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Asthma and obesity – variant of comorbid pathology

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Abstract: ***The prevalence of comorbidity disease among patients of different ages is quite high and tends to increase . The presence of several diseases in the one patient at the same time affects each of them for their weights, promotes earlier formation creates complications and difficulties for the therapy. Particularly noteworthy is the combination of diseases that share common or similar etiological and pathogenetic factors. One of the most common types of comorbidity is a combination of asthma and obesity. Modern research has found a direct link between the increase in the incidence of asthma with increasing body mass index, and in patients with bronchial asthma incidence of overweight and obesity is twice higher than in the average. The current of asthma in overweight patients is more severe and it is difficult to control. Excess weight has a negative effect on the function of the respiratory system. In the analysis of the basic pathogenetic link of these comorbidities identified violations of immune system, there is an imbalance of production of proinflammatory and antiinflammatory cytokines – interleukins, recorded development of oxidative stress, there is disruption of nitric oxide production and activation of one of the types of eicosanoids – leukotrienes . Thus, as shown by the results of studies, asthma and obesity, are diseases in the body – forming sustained inflammation. Currently described and formulated many mechanisms by which obesity on asthma, but the approaches to the treatment of this comorbidity condition developed only taking into account some of the pathogenesis. Many components of the pathogenesis of this combined states remain unexplored and possible correction – unexplored.***

Keywords: asthma, obesity, comorbid pathology..

1. Introduction

The treatment of comorbid conditions is an important and difficult in medical practice. Senescence of population, bad habits, physical inactivity, poor nutrition, impairment of environmental create conditions with constant stress of adaptation mechanisms in the organism of the modern person, and as a result the formation at the same time of several diseases. The prevalence of comorbid disease among patients on average 78,6%, and this condition as women occursin in 82% of cases, and in men - 72% of cases [2,5]. The number of comorbid diseases in one patient is significantly increased with age. So the researchers observed that multimorbidity in age less 19 years increased from 10% up to 80% in individuals 80 years and older [56]. The presence of several diseases at the same time influences each of them, burden them, encourages earlier formation of the complications and creates difficulties of therapy. The risk of death when the presence of two concomitant diseases is 5-10%, and when number of disease increasing to five – risk increases to 70-80% [62]. Special attention is given to the combination of disorders that have common or similar etiological and pathogenetics factors.

One of the common types of comorbidity is the combination of bronchial asthma and obesity. The prevalence of both diseases in recent years has increased significantly [33]. According to the WHO and GINA (2012) currently, approximately 300 million people worldwide suffer from asthma. The prevalence of asthma is on average from 7 to 15 % of the population in different countries, and this number is progressively increased. Deaths worldwide from this disease has also increased up to 250 000 cases annually. In turn, more than 30% of the world's population is obese, and WHO experts predict its increase in the future.

So, today we can note a parallel increase in the prevalence of obesity and asthma in worldwide.

According to Vortmann M., 2008 [71] among patients with asthma, 28 to 44% have different degrees of obesity. Modern studies of the incidence of asthma in patients with various level of body mass index (BMI) found a direct relationship of the increase in the incidence of asthma with increasing BMI [40]. At the same time it was revealed that patients with asthma the prevalence of overweight and obesity is twice higher than average in the population [67].

In patients with comorbid asthma and obesity remains low, the rate of achieving asthma control [16]. In GINA 2013 obesity along with genetic factors and sex of the patient is indicated as one of the main risk factors for development of asthma and worsening of disease control. The combination of asthma and obesity may contribute to mutual burdening and the formation of a "vicious" circle, joined by other pathogenetic mechanisms that worsen the course of asthma [34]. On the one hand, obesity even in the absence of asthma, leads to physiological changes in lung function [41]. It was noted that people with obesity spend more time in the room, thereby increasing the chances for development of ad due to the high content of room allergens, tobacco. And on the other hand, the presence of asthma reduces the physical activity of the patient, that the existence of increased appetite in patients receiving glucocorticoids leads to an increase in the weight of the patient. In addition, the frequency of hospitalizations of patients with obesity, in connection with the aggravation of asthma during the year of 2-4 times more compared to patients with normal weight and the same degree the severity of asthma, and depends on the severity of obesity. The need for systemic

corticosteroid therapy in patients with combined asthma and obesity is almost twice as high [50]. One of the essential features of the asthma course on the background of obesity is less pronounced, the effectiveness of the basic therapy with the use of inhaled corticosteroids, often accompanied by an increase in the daily dose of these drugs and reduces the quality of asthma control [37].

