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CARDIOVASCULAR AND METABOLIC IMPAIRMENT IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

Abstract

Since the moment when the obstructive nature of sleep apnea was first revealed, a lot of new in-formation on this disease has been obtained. Now obstructive sleep apnea (OSA) is recognized as an independent predictor of the development of impaired glucose tolerance (insulin resistance, fasting hyperglycemia), type 2 diabetes mellitus (DM2), resistant hypertension, cardiovascular death. The problem of identifying and treating patients with OSA is still actual. In real clinical practice, there is a need for an integrated approach to the diagnosis and therapy of comorbid OSA patients with metabolic disorder and cardiovascular diseases. **The objective** of this review is to assess the clinical and pathogenesis features of metabolic disorders, carbohydrate metabolism, basic metabolism, eating behavior, bodyweight fluctuations in patients with obstructive sleep apnea. **Methods**. In our work, we used a retrospective analysis of published clinical research data of domestic and foreign authors over the past 20 years. The review included studies with adequate design from the standpoint of good clinical practice (GCP) and evidence-based medicine. **The conclusion**. According to modern interpretation, obstructive sleep apnea is considered an independent disease with its pathogenic mechanisms, clinical and functional manifestations. There are several main causes of the effect of OSA on the metabolic component and the work of the cardiovascular system. Among them, intermittent hypoxemia, endothelial dysfunction, fluctuations in intrathoracic pressure, increased activity of the sympathetic nervous system, and the disorder of the structure of sleep are the leading ones. OSA is considered a disease capable of disabling patients of working age, dramatically changing the quality of life, and leading to early mortality due to cardiovascular disasters. Timely detection of clinical symptoms of OSA and the strategy of early administration of CPAP therapy significantly improve the quality of treatment and prognosis of comorbid patients.

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Ra — short leptin receptor, Rb — long leptin receptor, ROS — reactive oxygen species, BP — blood pressure, URT — upper respiratory tract, IL6 — interleukin 6, IR — insulin resistance, LA — pulmonary artery, LV — left ventricle, OSA — obstructive sleep apnea, BM — basal metabolism, RAAS — renin-angiotensin-aldosterone system, RCT — randomized clinical trial, DM — diabetes mellitus, FFA — free fatty acids, CVD — cardiovascular disease, TE — thermogenic effect, PA — physical activity, TNFα — tumor necrosis factor alpha

Introduction

The pathogenetic mechanisms underlying the development of metabolic and hormonal disorders in patients with respiratory disorders during sleep have not been fully studied. An important role is given to the increase in the activation of the sympathetic nervous system against nocturnal intermittent hypoxemia and deprivation of the vital stages of sleep — the main links in OSA pathogenesis [1]. Exposure to these causes disrupts metabolism and contributes to the progression of obesity in patients with OSA. There is a need to search for available clinical and pathogenetic predictors of

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individual predisposition to metabolic disorders in patients with OSA in order to justify the beginning of their primary prevention, the development of comprehensive programs for diagnosis and treatment of pre-existing disorders.

Obstructive sleep apnea (OSA) is a common disease affecting at least 20% of the adult population in urbanized countries [2], in which recurrent episodes of respiratory arrest (apnea) and partial reduction of respiration (hypopnea) occur during sleep lasting from 10 seconds. It has been proven that collapses of the upper respiratory tract repeating every night cause fragmentation of sleep, hypoxemia, hypercapnia, fluctuations in intrathoracic pressure, night-time increase in the activity of the sympathetic nervous system, development of systemic inflammation [3]. Currently, OSA is considered as an independent risk factor for cardiovascular disease (CVD) and metabolic disorders [4, 5].

OSA and Cardiovascular Diseases

The phenomenon of cyclic desaturation with rapid reoxygenation, known as intermittent hypoxia, initiates a cascade of vascular endothelial damage mechanisms [6]. Hypoxia and hypercapnia serve as potential stimulants of vasoactive substances (endothelin and vasopressin) that increase vascular tone leading to increased blood pressure (BP), left ventricular (LV) postload and its hypertrophy [7]. This chronic hypoxemia is accompanied by a reduced production of endogenous relaxing factors including prostacyclin, prostaglandin E2 and nitrogen oxide. These factors are the basis of pulmonary vasoconstriction and increased pressure in the pulmonary artery (PA), which contributes to the development of pulmonary hypertension, hypertrophy and dysfunction of the right ventricle [8]. After respiratory arrest there is always a period of hyperventilation with a typical increase in the amplitude of negative intrathoracic pressure which increases venous blood flow and leads to right atrium distension. Polycythemia, which develops in chronic hypoxemia, contributes to increased blood pressure in PA, increases blood viscosity and is a risk factor for thromboembolism and sudden death in patients with OSA [9].

