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AN INTEGRATED APPROACH TO THE MANAGEMENT OF WOMEN OF FERTILE AGE WITH METABOLIC SYNDROME

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Annotation: According to the definition of the World Health Organization, obesity is defined as an unusual or excessive accumulation of fat that can be harmful to health. It is a global medical and social problem for healthcare in all countries of the world and patients of all ages. The incidence of metabolic syndrome (MS) in the world is almost 40% of the adult population, and obesity is 13% (Lee et al., 2020). The global prevalence of obesity almost tripled from 1975 to 2016 and continues to grow.

According to modern concepts, the key factors leading to the development of metabolic disorders in MS are an increase in visceral fat mass and a decrease in peripheral tissue sensitivity to insulin with the development of compensatory hyperinsulinemia, which are associated with disorders of carbohydrate, lipid, purine metabolism and arterial hypertension [All-Russian Scientific Society of Cardiology (VNOK), 2021].

Keywords: Metabolic syndrome (MS), diabetes mellitus (DM), arterial hypertension (AH), reproductive age, obesity, glycemic index (GI), insulin, magnesium, vitamin D, myoinositol, D-chiroinositol.

In recent years, there has been a steady increase in the prevalence of obesity, diabetes mellitus (DM) and arterial hypertension (AH), risk factors that are closely related and combined within the framework of metabolic syndrome (MS) [1].

According to WHO, 1.7 billion people on the planet are overweight, and by 2025 the number of obese people in the world will reach 300 million people [2].

The high prevalence of MS in the early 21st century is considered a side effect of urbanization, as important factors contributing to the development of MS are excessive consumption of foods containing trans fats, simple carbohydrates and low physical activity.

The problems of the modern diet are excess calories, excess of light carbohydrates, deficiency of fiber and live plant foods in general, excess saturated, trans, omega–6 and oxidized fats, deficiency of macro- and micronutrients, excess salt, food intolerance, dietary disorders, deficiency of macro-, micronutrients in the prenatal period and in at an early age.

In addition, the lifestyle of a modern citizen is the cause of chronic emotional stress and intellectual overstrain, leading to a disorder of the neurohormonal regulation of autonomic functions [3].

Metabolic syndrome (MS) is one of the most common causes of anovulatory infertility, early pregnancy loss in women of reproductive age. The frequency of this pathology is about 30-35% in the structure of reproductive disorders and reaches 70% among patients with recurrent endometrial hyperplastic processes. Thus, MS is one of the most common diseases of young women [4]. Excessive content of adipose tissue in the body is accompanied by metabolic, hormonal, vascular and proinflammatory disorders [5], as a result, it seems advisable to consider existing ideas about the interactions between MS, obesity and the reproductive system of women.

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It has been established that the onset of pregnancy with a BMI of more than 30 kg/m2 takes significantly longer than with normal body weight, and obesity becomes a risk factor for gestational diabetes, preeclampsia, premature rupture of fetal membranes, fetal growth retardation, asphyxia, cesarean section [6] In addition, it has been proven that obesity before and during pregnancy contributes to maternal mortality. In more than 50% of all maternal deaths in the UK, patients were overweight or obese [7].

Therefore, obese women of reproductive age should actively modify their lifestyle before conception or in early pregnancy [8].

In the treatment of MS, measures aimed at lifestyle modification, including normalization of body weight, quitting smoking, and increasing the degree of physical activity, are paramount. Among the components of the diet that provide correction of the main manifestations of MS, the most important are the energy value of the diet, the amount and qualitative composition of fat, protein, carbohydrates, dietary fiber, vitamins, macro- and microelements, minor components of food [9].

Metabolic syndrome is more related to the type of proteins, fats and carbohydrates than to their absolute amount. Various diets with different protein, fat and carbohydrate contents were studied. One of the studies involved more than 750 overweight subjects from eight European countries. Initially, 938 subjects were on a very low calorie diet (from 800 to 100 kcal per day) for 8 weeks. Subjects who managed to achieve an 8% weight loss were then randomly assigned one of five diets to help maintain their weight, and followed for another 26 weeks. None of the dietary recommendations included calorie restriction, as part of the goal was to determine whether macronutrient and glycemic index recommendations affected calorie intake and satiety. As a result of the study, it was concluded that a diet with a high protein content and a reduced content of foods with a high glycemic index has a beneficial effect on the concentration of insulin in the blood [10].

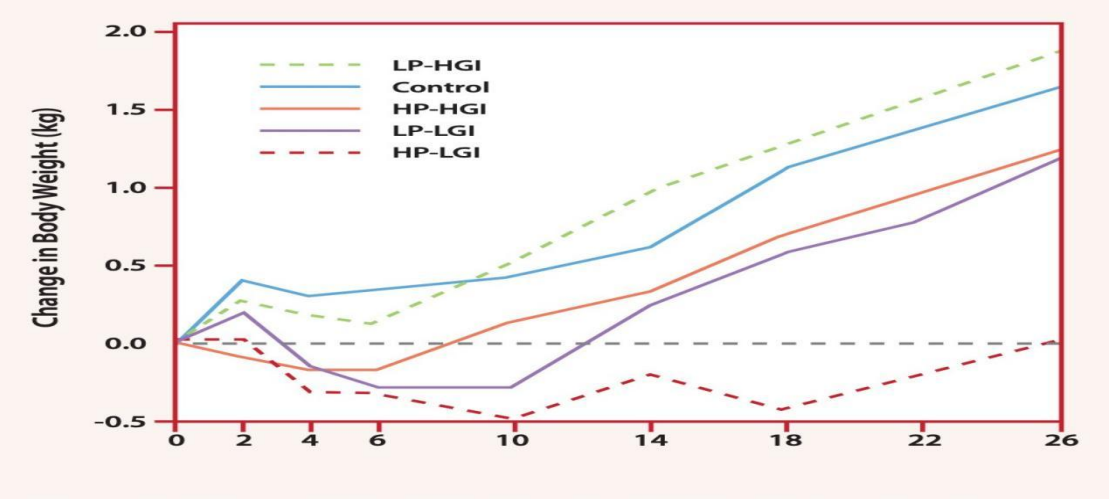

Figure 1. Change in body weight after an 8% decrease in body weight, depending on macronutrients and glycemic index instructions.