The first studies of the interaction of asthma and obesity has been demonstrated in work on mice, and laid the beginning of the study of pathogenesis and the nature of the relationship of these diseases [64]. So, the researchers noted that airway reactivity was increased in mice suffering from obesity, even without problems of the respiratory system. This resulted in increased attention of researchers to the features of the asthma on the background of overweight and obesity [34,40,42,55], however, the pathogenetic peculiarities of combined course of these diseases is not fully elucidated.

Impact of overweight on the function of the respiratory system simultaneously is implemented through several mechanisms, among them changes in respiratory mechanics, immunological and hormonal disturbances [66].

In healthy persons a mechanical effect of excess weight manifests by influencing the physiology of respiration due to excessive deposition of adipose tissue on the diaphragm, on the internal surface of the chest and around the ribs as well as a decrease in the elasticity of the chest walls. This leads to difficulty in increasing the volume of the thorax on inspiration. Excess fatty tissue in the mediastinum restricts the mobility of the lungs, in the abdominal cavity contributes to the development of dysfunction of the diaphragm, limiting its excursion [34,61]. Changes in the mechanical properties of the respiratory system manifested in the disorders of external respiration function: high BMI was a reduction of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and vital capacity (VC). The reason for lower respiratory volumes was a decrease in the function of the respiratory muscles, the presence of smaller-diameter distal airways, compared with individuals with normal body weight [42].

At the same time marked the formation of reducing the elasticity of lung tissue and increased airway resistance that results in the violation of external respiration function by mixed type. Due to a decrease a lung volumes restrictive component is formed of respiratory function disorders, and obstructive – due to the constriction of the distal airways [21,61]. In individuals with asthma and obesity noted a more significant decrease in FEV1 and other respiratory volumes, and the reduction of body weight in patients with asthma and obesity leads to an improvement of respiratory function and reduce the severity of asthma symptoms [41,45,66]. So when weight loss for every 10% of the initial, there was an increase FVC of 92 ml, and the increase FEV1 of 73 ml [45].

In patients with overweight asthma occurs in more severe form, it is difficult controlled and the results of the study accompanied by a 4.6 times higher risk of hospitalization compared with asthmatic patients without obesity. The presence of systemic inflammation, support the active substances produced by adipose tissue changes of clinical and biological response to corticosteroid therapy. One of the reasons for reduced response to therapy with steroids in these patients is the predominance of neutrophilic, but not eosinophilic inflammation in the bronchi [11,13]. The combination of these factors explains possible reasons that the asthma in such patients is difficult to control.

Patients who are obese and overweight more often recorded gastroesophageal reflux disease (GERD), the frequency of which increases with increasing BMI. On the one hand GERD increases the frequency of bronchial obstruction in patients with asthma by activation of gastric contents in the esophageal-gastric reflux and nerve vagus stimulation, and by direct microaspiration of stomach contents, leading to exudative inflammation of the bronchial mucosa and bronchial hyperreactivitye. On the other hand, the presence of asthma leads to the development and maintenance of gastroesophageal reflux because of an increase in the pressure gradient between the thorax and the abdomen.

Many pathophysiological relationships are found between asthma and obstructive sleep apnea. So the increased vagus nerve tonus contributes to bronchoconstriction, and inflammation of the upper respiratory tract, support the inflammation of the distal bronchi, and as a result, disorders of the central regulation of breathing and bronchial tone [34].

According to the modern concept asthma is chronic inflammation of the respiratory tract of various etiologies, involving immune and non-immune mechanisms [20]. The basis of pathogenesis of asthma is the disbalance of T-lymphocytes helper (Th) with activated Th type II, resulting in the development of chronic local inflammation. The disbalance of subpopulation structure of T-lymphocytes in asthma is accompanied by stimulation of B-lymphocytes, combined with dysimmunoglobulinemia [3]. The immune inflammatory response is manifested by the development of cellular and humoral reactions. However, the division into cellular and humoral rather conditional, since the immune response is a unified process involving various cellular elements depending on the type of antigen, with the obligatory participation of specific antibodies and other humoral factors (mediators, cytokines, immunoglobulins, CEC, etc.), which may be disturbed in various pathological conditions [17, 27, 68].

The violations in the immune balance can be regarded as a secondary immunodeficiency [4]. Proof of this is revealed in patients with asthma a reduction in overall population of T-lymphocytes in the blood serum and the disbalance of cellular immunity. The intensity of immune imbalance correlates with the degree of severity of the disease, patient's age and period of disease onset, features of therapy, the presence of comorbid pathology. The presence of concomitant visceral obesity, on the one hand, strengthen immune abnormalities in patients with asthma [26], which leads to inefficiency of basic treatment and creates conditions to the use of complementary medicines, for example, quercetin [25]. On the other hand, obese patients revealed increased immune responses mediated by Th2 under the influence of constant excess synthesis of IL – 6 [31].