Disorders of autonomic functions in combination with activation of the renin-angiotensin-aldosterone system (RAAS) and decreased sensitivity of the kidney to the natriuretic hormone can cause persistent drug refractory hypertension and congestive heart failure [10].

OSA and Obesity

OSA can be both an independent disease and a syndrome developing with other pathologies. The prevalence of OSA in patients with overweight exceeds 30%, reaching up to 50–98% in patients with morbid obesity [11]. There is convincing evidence that it is the abdominal type of obesity in patients with OSA, as well as the deposition of visceral fat in the pharynx that contribute to the narrowing of the upper respiratory tract and the development of respiratory arrest during sleep [12].

Normally, the lumen of the respiratory tract is an ellipse with long transverse and short anteroposterior axes. In obesity the shape changes to an oval with long anteroposterior and short transverse axes. According to magnetic resonance imaging of the neck in patients with OSA, such change in the shape of the pharynx with marked luminal narrowing is due to the presence of fat deposits in the soft tissues of the pharynx. With decreased tone of the pharyngeal muscles the probability of the pharynx collapse at the level from palatine uvula to the epiglottis increases. The amount of fat in the lateral walls of the pharynx is a predictor of respiratory disorders and correlates with the severity of OSA. However, visceral fat is not only a mechanical barrier to air passage through the respiratory tract, but also an important structure that triggers metabolic disorders in patients with OSA. For this reason, the measurement of neck circumference is required along with the measurement of waist circumference and body mass index in obese patients [13].

In addition to energy deposition, adipose tissue is a complex hormone-active organ that plays an important role in the regulation of energy balance and homeostasis of the body as a whole [14]. Adipocytes produce about 600 adipokines, which are bioactive substances acting on the basis of paracrine, autocrine, or endocrine effects, and performing communication with the central nervous system, heart, muscle tissue, blood vessels, pancreas, other organs and tissues [15]. Adipokines include classical cytokines, chemokines, proteins of alternative complement system; proteins regulating vascular

homeostasis, angiogenesis, blood pressure, lipid and carbohydrate metabolism [16]. The most studied adipokine of adipose tissue is leptin which means 'thin' or 'spindling' when translated from Greek. Adipocytes secrete leptin in amounts proportional to the mass of adipose tissue. There is evidence of the auto-paracrine leptin effect on the metabolic activity of adipocytes: inhibitory in respect of lipogenesis and stimulatory in relation to lipolysis [17]. In the blood, leptin circulates both in the free and in protein-bound state. Leptin receptors belong to the class of cytokine of type 1. There are 2 isoforms of leptin receptors: long receptor (Rb) localized in the brain and short receptor (Ra) — in peripheral organs and tissues. Rb receptor is localized in satiation center — in ventromedial nucleus of the hypothalamus, as well as in the arcuate, dorsomedial and paraventricular nuclei. Leptin integrated into the feedback system with hypothalamic neuropeptides, especially with neuropeptide Y, is involved in the regulation of energy balance. After penetration into the hypothalamus leptin suppresses appetite through the limbic lobe and brain stem. By stimulating the activity of the sympathetic nervous system, leptin reduces energy consumption and increases its expenditure. The presence of leptin receptors in peripheral organs and tissues (fat, liver, skeletal muscles, pancreas, ovaries, prostate, placenta, kidneys, and lungs) explains its effect on hematopoiesis, angiogenesis, immune responses, blood pressure, and bone metabolism [18].

