleep apnea, obesity and impaired glucose homeostasis [34]. Severity of OSA is independently and positively correlated with increase of HbA1c levels [35] On the other side, OSA is considered as independent risk factor for T2DM, and both OSA and T2DM are important risk factors in patophysiology of metabolic syndrome and cardiovascular disease [15,19]. According to several studies that have investigated association between OSA and obesity, neck circumference (NC) and visceral obesity are more related to OSA than BMI [36,37]. In "Standards of Medical Care in Diabetes," a result of consensus of American Diabetes Assosiation, measurement of NC is recommended for clinical screening of OSA, especially in patients with T2DM. NC > than 17 inches in men and > 16 inches in women are significant cut-off values [37]. NC is also considered as independent factor for estimation of metabolic syndrome and insulin resistance, as NC > 38 cm predicted metabolic syndrome with 54% sensitivity and 70% specificity, and in prediction of OSA showed 58% sensitivity and 79% specificity [38].

While polysomnography is considered a standard method for estimation of OSA, there are several criteria for diagnosis of diabetes and pre-diabetes: fasting blood glucose concentration > 7 mmol/L, HbA1C > 6,5% or random blood glucose concentration > 11,1 mmol/L. Homeostasis model assesment of insulin resistance (HOMA-IR) score and HOMA-β score for quantifying the β -cell function are also widely used for insulin resistence validation, especially in clinical and epidemiologic studies [39]. Many studies confirm the association in patohysiological factors between OSA, type 2 diabetes and obesity, and these conditions also share some independent risk factors, like age, inadequate nutrition, sedentary life style and genetic factors [7,15, 19]. European Sleep Apnea Cohort Study results showed increased prevalence of OSA in diabetic subjects, and the severity of OSA was independent predictor of glycemic control, as the positive association between OSA severity indices and HbA1c levels was estimated in non-diabetic subjects [40]. Ten studies, including extensive meta-analysis of the SHSS Atherosclerosis Risk in Communities study have confirmed increased (1.35-fold) risk for OSA patients for developing T2DM regardless of body mass index (BMI) and age. The studies are well-described in the review of Reutrakul et al. [15]. Beside of being the independent risk factor for T2DM, OSA is more prevalent in adult patients with diabetes than in non-diabetics, and prevalence of OSA in diabetics was 58-86% [13-15].

Common pathophysiological mechanisms in OSA and T2DM

Although it is still unknown whether presence of OSA can induce T2DM, studies on animals and in heathly volunteers indicate that intermittent hypoxia (IH) and sleep disturbance could be predisposing factors for impaired glucose metabolism, insulin resistance and T2DM in OSA patients. In study of N. Sokucu et al. that was performed in non-diabetic OSA patients, elevated blood level of hemoglobin A1c (HbA1c) has been found, and HbA1c level was negatively correlated with minimum oxyhemoglobin desaturation levels (r = –0.302, P = 0.018), and positively correlated with mean desaturation index (r =0.263, P = 0.041) [41]. In extensive study including 1599 OSA patients without diabetes, Priou et al have observed positive correlation between severity of OSA and HbA1c levels, with dose-response relationship between AHI and percentage of patients with HbA1c > 6.0% ranging from 10.8% for AHI < 5 to 34.2% for AHI ≥ 50. increasing [42]. In the same study, significance of AHI as independent factor remained high after adjustments for other factors, like age, sex, smoking habits, BMI, cardiovascular morbidity, daytime sleepiness, depression, and insomnia [42]. Positive association between level of HbA1c with percentage of sleep time with oxyhemoglobin saturation below 90% (β = 0.470, P = 0.01) was also detected, and negative correlation was estimated with normal oxyhemoglobin saturation [43]. Obstruction of upper airways, hypopnea and apnea cause lower oxygen blood saturation, intermittent sleep with augmented stress, hormonal dysbalance and systemic inflammation. IH has a central role in pathogenesis of metabolic disturbance and diabetes in OSA, as it is at least partly responsible for decrease in insulin sensitivity, and decrease of glucose and oxygen utilisation at the level of the whole organism, which was confirmed in animal model and in humans. Group of Gozal et al. showed that sleep fragmentation with IH in mice

induced insulin resistance, increased oxygen stress and systemic inflammation, with release of proinflammatory cytokines from activated M1 macrophages [44]. These factors were associated with beta-cell dysfunction and apoptosis [44,45]. Cessation of the exposure to IH has only partially reversed the metabolic changes and eventually was followed with the worsening of beta cell function [46] In healthy human adults, acute IH induced transient elevation of blood glucose concentration [47] and impaired insulin sensitivity with an increased sympathetic nervous system activity [48].