As can be seen, the status of the main indicators of the immune system in patients with asthma associated with obesity, rather contradictory, which creates prerequisites for in-depth study of immune disorders with such comorbidity.

A product of activated immune cells are the cytokines. In asthma, the most studied are the pro - and anti-inflammatory cytokines – interleukin (IL)-1β, IL-4, IL-6, IL-8, IL—10, TNF-α. They participate in regulating the extent and duration of inflammatory and immune responses, markers of the effectiveness of the therapy asthma [32].

Adipose tissue is now considered not as a passive energy storage, and as an important endocrine organ with a number of

effects, including on the immune system and the cytokine profile [44]. In particular, adipose tissue is a source of secretion of several proinflammatory mediators - adipokines, cytokines, such as TNF-α, IL-4,IL-5,IL-6,IL-13, vascular endothelial growth factor. At the same time of obesity inhibited the synthesis of anti-inflammatory cytokine adiponectin and IL-10 [26]. In patients with obesity, much attention is paid IL - 6, which is one of the key mediators of inflammation in obesity. It is known that about 30% of the total circulating blood IL-6 accounts for synthesized in adipose tissue. With obesity levels IL-6 is increased under the influence of TNF-α and IL - 1.

Increasing the concentration of proinflammatory IL-1β, IL-6 and reduced anti-inflammatory IL - 4 when obesity in patients comorbid with deforming osteoarthritis [19] and nonalcoholic steatohepatitis, associated with chronic bronchitis [15]. At the same time, IL-4 is the key pro-inflammatory cytokine in asthma. Obesity in patients with asthma was accompanied by decrease of IL-10 [26].

Taking into account the above, the serum content and peculiarities of interaction of these cytokines in the combination of asthma and obesity are of research interest, since the disbalance of cytokine production towards proinflammatory ones can be a factor in maintaining systemic inflammation

In the pathogenesis of obesity great importance is the disturbance of leptin metabolism as one of the hormones secreted by adipose tissue. Leptin is a protein encoded in the genome of the fat cells, causing obesity. Leptin is involved in the regulation of body weight. The level of leptin increases with obesity in men and women. Studies on the correlation between the concentration of leptin in serum and degree of obesity showed that the concentration of leptin increased in patients suffering from obesity. Reducing body weight by 10% leads to decrease of leptin concentrations by 53%. On the contrary, a 10% weight gain on 300% increases in serum leptin. The effects leptin is the signal of satiety, thus inhibiting appetite, increase energy consumption and participation in the regulation of breathing [14]. Also the leptin action on T-cell immunity, which is manifested in the synthesis of proinflammatory cytokines through stimulation of T-helper cells [49]. Leptin stimulates hypersympathicotonia and contributes to increasing the level of adrenocorticotropic hormone, cortisol, aldosterone [51]. Last studies in vitro showed that leptin is also able to stimulate the activity of growth factor vascular endothelial smooth muscle cells of the airways [69], the improvement of which can lead to stimulation of subepithelial neovascularization, increased vascular permeability and formation of endothelial dysfunction.

One of the effects of leptin is effects on inflammation via the increased synthesis and release of leukotrienes from alveolar macrophages and lymphocytes [52]. These findings were confirmed in studies that demonstrated the regulatory effect of leptin on system IL. So, there is a marked increase in the production of IL-3, IL-6 and TNF-a [53], expression of adhesion molecules on endothelial cells [46] under the action of leptin. Because of the ability of leptin to induce T-immune response and cytokine production *in vivo* and *in vitro*, it can be considered a mediator between adipose tissue and inflammatory process.

However, studies that are characterized by violations of the content of various cytokines, in particular leptin, and resistin in patients with combined asthma and obesity, as well as ways of their correction is not enough. In addition, several studies [38,39] the research of the relationship of the increased level of serum leptin and risk of development of asthma was not found dependencies between the studied parameters. In contrast, others had shown higher concentration of serum leptin in patients with bronchial asthma [26,65]. All of the above stimulates interest in the study of the leptin level and its relationship with other pathogenetic mechanisms in patients with bronchial asthma, combined with obesity for the understanding of pathogenesis and development of more effective treatment of this comorbidity.

Finding the most informative markers of activity of inflammatory process in patients with asthma of varying severity, and with asthma, associated with obesity, showed the importance of determining the level fractalkine [28].

