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OBESITY IN MENOPAUSAL WOMEN

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Obesity is one of the most important medical and social problems of modern society. This pathology is one of the most common chronic diseases in the world. The review studies pathogenetic mechanisms of obesity during menopause, as well as the participation of sex hormones in fat tissue metabolism. A better understanding of the causes and mechanisms of weight gain during this period of a woman's life suggests that obesity is not inevitable and can be effectively countered by the implementation of the principles of healthy lifestyle, and if necessary, by medicated correction as well.

Key words: obesity, menopause, pathogenesis, sex hormones, metabolism of adipose tissue.

Obesity is one of the most important medical and social problems of modern society. This pathology is one of the most common chronic diseases in the world. According to the World Health Organization [7] in 2016 39 % of adults over the age of 18 (39 % of men and 40 % of women) were overweight and about 13 % of the adult population of the planet (11 % of men and 15 % of women) were obese. Epidemiological studies have shown that overweight and obesity predispose the development of 44 % of cases of type 2 diabetes and 23 % of cases of coronary heart disease and 7–41 % of cases of some types of cancer [7].

The activity of the reproductive system has a significant effect on the functioning of the organism as a whole [2]. A specific category of people at high risk of obesity development is menopausal women. The causes of weight gain after the onset of menopause are reduced physical activity, stress and natural aging in itself, what contributes to the slowdown of the process of «burning» calories. However, a key role in the pathogenesis of obesity during the menopause is estrogen deficiency. It has been proved, that estrogen deficiency leads to the decrease of the intensity of lipolysis, what is followed by the accumulation of adipose tissue, mainly in the anterior abdominal wall [10]. It was shown, that obesity and metabolic syndrome occur in women during menopause 3 times more often than before it [15]. It was demonstrated that menopause is an independent predictor of metabolic syndrome [11]. Surgical menopause occupies a special place among estrogen-deficient conditions. It was established that surgical menopause, which happened at the reproductive age, is characterized by a significant progress both of the frequency of occurrence of individual risk factors and their combinations [6].

Pathogenetic mechanisms of obesity at menopause

The studies in recent decades have shown that fat tissue is not only the largest source of energy in the body, but also an endocrine organ (white fat tissue) [4]. Adipocyte cells produce peptide substances – adipose-cytokines or adipokines (more than 50 adipokines are known) involved in the regulation of energy homeostasis, insulin action and lipid metabolism [5].

Visceral fat, being hormonally active, carries out various functions in the body [12]:

- stimulation of lipogenesis (angiotensinogen, angiotensin II, protein, stimulating acylation, insulin-like growth factor 1, visfatin)
- increased insulin resistance (tumor necrosis factor- α , interleukin-6, resistin)
- procoagulant activity (tumor necrosis factor- α , interleukin-6, inhibitor of tissue plasminogen activator I, transforming growth factor beta, tissue factor)
- stimulation of angiogenesis (leptin, interleukin-8, vascular endothelial adhesion molecule type 1 [VCAM-1], transforming growth factor beta [ICAM-1], vascular endothelial growth factor [VEGF], fibroblast growth factor 2 [FGF-2], macrophage chemotactic protein-1 [MCP-1], interferon- α inducible protein-10 [IP-10], monobutyrin).

As a result of the action of biologically active substances synthesized by fat depots, cardiovascular diseases and metabolic disorders are developed in a patient with obesity.

The pro-inflammatory adipokines (in particular, interleukin-1, interleukin-6, leptin, resistin and tumor necrosis factor- α , etc.) are central to the development of cardiovascular diseases, insulin resistance, dyslipidemia, arterial hypertension (AH), atherosclerosis, metabolic syndrome, diabetes mellitus, non-alcoholic steatohepatitis (NASH) and malignant neoplasms [4]. In addition, obesity is associated with other problems of menopause, such as vasomotor symptoms, sexual disorders, osteoporosis, urination disorders, etc. It should be noted that a number of factors have an impact on the correct interpretation of BMI, including ethnicity, muscle mass, age and pattern of fat distribution in obesity.

Undoubtedly, weight gain during menopause is common, what is mostly due to the hormonal changes characteristic for this period. One should also take into account genetic predisposition, unhealthy eating habits, sedentary lifestyle, the presence of diseases (Cushing's disease, hypothyroidism, etc.), drug administration (e. g., corticosteroids, glitazones, etc.), etc.

Estrogens

Estrogens in women are responsible for the accumulation of fat in subcutaneous tissue, especially in gluteal and femoral regions. The biological effect of estrogens is realized in combination with the receptors belonging to the family of nuclear receptors. The studies of the recent years have established the existence of two types of estrogen receptors (RE α , RE β), which are transcription factors which regulate the expression of target genes. However, it is considered that in addition to the genomic effect, estrogens can also act with the help of non-genomic mechanisms, depending on the activation of specific receptors located on the cell membrane.