Most patients with OSA have not only elevated blood leptin levels, but also resistance to leptin. There is no clear concept of mechanisms for sensitivity to leptin in patients with OSA, but there are several hypotheses. According to one of them, there is a slowdown in the penetration of leptin through the blood-brain barrier. According to another hypothesis, decrease in sensitivity to leptin is associated with a breakdown in the work of a specific transport protein, since the hormone circulates in a bound state. The third reason may be a decrease in the sensitivity of hypothalamic receptors to leptin and the disruption of its interaction with said receptors [19]. Excessive amount of leptin and especially resistance to leptin in patients with OSA can cause carbohydrate and lipid metabolism disorders, as well as many potentially atherogenic effects: induction of endothelial dysfunction, impaired platelet aggregation, migration, hypertrophy and proliferation of vascular smooth muscle cells [20].

Tumor necrosis factor alpha (TNFα), insulin, glucocorticoids, estrogens and interleukin-1 stimulate the secretion of leptin. The following substances inhibit the secretion of leptin: catecholamines, androgens, free fatty acids, growth hormone, thyroid hormones, as well as overeating and high fat foods. The second most important adipokine in the pathogenesis of metabolic disorders in patients with OSA is TNFα.

In adipose tissue, ***TNFα*** is suppressed by both adipocytes and preadipocytes. In this case, the cytokine itself affects the differentiation of fat cells and apoptosis of pre- and adipocytes. The increase in TNFα production is associated with the development of insulin resistance, especially in adipose tissue in patients with OSA. Under its influence, the activity of tyrosine kinase of insulin receptor decreases, and phosphorylation of serine substrate of insulin receptor 1 increases; expression of GLUT4 in fat and muscle tissue decreases. Through the activation of hormone-sensitive lipase in adipocytes, TNFα stimulates lipolysis and inhibits the activity of lipoprotein lipase [21].

In the liver, TNFα suppresses the expression of genes involved in glucose uptake and metabolism, fatty acid oxidation; increases the expression of genes involved in de novo synthesis of cholesterol and fatty acids. TNFα has a direct inhibitory effect on the secretion of thyroid hormones and deiodinase activity in the thyroid [22].

Interleukin 6 (IL6) is the third most important cytokine produced by visceral adipocytes, which, in patients with OSA, is associated with disturbed energy homeostasis, thermogenesis, pulsed secretion of luteinizing hormone, growth hormone. By stimulating the formation of C-reactive protein, IL-6 contributes to the development of endothelial dysfunction and the risk of cardiovascular complications in patients with OSA. This cytokine reduces the expression of lipoprotein lipase exerting a local effect on the absorption of free fatty acids (FFA) by adipocytes. IL-6 has a direct effect on metabolic processes in the liver by suppressing the sensitivity of insulin receptors therein. TNFα, glucocorticoids and catecholamines stimulate IL-6 production [23].

Adiponectin is secreted exclusively by mature adipocytes. Normally, adiponectin reduces insulin resistance by stimulating phosphorylation of tyrosine (insulin receptor); reduces FFA intake in the liver and stimulates their oxidation by activating protein kinase contributing to the reduction of glucose production by the liver and synthesis of VLDL triglycerides. In muscle tissue adiponectin stimulates FFA oxidation, reduces intracellular lipid accumulation and improves the sensitivity of muscle tissue to insulin. The experiment also showed that adiponectin had anti-inflammatory and antiatherogenic effects. In the vascular wall, adiponectin inhibits adhesion of monocytes to the endothelium by reducing the expression of adhesion molecules, suppresses the transformation of macrophages into foam cells, reduces proliferation and migration of smooth muscle cells, LDL uptake of the evolving atherosclerotic plaque and production of TNF-α in macrophages. Adiponectin increases nitrogen oxide production in endothelial cells, stimulates angiogenesis. In patients with OSA, reduction of adiponectin synthesis leads to a decrease in its protective properties against the vascular wall due to the progression of atherosclerosis because of lipid metabolism disorders (high levels of LDL, VLDL, triglycerides, significant increase in atherogenic index) [23].

Resistin is produced mainly by preadipocytes and to a lesser extent by mature adipocytes of visceral adipose tissue. The role of this polypeptide in insulin resistance development mechanisms has not been completely elucidated in patients with OSA. With regularly recurring episodes of apnea throughout sleep time, hypertrophy and hyperplasia of adipocytes occur in adipose tissue. As a result the production of cytokines changes, their function is impaired and consequently systemic metabolism fails [23].