An important link of pathogenesis as asthma, and obesity, is oxidative stress [6, 22]. Developing when asthma exacerbations oxidative stress, which is accompanied by increased production of reactive oxygen causes increased activity of processes of lipid peroxidation and decrease in the activity of antioxidant protection [10]. Oxidative stress stimulates the formation of a number of proteolytic enzymes such as matrix metalloproteinases, hematopoietically serine proteinase, cathepsin G, which have a damaging effect on the vascular endothelium of the pulmonary circulation and interstitial tissue of the lung tissue, stimulates the formation of angiotensin II and increased sensitivity of vessels to it [12].

Patients with bronchial asthma have a decrease in the activity of enzymes of antioxidant protection, which is persists in remission with the accumulation of free-radical metabolites (hydroperoxides, diene conjugate, malonic dialdehyde). Such changes have been observed in various biological fluids – plasma, secret of the bronchial tree and exhaled breath condensate. One of the main sources of production of significant quantities of superoxide anion — the main precursor of free radical compounds in the body patients with asthma are eosinophil granulocytes [63]. Proven direct participation of lipid peroxidation in the formation of bronchial obstruction [22]. It was noted the processes of lipid peroxidation regardless of etiological variant of asthma to change: in winter and spring developed a syndrome of hyperlipoperoxidemia (increasing the level of diene conjugate) against a relative antioxidant deficiency (decrease of antioxidant protection activity) [36] that could create the conditions for the exacerbation of the disease. Intensification of lipid peroxidation increased with the degree of severity of the disease [8].

The development of obesity is also accompanied by the occurrence of oxidative stress in the body [43]. This state acts as one of the most important pathogenetic links the formation of metabolic disorders in the development of obesity and is associated with the capacity constraint of the antioxidant system in the body. In obese patients determined the level of antioxidant protection is lower than in patients with normal body weight, and its level is inversely correlated with the severity of central obesity. It is assumed that the sources of oxidative stress in obesity are hyperglycemia, hyperleptinemia, hyperlipidemia, increased the rate of formation of free radicals and the presence of chronic inflammation [70], which is accompanied by inadequate levels of antioxidant protection. One of the factors contributing to low levels of antioxidant protection in obesity is probably a feature of the diet of obese people with inadequate intake of foods containing antioxidants: fruit, vegetables, legumes, and also insufficient physical activity [59]. Episodic bronchial obstruction in asthma,

combined with the constant violation of respiratory function due to obesity, contributing to hypoxia and increase oxidative stress. Development of actions for rational correction of the lipid peroxidation - antioxidant protection system from patients with asthma, comorbid with obesity, is an important direction of pathogenetic therapy.

Obesity is characterized by a high content of not only the active oxygen species, but also active forms of nitrogen. The impaired production of nitric oxide (NO) is an important link of pathogenesis of asthma and obesity in conditions of oxidative stress. The NO molecule has a high biological activity, the ability to quickly penetrate cell membranes and to sell their function on metabolic processes in the cells of synthesis and in the adjacent cells. NO healthy person causes vasodilation, regulate inflammation and immune protection, antioxidant, anti-inflammatory properties, regulates the tone of smooth muscles of internal organs and increases the activity of ciliated epithelium and mucociliary transport in the respiratory tract, is a mediator of bronchodilatory. In asthma, the secretion of NO increases sharply, and in this situation the molecules NO interacting with the active oxygen species, turn into active forms of nitrogen. Thus, the interaction of NO with superoxide radical leads to the formation of highly reactive oxidant – peroxynitrite (ONOO-), which is able to interact with many biomolecules and has a toxic effect on the tissues and cells. The activity of alveolar macrophages altered by high concentrations of NO metabolites (NOx) in inflammation, there is a stimulation of the activation of cyclo - and lipooxygenase and production of leukotrienes [22], which contributes to the increasing incidence of inflammation and clinically – longer lasting asthma attack.

Obese patients revealed decrease in the levels of NOx metabolites – nitrites and nitrates of blood and marked by its negative correlation relationship with glycemia, blood lipid levels and no dependence on the age and gender of examined persons [29], but the interaction and nitrazepam oxidative stress in the development of asthma and obesity need to be further explored.

A powerful source of NO in the human body is the endothelium. An important role of endothelial dysfunction was demonstrated in the development of chronic pulmonary heart disease with chronic obstructive pulmonary disease [23]. The multidirectional content of metabolites of NO in patients with asthma and obesity forms an interest for their study in the combination of these diseases.