Other sex hormones – androgens, contribute to the accumulation of fat in the area of the anterior abdominal wall. The development of obesity with unfavorable metabolic redistribution of adipose tissue from the peripheral to the central type during the menopause is explained by the changes in energy balance, fat cell regulation, increased glucocorticosteroid stimulation, influence of growth factors, relative hyperandrogenism in conditions of estrogen deficiency. Another important factor contributing to the development of central obesity is a decrease in the secretion of globulin binding sex hormones (SHBG) in the liver, what increases the bioavailability of androgens. It is emphasized that in postmenopausal women the risk of abdominal obesity development is 4.88 times higher than in premenopausal ones [14].

The exclusion of ovarian steroidogenesis includes a number of compensatory mechanisms of non-ovarian estrogen production. It was established that along with the hormone synthesis in the ovaries, fat tissue is the place of extragonadal synthesis of sex hormones from androgens. Consequently, the level of sex hormones in the blood determines the pattern of distribution of fatty tissue, as the accumulation, intensive aromatization of sex hormones and their secretion occurs in it. The increase of the production of postmenopausal estrogens according to the increasing weight is associated with the participation of adipose tissue in the process of aromatization of androgens. Consequently, the body weight is positively correlated with the level of estrone and estradiol in the blood. As a result, the mass of visceral fat is increased during menopause by 44 %, and the weight of the guinean fat rises roughly by 32 % [8]. Estrogens derived from aromatase are not expected to have protective properties for insulin sensitivity and cardiovascular diseases, as well as for increased risk of type 2 diabetes, AH and dyslipidemia, what is manifested by a higher incidence of cardiovascular diseases in women at postmenopausal period.

Sex hormones and fat tissue metabolism

Stimulation of RE α in adipose tissue affects the metabolic activity of adipocytes. With the help of RE α , the positive effect of estrogens on fat distribution, glucose metabolism and inflammation is realized [9]. At the same time, actually the metabolism of adipose tissue is regulated primarily by the adrenergic system. Lipolysis is increased during stimulation of β -adrenergic receptors, whereas activation of α 2A receptors has antili-

polytic effect and contributes to fat accumulation. It has been demonstrated that estradiol increases the expression of $\alpha 2A$ receptors in subcutaneous adipose tissue in women and does not affect these receptors in visceral fat deposits [17]. Another study showed that the activation of RE α stimulates β -adrenergic receptors in visceral tissue and enhances lipolysis, leading to the decrease of adipose tissue in the anterior abdominal wall region. It has been established that estrogens increase fat oxidation in skeletal muscles and inhibit lipogenesis in the liver and muscles [14]. Thus, the deficiency of estrogen, caused by menopause, is accompanied by an increase in visceral fat deposits. In return, abdominal obesity is a major factor in the pathogenesis of insulin resistance and metabolic syndrome. Visceral adipose tissue is considered a potential mediator between the status of menopause and the degree of insulin resistance. However, further research is necessary in this field. It should be mentioned that the most severe metabolic disorders in the postmenopausal period are found in women with abdominal obesity and insulin resistance. The relationship between the degree of visceral obesity and insulin resistance depends not only on the content of estrogens, but also of other sex hormones.

Fat tissue, especially in obese patients, is the source of a range of adipokines. One of the most important adipokines is leptin, a key regulator of energy balance in the body. Leptin transmits information about energy reserves from fat tissue to the brain; the brain, mostly the hypothalamus, supports energy homeostasis and normal body weight by the regulation of food intake and energy output [21]. It was demonstrated that the content of leptin in the blood is increased with an increase of the mass of adipose tissue, and its secretion in the subcutaneous fat tissue is higher than in the visceral fat depots. The level of leptin reflects not only the amount of accumulated fat, but also the disturbance of energy metabolism. It was established that estrogens potentiate the action of leptin, increasing the expression and sensitivity of its receptors in the hypothalamus [13].

There is an inverse correlation between the levels of estrogen and adiponectin, another important cytokine which has anti-inflammatory and anti-atherogenic effects [20]. As opposed to other adipokines, the secretion of which is increased in proportion to the increase in fat tissue mass, the concentration of adiponectin in the blood correlates back with the mass of adipose tissue. Adiponectin in muscle tissue increases fat oxidation, reduces intracellular accumulation of lipids, improves the sensitivity of muscles to insulin; in the liver – it reduces the intake of fatty acids and stimulates their oxidation; in vessels – it exhibits anti-inflammatory and anti-atherogenic properties; in the heart – affects myocardial remodeling after ischemic injury. In addition, estrogens inhibit the production of pro-inflammatory cytokines secreted in adipose tissue, such as interleukin-6 or tumor necrosis factor- α [18].