Nocturnal Hypoxemia, OSA and Basal Metabolism

Patients with OSA are characterized by the development of energy imbalance (mismatch between energy consumption and expenditure) as a result of disturbance of several major factors affecting energy consumption.

The first one is the level of basal metabolism (BM). It should be proportional to body weight (without fat) and body surface, meet energy expenditure on maintenance of basic physiological functions in standard conditions (in a state of wakefulness and rest, warmth, at least 12 hours after eating).

The second one is thermogenic effect (TE). It represents a specific dynamic action of food which is about 5–15% of the total energy expenditure and is associated with additional energy consumption on digestion with the stimulation of metabolism due to the influx of a new substrate. The third factor is physical activity (PA) [24].

Intermittent hypoxemia is a triggering mechanism of disturbance in basal metabolism in this category of patients. Recent publications report that desaturation index is inversely proportional to energy consumption in sleep and during wakefulness. Postalimentary thermogenesis in obese individuals is significantly lower than in individuals with normal body weight, which may partly be due to disturbance of the sympathetic nervous system activity, as well as to disturbance of sensitivity of β-adrenergic receptors to catecholamines. Disturbance of adaptive thermogenesis function in patients with OSA causes a marked increase in body weight and also creates difficulties with its reduction. A number of scientific papers managed to establish an independent relationship between energy consumption at rest and the severity of respiratory disorders in sleep. As the severity of OSA increases, the respiratory coefficient increases, which leads to the oxidation of carbohydrates instead of fats and to the activation of stress systems. These mechanisms are predisposing for the development of obesity in patients with respiratory disorders at night [25].

Oxidative stress also contributes to the potential mechanisms of metabolic disorders in patients with OSA. The hypoxia/reperfusion cycle in OSA is the basis for increasing the production of reactive oxygen species (ROS). In the human body most metabolic and physiological processes occur with the participation of oxygen, resulting in the formation of aggressive oxygen forms or highly reactive oxygen radicals in cells. The latter include hydrogen peroxide, hydrogen radical, superoxide

anion radical, hypochloric acid and many others. Normally, mitochondria produce intracellular oxygen radicals, which in physiologically low concentrations are involved in the regulation of synthesis of prostaglandins, leukotrienes, thromboxanes, provide cellular immunity, and regulate the growth and differentiation of body cells. In large quantities they can activate free radical oxidation of lipids, damage RNA and DNA, fats and proteins (including enzymes), leading to tissue damage and cell death [26].

To maintain the balance of free radicals, the body employs an antioxidant system which includes urates, glutathione, ubiquinone, thioredoxin, some proteins (ferritin, transferrin, ceruloplasmin, lactoferrin), etc. Oxidative stress occurs when there is an imbalance between reactive oxygen species and the antioxidant system. Intermittent hypoxia accompanying OSA leads to the activation of some NADPH-oxidases, which promotes oxidative damage and increased inflammatory response [27].

In addition to systemic hypoxemia, an increase in fat mass in patients with OSA is accompanied by local hypoxia, which causes the development and maintenance of inflammation of adipose tissue. As a result of the inflammatory reaction, c-Jun-N-terminal kinase (JNK), Kappa bi kinase inhibitor (IKK) and protein kinase are activated. This leads to the release of the nuclear transcription factor of Kappa bi nuclear factor (NF-κB) and hypoxia-induced factor-1 (HIF-1) in cytosol in both adipocytes and macrophages. NF-κB migrates into the cell nucleus and stimulates gene transcription of numerous regulatory substances, including adipokines. Cytokines induce an inflammatory shift in adipocytes which causes an even greater increase in cytokine production. This fact served as the basis for the idea that inflammation of adipose tissue is a self-sustaining process: once initiated, it progresses without the presence of additional factors. At the same time, the more severe night hypoxemia in patients with OSA is, the faster and more significant the inflammation of adipose tissue develops. The typical morphological sign of adipose tissue inflammation is its infiltration by macrophages. In this case, they can be up to 40% of all cells of adipose tissue. With the progression of inflammation secondary to respiratory arrest, fibrosis characterized by the accumulation of connective tissue cells and extracellular matrix in the form of an amorphous zone around hypertrophied and/or dead adipocytes develops [28].