One of the protective factors for the vascular endothelium and myocardium from damage induced by oxidative stress in obesity, is adiponectin [47.72]. Recent studies have shown that adiponectin is synthesized by adipocytes of white adipose tissue and has anti-inflammatory and antiatherogenic properties, has a positive effect on lipid and carbohydrate exchanges. Unlike other adipocytokines (TNF-α, IL-6, resistin) levels which increase in proportion to the mass of adipose tissue, adiponectin in obesity is defined in lower concentrations than in persons with normal body mass index. Several studies have shown that the adiponectin level decreases with increasing degree of obesity, namely the accumulation of visceral fat mass [62]. The decrease in body weight is one of the effective strategies of increasing the concentration of adiponectin in plasma. The level of this hormone significantly increased during fasting and reduced mass on the background of hypocaloric diet in obese patients [35,57,72]. In conditions of oxidative stress in obesity active forms of oxygen able to suppress adiponectin production in adipocytes.

Adiponectin helps stimulate the synthesis of NO in the vascular endothelium, inhibition of production of TNF-a, can induce the adhesion of monocytes and to inhibit the expression of adhesion molecules [48,72]. In studies Salmenniemi et al. (2004) proved that low levels of adiponectin are responsible for the endothelial damage and the development of systemic chronic inflammation. At the same time, adipokines such as leptin and resistin lead to the dysfunction of the endothelium [34]. Endothelial dysfunction has a significant pathogenic role in the formation of the microvascular complications, which are the basis for changes in macrovascular status, particularly the formation of chronic pulmonary heart disease in chronic bronchial mast [23]. Oxidative stress in combination with nitrazepam stress, increased production of proinflammatory cytokines, which are important elements in the pathogenesis of asthma, may be factors in the development of endothelial dysfunction when it is combined with obesity. Taking into account a variety of factors that change the function of the endothelium, both in asthma and obesity, the features of formation, clinical manifestations of endothelial dysfunction and its significance in the development of complications with such co-morbidity require study for the development of a pathogenetically justified correction.

However, the question devoted to the study of the dynamics of adipokines and their connection with the formation of endothelial dysfunction in patients with bronchial asthma, combined with obesity, remain poorly understood.

In patients with asthma, LT participation in the formation and maintenance of inflammation was demonstrated. Their activation causes bronchial obstruction due to spasm of the respiratory muscles, the development of edema of the bronchial mucosa due to outlet fluid and protein from the vessels, and increased secretion of mucus. The greatest attention of researchers was drawn to the changes cysteinyl LT 4 and LT 5 (C, D, E etc.). So in the study of the spectrum of LT in children was noted in leukocytes of healthy children is dominated by LT 5 - metabolites of polyunsaturated fatty acids (ω-3). In children with bronchial asthma were recorded in the increased synthesis of proinflammatory sulfidopeptide LT 4 (derivatives of ω-6 polyunsaturated fatty acids), LT C4 and LT E4, and in the presence of obesity there was an increase in the level of LT D4, the change of the ratio between leukotriene 4-th and 5-th series, as well as between different types sulfidopeptide (C,D,E) and non-sulfidopeptide (B) leukotrienes, which are synthesized by neutrophilic leukocytes. The formation of severe asthma in the current time is associated with the prevalence of neutrophilic inflammation in the tracheobronchial tree [11].

Inhibitors sulfidopeptide leukotriene (montelukast) helps to decrease levels of leukotriene C4, E4, D4. However, these drugs do not affect the level LTB4 that leads to the search of ways to correct this particular leukotriene. In this regard, the interest is a study that revealed a decrease in its level in children with obesity in comparison with healthy children, which obviously was associated with an increased consumption of the common precursor LTB4 and cysteinyl LTD4 and LTE4 - LTA4 – formation LTB4 and LTE4 [7,13]. Herewith none of the patients with obesity have not been identified LTD5 the predominant form of LT in healthy children, according to the authors, is probably associated with insufficient intake polyunsaturated fatty acids, especially ω-3 class in their diet, which indicates positive outlook for use of drugs-ω-3 for the

correction of leukotriene B4 production in patients with bronchial asthma and obesity.

Thus, as shown by the results of studies asthma and obesity are a disease forming in the body sustained inflammatory process. In the first case, more local, focused mainly in the walls of the Airways, in the second case is much more widespread, affecting many organs and systems. Currently described and formulated many of the mechanisms of influence of obesity on asthma, but the approaches to treatment of this comorbid condition is developed only taking into account some elements of the pathogenesis. Many components of the pathogenesis of this combined condition are unexplored and possible ways of their correction unexplored. This is what should determine the direction of scientific research to improve the efficiency of treatment of patients with this common comorbidity and may reduce the frequency of its manifestations.

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