From a clinical point of view, the effect of sex hormones on the metabolism of fat deposits and the state of lipid metabolism deserves attention. In postmenopausal women, estrogens stimulate the maintenance of a favorable lipid profile, while an increase in androgen levels has an atherogenic effect [3]. During the perimenopausal period women often show an increase of blood pressure. The influence of the reduction of estrogen levels on blood pressure is preconditioned by:

- a relative increase in androgen levels
- activation of the renin-angiotensin system (higher levels of renin)
- increased endothelin-1 content in blood plasma
- high salt sensitivity
- increased insulin resistance
- increased activity of the sympathetic nervous system
- increased weight.

It was established that AH prevalence in women over the age of 55 is increased in comparison with men [1]. This pattern is not traced at a younger age. The pathogenesis of AH in women in perimenopausal period is quite complicated. However, the deficiency of estrogen, leading to the dominance of the effects of vasoconstriction over vasodilation is determinant. It was noted that estrogen deficiency is accompanied by a decrease of prostacyclin and nitric oxide levels in blood [1]. It was found that the introduction of estrogens during physiological menopause is not accompanied by a significant decrease of blood pressure, confirming the diversity of pathogenetic mechanisms of the development of arterial hypertension, for example, the contribution of the renin-angiotensin-aldosterone

system, etc. Significant contribution of such factors as obesity, insulin resistance and inflammation to the development of hypertension should also be taken into account.

Control of appetite and energy balance as a whole is constantly carried out in the

Do estrogens affect appetite?

central nervous system, mainly in the hypothalamus. In this area there are arched, paraventricular and ventromedial nuclei. Activation of specific neurons in these structures initiates orexigenic (increases food intake) or anorexigenic (reduces appetite) effects. In this region, both types of estrogen receptors, predominantly RE α , are expressed. It has been experimentally established that, by activation of RE α estrogens regulate the activity of the proopiomelanocortin (POMC) neurons of the arcuate nucleus of the hypothalamus, which cause a feeling of satiety and lead to anorexia [16]. It was demonstrated, that in presence of estrogens the expression of the neuropeptide Y – orexigenic peptide produced in the hypothalamus [20], is inhibited. Consequently, estrogens participate in the central regulation of energy metabolism and reduce appetite at the level of CNS. It is assumed that a rapid decrease of the levels of these hormones contributes to a significant increase of appetite.

Conclusion. Menopause is usually the cause of many problems for women, one of which is a weight gain. It is proved that obesity is an independent and the most significant risk factor for the development of coronary heart disease, type 2 diabetes mellitus, etc. In addition, obesity and menopause are mutually aggravating factors in terms of the development of cardiovascular and metabolic diseases, as well as premature death. Considering the growing incidence of overweight and obesity in the entire population, the problems of metabolism occurring in menopausal women should be considered not only as an individual problem, but also as a socioeconomic one. A better understanding of the causes and mechanisms of weight gain during this period of a woman's life suggests that obesity is not inevitable and may be effectively countered by the implementation of the principles of healthy lifestyle, and if necessary, by medicated correction as well.

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ОЖИРІННЯ У ЖІНОК В МЕНОПАУЗІ

О. М. Біловол, І. І. Князькова, В. М. Мищенко, М. В. Богун (Харків)

Ожиріння – одна з найбільш важливих медико-соціальних проблем сучасного суспільства. Ця патологія відноситься до числа найбільш поширених хронічних захворювань у світі. В огляді літератури розглянуто патогенетичні механізми ожиріння в менопаузі, а також участь статевих гормонів в метаболізмі жирової тканини. Ожиріння не є неминучим, а, враховуючи причини і механізми збільшення маси тіла в цей період життя жінки, можливо ефективно йому протистояти за допомогою здорового способу життя і необхідної медикаментозної корекції.

Ключові слова: ожиріння, менопауза, патогенез, статеві гормони, метаболізм жирової тканини.

ОЖИРЕНИЕ У ЖЕНЩИН В МЕНОПАУЗЕ

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Ожирение – одна из наиболее важных медико-социальных проблем современного общества. Эта патология относится к числу наиболее распространённых хронических заболеваний в мире. В обзоре литературы рассмотрены патогенетические механизмы ожирения в менопаузе, а также участие половых гормонов в метаболизме жировой ткани. Ожирение не является неизбежным, а, учитывая причины и механизмы увеличения массы тела в этот период жизни женщины, возможно эффективно ему противостоять с помощью здорового образа жизни и необходимой медикаментозной коррекции.

Ключевые слова: ожирение, менопауза, патогенез, половые гормоны, метаболізм жировой ткани.