Data on the presence of innate immunity receptors in adipocytes, Toll-like receptors (TLRs), primarily TLR4, are of particular interest for understanding the pathogenesis of metabolic disorders in patients with OSA as a result of inflammation of adipose tissue. A specific ligand of TLR4 is lipopolysaccharide (LPS). Activation of TLR4 involves intracellular kinases. They provide the transfer of the nuclear factor NF-κB into the cell nucleus with the subsequent activation of the formation of proinflammatory genes encoding the synthesis of cytokines, chemokines, adipokines. Stimulation of TLR4 in isolated adipocytes increases the secretion of IL-6, TNFα, resistin and decreases adiponectin level. The combination of these reactions causes the development of insulin resistance (IR) in adipocytes, hepatocytes and muscle cells. Activation of TLRs significantly increases lipolysis. It was found that the presence of TLR4 is a necessary condition for the infiltration of the gastrointestinal tract by macrophages, i.e. a condition for the development of inflammation in adipose tissue [29].

Eating Disorder in Patients with OSA

Eating disorder contributes to excessive weight gain in most patients with OSA. There is a failure of the systems controlling the internal need for food. Programs on excessive storage of nutrients start with blunting satiety and slowing energy consumption.

The energy balance is regulated by two types of neurons in the arcuate nuclei [30]:

1. Proopiomelanocortin neurons (POMC) that produce alpha-melanocyte-stimulating hormone (α-MSH), cocaine and amphetamine-mediated transcripts (CART). They reduce food consumption and increase energy consumption.
2. Neurons producing melanin-mediated protein (AGRP, or agouti-related protein) and neuropeptide Y (NPY, NPN). They increase food consumption and reduce energy consumption.

Alpha-melanocyte-stimulating hormone secreted by POMC-neurons stimulates melanocortin

receptors (MCR3 and MCR4) of paraventricular nuclei, which then activate the neuronal pathway projected onto the nucleus of the solitary tract and increase sympathetic activity and energy consumption. Melanin-mediated protein acts as an antagonist of MCR4 [31].

Insulin, leptin and cholecystokinin (hormones inhibiting AGRP- and NPY-neurons and stimulating adjacent POMC- and CART-neurons) reduce food intake [32].

Ghrelin is produced mainly by P/D1-cells of the mucous membrane in the fundus of the stomach. Ghrelin activates AGRP- and NPY neurons and stimulates food intake. It circulates in the blood mainly in an inactive form and becomes biologically active (acylated ghrelin) in response to fasting. During sleep there is an increase in total ghrelin with a decrease in the total/active ghrelin ratio compared to wakefulness. Distension receptors of the stomach activate sensory afferent pathways within the vagus nerve and together with gastrointestinal hormones (peptide YY (PYY) and cholecystokinin) suppress appetite and further food intake [33].

Hypothalamus and brain stem structures (arcuate nucleus, paraventricular nucleus, single pathway nucleus, dorsal motor nucleus of the vagus nerve, etc.) are involved in the perception of satiety signals mediated by hormones, adipokines, neuropeptides and their metabolites and in the transformation of the information into behavioral reactions. However, the functional organization of the hypothalamus or other nerve centers responsible for eating behavior in people with obesity is different from that in people with no excess body weight. The transformation of the peripheral signal occurs via neurotransmitters which include catecholamines (dopamine, adrenaline and norepinephrine) and indolamines (serotonin). Dopamine, norepinephrine and adrenaline are successive links in sequence of transformations of amino acid tyrosine. The role of dopaminergic neurons in the regulation of eating behavior is extremely important [34].

There are known 5 types of dopamine receptors which are divided into 2 subtypes depending on the effects on adenylate cyclase — D1-like (D1, D5) — activating and D2-like (D2, D3, D4) — inhibitory. The role of D1-like receptors in the regulation of eating behavior has not yet been proven. The role of D2-like receptors is determined not only by their number, but also by the location [35].