Intermittent hypoxia is not the only mechanism that impairs glucose homeostasis in OSA patients. Although it is still unknown which factors in OSA patients may lead to diabetes, multiple factors are proposed as potential connection between IH and disturbed glucose metabolism: genetic factors, oxidative stress and inflammation, disturbed hypothalamo-pituitary-adrenal (HPA) axis with increased levels of circulating cortisol and free fatty acids, adipokines, elevated levels of endothelin-1 from damaged vascular endothelium, and increased activity of sympathetic system [15].

A recent genetic study with genotyping for single nucleotide polymorphysms (sRNPs) in patients with both OSA and T2DM indicated a possible link between polymorphysm of gene encoding apolipoprotein A-V (*APOA5* rs3135506), particularly in overweight patients [15]. APOA5 is an important regulator of triglyceride metabolism, and CC homozygotes of APOA5 rs3135506 have predisposition for triglycerideridemia [49]. Polymorphysms of APOA5 gene were previously linked to increased risk for diabetes, high BMI, ischemic stroke and cardiovascular disease [50].

The common link between factors and conditions that are connected both with OSA and T2DM might be the increased lipolysis and elevated levels of free fatty acids (FFA) in circulation induced by IH. Obesity with plenty of circulating nutrients can certainly potentiate those metabolic impairments [51,52]. It is known that high blood levels of FFA impair increase insulin resistance and glucose uptake by peripheral cells by multiple mechanisms on the level of peripheral cells [53] FFAs impair glucose metabolic utilization by muscles, via inhibition of glycolytic enzymes [54], or inhibition of tyrosin kinase-mediated signaling mechanisms downstream of insulin receptor [53]. Increased circulating FFA levels also negatively affect insulin secretion from pancreatic beta cells [55] and may cause inflammatory response in beta cells via activation of Toll-like receptors 2 and 4, acting like damage-associated molecular patterns that induce production of pro-inflammatory cytokines and recruit innate immune cells in the beta-cell surrounding [56]. Beside hormones that can cause or contribute to hyperglycemia (cortisol, growth hormone, epinephrine), activation of sympathetic nervous system, via β-adrenergic receptors, adipokines (resistin) and cytokines (TNFalpha, IL-6), adipocyte hypoxia is one of the factors that regulates lypolysis. A support for strong causal link between hypoxic condition, elevated circulating FFA and diabetes is seen in OSA patients after CPAP withrawal, in whom elevated levels of circulating FFA, glucose and cortisol were detected [52]. In a recent study that included 118 participants with or without sleep disordered breathing, severity of hypoxia assessed by AHI was as independent factor, in positive correlation with adipocyte insulin resistance, lypolisis with elevated FFA levels, and decrease of glucose- and insulin-mediated suppression of lipolysis [53]. Reversely, in patients with T2DM, presence of OSA increased lipolysis by 42% in comparison with patients with T2DM only, and this effect was independent from gender, BMI or waist circumference [51]. The main source of circulating FFA are adipocytes which have an important role in glucose homeostasis and they exert many of their role via secretion of numerous adipokines, including resistin, adiponectin and leptin. Adipose tissue macrophages, especially those from visceral abdominal fat, are an important source of inflammatory cytokines including IL-6 and TNF-α. These cytokines, in orchestra with other molecules involved in inflammation, like chemokines, adhesion molecules, C-reactive protein (CRP) and other acute-phase reactants, are found to be increased in OSA [57,58]. They contribute to worsening of metabolic homeostasis and may increase the risk for cardiovascular events in OSA patients [57-62]. It is shown in model *in vitro* that exposure of adipocytes to intermittent hypoxia mimicking hypoxic episodes in OSA, results in expression of adipokines that participate in insulin resistance, impaired glucose tolerance. and chronic mild inflammation [63]. In patients with untreated OSA, elevated plasma levels of proinflammatory resistin and decreased plasma antiinflammatory adiponectin levels were detected [64,65] which was associated with elevated plasma levels of interleukin 6 and activation of nuclear factor kappa B (NF-κB) [58]. Also, production of a potent inflammatory cytokine, TNF-α in OSA patients, is positively associated with severity of OSA, and negatively associated with adiponectin. TNF-α may increase a predisposition for T2DM and cardiovascular events as it decreases the synthesis of adiponectin which has a protective role in T2DM [66] Some studies indicate that treatment with CPAP efficiently reduces levels of TNF-α [67] and elevates adiponectin levels, although in this studies changes in insulin resistance index and BMI were not noticed [65].

In a search for sensitive and specific biomarker that could predict the development of diabetes and cardiovascular complications in a individual with OSA, two different author groups were performed extensive literature meta-analysis of many plasma inflammatory biomarkers (C-reactive protein, TNF-α, IL-6, IL-8, adhesion molecules ICAM-1), oxidative stress biomarkers (NADPH oxidase, nitric oxide) and biomarkers of carbohydrate and lipid metabolism (HbA1C, FFA and lipoproteins, levels of leptin, adiponectin and resistin) in OSA patients. All these different serum-derived parameters were proposed for the possible purpose of screening or clinical assessment of OSA [57,

[68]. However, still there is no ideal serum-specific biomarker that is consistently and specifically associated with both OSA and diabetes, and that could substitute time-consuming diagnosis with polysmonography and predict long-term complications [57,58]. The results linking a specific serum parameter and diagnosis or prognosis were often contradictory or non-consistent, and may depend of the other individual factors like disease stage and other comorbidities [57,58].