Norepinephrine implements its action in the cells of paraventricular and ventromedial nuclei of the hypothalamus. Exposure to α1-, β2- and β3-adrenergic receptors leads to decreased appetite, while stimulation of α2-receptors, on the contrary, stimulates appetite. Serotonin is one of the most important transmitters involved in the regulation of energy homeostasis, which consists in stimulation of some types of neurons and inhibition of others in the hypothalamus by peripheral hormones. It is a compound which, in the human body, has a hormone and neurotransmitter function. Its highest concentration is observed in the pineal gland, where it serves as a precursor for melatonin biosynthesis. Melatonin is the main component of the body's starting system, the function of which is to transmit information on light regime to the body with regulation of the sleep-wake cycle [36].

Serotonin is synthesized from tryptophan. The effects of serotonin are realized through its receptors. In the pathogenesis of obesity, only part of them is involved: 5-HT2C, 5-HT1A and 5-HT2B as well as the still underexplored 5-HT6 [37].

The target of serotonin action is the melanocortin system. In the arcuate nuclei of the hypothalamus, serotonin activates POMC/CART-neurons, which leads to increased production of α-MSH and, consequently, decreased food intake, and interaction with ATP-neurons prevents the suppression of α-MSH secretion. The serotonin produced in the digestive tract also contributes to energy regulation by stimulating the motility of the gastrointestinal tract and the secretion of hydrochloric acid in the stomach and bicarbonates in the duodenum and carries vasoactive properties in the mucous and submucous membranes and determines the sense of taste. The following is necessary for the production of serotonin in the body: 1) dietary intake of tryptophan — essential amino acid needed for the direct synthesis of serotonin in the synapses; 2) glucose intake, stimulation of insulin release into the blood, stimulation of catabolism in the tissues and, consequently, increased tryptophan level in the blood [38].

Bulimia and addiction to carbohydrate-rich food may be directly related with these facts. Serotonin can cause a subjective feeling of satiety, and when the body takes in food, including tryptophan,

production of serotonin increases, which lifts the mood. The brain quickly establishes the connection between these phenomena — and in the case of depression (serotonin fasting) it immediately requires additional tryptophan or glucose intake with food. The most tryptophan-rich foods that are almost entirely composed of carbohydrates, such as bread, bananas, chocolate, or pure carbohydrates: sugar or fructose [39].

The reason for the failure of the normal functioning of hypothalamus and pineal body centers responsible for the energy balance in patients with OSA is hyperactivation of the sympathetic nervous system, which is repeated every night, as a result of intermittent hypoxemia and sleep structure disorders. This leads to an imbalance of hunger and satiety, disruption of the daily eating rhythm.

Night eating syndrome often develops when patients have a strong feeling of hunger in the evening and at night. They cannot sleep without eating too much food. However, in some cases it does not bring satisfaction. Mental disorders can often develop. A sharp increase in food consumption, an increase in calorie intake due to easily digestible carbohydrates and fats in patients with OSA is a kind of protective mechanism against anxiety and emotional discomfort. Reduced physical activity due to excessive daytime sleepiness further exacerbates weight gain and contributes to the progression of night respiratory disorder. A vicious circle is formed. A large proportion of the consumed nutrients unbalanced by the processes of liposynthesis is transformed into metabolically inert fat mass. The growing metabolic needs are compensated with excess food. This leads to inadequate use of the energy resource or cell starvation which in sleep apnea phenomena is supplemented by oxygen starvation with even greater accumulation of visceral fat [40].

OSA and Carbohydrate Metabolism Disorders

Currently, OSA is considered as an independent risk factor for glucose intolerance (insulin resistance (IR), fasting hyperglycemia) and diabetes mellitus (DM). According to randomized clinical trials (RCTs), the development of carbohydrate metabolism disorders occurs in 29.6% of patients with mild OSA, in 50% of patients with moderate OSA and in 61.8% of patients with severe apnea. Epidemiological studies conducted in different countries and populations revealed a significant relationship between the apnea-hypopnea index and the risk of IR, DM2 development [41].

One of the objectives of the multi-center population-based cohort study, Sleep Heart Health Study (2004), was to identify the relationship between OSA, glucose intolerance and insulin resistance in the general population. Polysomnography, detection of insulin, fasting glucose, HOMA-index and OGTT were performed in 2,656 patients. Compared with the reference group (IAG < 5/h), in patients with moderate to severe OSA the odds ratio for glucose intolerance was 1.27 and 1.46, respectively, after adjustment for age, sex, BMI and waist circumference. HOMA index increased in the studied subjects as the average saturation decreased during sleep. It is known that the increase in body weight, especially due to visceral fat, is a risk factor for the development of IR. The results of the Sleep Heart Health Study showed that OSA is associated with abnormal fasting glucose level and glucose intolerance regardless of gender, age, race, BMI and waist size. The authors concluded that OSA leads to impaired glucose metabolism regardless of obesity. Sleep apnea increases the risk of developing diabetes through pathophysiological mechanisms different from those in obesity [42].

A number of studies have found that each additional sleep apnea increases fasting insulin levels and HOMA-index by 0.5% in one hour of sleep. In addition, the level of HbA1c and fasting glucose are higher in patients with OSA compared to those who did not have respiratory arrest at night regardless of body mass index [43, 44].

A number of population studies have demonstrated disorders of carbohydrate metabolism not only in OSA, but also in the presence of snoring. Follow-up study of 2,668 men aged 30–69 years for over 10 years showed that snoring men with obesity are 7 times more likely to be at risk of developing diabetes than non-snoring men with obesity regardless of age, weight gain, smoking, alcohol and physical activity [45].

Data from another study titled Nurses' Health Study involving 69,852 nurses aged 40–65 years without diabetes, cardiovascular diseases and tumors at the time of the study showed that for 10 years constant snoring leads to a 2-fold increase in the risk of developing DM2 regardless of age and BMI. It was found that when severity of OSA increased regardless of age and BMI, fasting and post-exercise glucose levels increased, and insulin sensitivity decreased [46].

The pathogenesis of carbohydrate metabolism disorders in patients with OSA includes several interrelated links. Intermittent hypoxia and fragmentation of sleep cause an increase in the activity of the sympathetic nervous system and in the level of catecholamines; there is an increase in cortisol levels associated with impaired regulation of the hypothalamic-pituitary-adrenal axis. Catecholamines stimulate glycogenolysis, gluconeogenesis and glucagon secretion. In addition, the activation of SNS stimulates lipolysis, thereby increasing the circulation of free fatty acids and glycerol in the portal bloodstream. By entering the liver, FFAs become a substrate for the formation of atherogenic lipoproteins, and also prevent the binding of insulin to hepatocyte. Insulin resistance of hepatocytes leads to a decrease in glycogen synthesis, activation of glycogenolysis and gluconeogenesis. With the depletion of pancreatic B cell function, decompensation of carbohydrate metabolism occurs, first in the form of impaired fasting glycemia, glucose intolerance, and then as type 2 diabetes [47].

Oxidative stress initiates systemic inflammation which affects the metabolism and secretion of adipose tissue, increases levels of circulating interleukins and TNFα. The anti-steatogenic effect of leptin is impaired. Normally, by affecting the activity of AMP kinase, it increases fatty acid oxidation in muscles, reduces the content of intramyocellular lipids, increases tissue sensitivity to insulin, thereby protecting the body against the development of lipotoxicity. In the treatment of patients with OSA in combination with metabolic and hormonal disorders it is important to prevent the development of pharyngeal collapse, to decrease of the sympathetic activity secondary to nocturnal hypoxemia, and to eliminate coarse fragmentation of sleep. It is necessary to break the vicious circle of vascular endothelial damage, to reduce cardiovascular risks, to normalize carbohydrate and lipid metabolism, and to restore adequate processes of energy metabolism and eating behavior of patients [48].

According to the results of several studies, respiratory support using different variants of masks in constant positive airway pressure (CPAP) mode is able to solve set tasks. Respiratory support is aimed at creating an air stent that counteracts the development of upper respiratory tract collapses (URT) and sleep apnea [49].

Unfortunately, the effect of CPAP therapy on metabolic syndrome remains little-understood. In most studies, there was a significant stabilization of blood pressure using CPAP [50]. In studies on the effects of CPAP therapy on insulin resistance and lipid profile conflicting results were reported. The choice of ventilation support modes, duration thereof and development of algorithms for complex treatment of patients with OSA and metabolic syndrome require further studies [51].

Conflict of interests

The authors declare no conflict of interests.

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