Chronic inflammatory reaction and oxidative stress can be linked with increased cortisol level in OSA patients. In OSA patients after withrawal of CPAP, increase of nocturnal levels of cortisol, with elevated levels of FFA and glucose was detected, and preexisting diabetes in OSA patient augmented hyperglycemic response. In the same study, increased sympathetic activity (heart rate) was also noticed [52].

Glucose intolerance in OSA and risk for developing T2DM may be potentiated by the increased sympathetic activity in patients with OSA as a result of chemoreceptor reflex and stimulation of nucleus tractus solitarii caused with IH and sleep fragmentation [69,70]. Increased sympathetic tone negatively affects insulin secretion by beta pancreatic cells, and contributes to the insulin resistance. In OSA patients with prediabetes, it is found that one week of treatment with CPAP significantly decreased circulating levels of daytime and nighttime norepinephrine levels in plasma [71, 72] In obese patients with T2DM, presence of autonomic neuropathy caused by diabetes, increases risk for OSA, impairing mechanoreceptor reflex in upper airways [73].

The connection between metabolic, hormonal and autonomnous nervous system factors that are common to both OSA and diabetes may worse the clinical outcome of these both diseases separately, or potentiate clinical worsening when they are found simultaneously in the same patient. Beside this connection which is more investigated, last several years increased interest has grown with a scope on the possible increased risk for colorectal cancer in patients with OSA and T2DM. Results of Zhou et al. showed that in the T2DM patients with OSA circulating CEA levels were significantly higher ($p<0.05$) than that in those without OSA. Beside the fact that the AHI score was independently linked with risk of increased CEA level in T2DM, in the male patients linear correlation was noticed between AHI score and CEA levels, with the highest CEA levels in the patients with AHI≥30 [74]. Furthermore, the highest CEA levels were measured in male patients with T2DM with obesity and had HbA1c level ≥7% [74]. Currently, the more data are required for the explanation of the possible pathogenetic connection between OSA, T2DM and colon cancer. Obesity may present the common link, as it is known that high-energy content and low-fiber nutrition can elevate levels of circulating IGF-1 and adipokine levels that can contribute to chronic inflammation, impaired immune system and growth of cancer cells [74].

The role of CPAP treatment in prevention of diabetes and its complications

It is still a question of debate whether CPAP, as a golden standard therapy for OSA, can prevent T2DM and its macrovascular and microvascular complications, and still there are no long-term data that consistently prove lower T2DM incidence in CPAP-treated OSA patients [26]. Some randomized controlled studies didn't show any significant effect of CPAP on glycemic parameters. There are sveral possible reasons for that, including poor patient compliance to CPAP. In some studies, CPAP was applied for a relatively short period (3,6 and 4,3 hours per night) [75-77]. Results of meta-analysis performed by Labarca et al. have showed that even more than 12 weeks of CPAP application didn't improve glycated hemoglobin levels [78]. However, two studies where CPAP treatment was applied in 8-hour sleep period during at least 1 week reported statistically significant fall in fasting and 24-hour glucose levels in patients with OSA and T2DM [71,72]. Although glycemic control was not significantly improved in mild or moderate OSA treatment by CPAP [79], in patients with severe OSA, CPAP treatment may prevent severe chronic diabetic complications [80]. Among ongoing studies, an extensive open-label, parallel-arm, randomised control trial cohort study SLEEP T2D is published as a preliminary project, with the aim to assess the impact of CPAP on microvascular complications in patients with T2DM during a period lasting at least two years [81].

Conclusion

In conclusion, obstructive sleep apnea and diabetes are both common diseases that coexist very often. They have common independent predisposing and pathogenetic factors, and the main of them is obesity. However, they can share many other pathogenetic factors like chronic inflammation, oxidative stress, hormonal changes and autonomic nervous system disbalance. This may lead to the additive or even synergistic effect in a patient, leading to accelerated development of atherosclerosis and its cardiovascular complications, and other possible conditions, including cancer. As OSA, obesity and diabetes type 2 are linked with increased risk for cardiovascular complications (including miocardial infarction, ischemic stroke, severe hypertension and arrhythmias), cardiovascular morbidity and mortality, special focus should be put on the early recognition of OSA simptoms in the patients with T2DM, and *vice versa*, patients with OSA should be regularly checked for presence of glucose intolerance or insulin resistance, in order to prevent long-term consequences. In all of these patients, special attention have to focused also on assesment and treatment of obesity.

Conflict of interest

The authors of this manuscript declare any conflict of interest.

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