The pathophysiology of MS is quite complex. The formation of insulin resistance and MS is influenced by both exogenous and endogenous factors. Exogenous factors include:

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decreased physical activity, high-carbohydrate diet and consumption of excessive amounts of animal fats, lack of biologically active substances in food (in particular, magnesium, B vitamins, vitamin D). Endogenous factors include hormonal disorders (increased cortisol, increased testosterone in women, decreased progesterone, decreased somatotropic hormone, catecholamine balance disorders), aseptic inflammation of the hypothalamus and metabolic disorders of visceral adipose tissue (abnormal changes in the intensity of lipolysis and liponeogenesis, changes in the endocrine functions of the adipose tissue itself, which secretes leptin, adiponectin and factor into the bloodstream tumor necrosis-α) [11].

The results of fundamental and clinical studies have shown that MS is associated with deficiencies of various micronutrients: magnesium, zinc, vitamin D and myoinositol [12]. Deficiencies of these micronutrients, especially combined ones, stimulate the development of such components of MS as impaired glucose tolerance, dyslipidemia and obesity

According to the PubMed search engine, 649 summaries and full-text articles on the problem of MS with vitamin D deficiency were published from 1990 to 2020. It is noted that the number of papers devoted to the study of this problem has increased significantly over the past 10 years.

Currently, a sufficient number of clinical studies have been accumulated on various biological effects of vitamin D and its beneficial effect on human health [13]. Recent studies have shown the important role of a normal level of vitamin D provision in maintaining human health [14]. Vitamin D is involved in regulating the synthesis of sex hormones – progesterone, testosterone and estrogens, which ensure proper maturation of follicles and a safe pregnancy.

To date, the relationship between the concentration of 25hydroxyvitamin D (25(OH) is being actively studiedD) in blood serum and MS (Maroufi N.F. et al., 2020; Weldegiorgis T.Z. et al., 2020). Thus, the results of a 20-year prospective study of CARDIA, which initially included young people at risk of developing CVD, showed that the normalization of the level of 25 (OH)D is associated with a reduced risk of developing AO, carbohydrate metabolism disorders and lipid metabolism disorders (reduction of high-density lipoprotein cholesterol (HDL cholesterol)) regardless of age, gender, race[15] In addition, in a single-stage study conducted in China, it was found that people with severe vitamin D deficiency (25(OH)D less than 10 ng/ml) had a 1.5 times higher risk of developing MS compared to individuals, Whose level is 25(HE)D exceeded 10 ng/ml [16].

Magnesium is one of the most important bioelements that are of fundamental importance for maintaining metabolic functions in the body. Data from experimental, clinical and epidemiological studies indicate that sufficient intake of magnesium from food and magnesium preparations contributes to the normalization of tissue and cell sensitivity to insulin [17], and a decrease in the severity of the manifestation of MS components [18]. Especially magnesium taurate (magnesium combined with the amino acid taurine)-it helps very well with high glycated hemoglobin, heart problems (arrhythmias, tachycardia).

Magnesium is an important mediator of both carbohydrate and lipid metabolism, therefore, its reduced plasma level is associated with a more pronounced expression of MS components. For example, observations of a group of 117 overweight and obese patients showed that the lower the magnesium levels, the more components of MS characterized the patient's condition [19]. The daily intake of magnesium in the group of patients with MS (n=200) was inversely proportional to the values of metabolic biomarkers of insulin resistance (fasting glucose levels, insulin levels, HOMA-IR index). The risk of elevated HOMA-IR index (>3.6) was 71% lower (HR 0.29, 95% CI 0.12–0.72, $p<0.01$) in participants with the highest magnesium intake (>300 mg/day) [20].

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Table 1. The relationship of serum magnesium levels and some metabolic parameters (ARIC study, data at the time of the start of the study) [21]

Parameter	Quintile of magnesium (mmol/l)						p
	<0,70	0,70–0,75	0,75–0,80	0,80–0,85	0,85–0,90	>0,95	
Number of patients (%)	426 (16)	552 (21)	689 (26)	522 (20)	297 (11)	136 (5)	-
BMI, kg/m2	29,1±6,4	29,8±6,4	29,1±5,8	29,0±5,8	29,0±5,9	28,0±4,0	0,03
Waist Circumference:hip circumference	0,92±0,07	0,91±0,08	0,90±0,08	0,91±0,08	0,91±0,07	0,90±0,07	0,007
Taking diuretics, %	30	24	22	22	19	22	0,02
Serum potassium, mmol/l	4±0,5	4.1±0,4	4,2±0,4	4,2±0,4	4,3±0,5	4,3±0,4	0,001
Fasting insulin, pcmol/l	85±62	86±65	77±54	78±52	77±69	71±39	0,01

From a physiological point of view, magnesium is required for energy metabolism – the processes of splitting proteins, fats and carbohydrates and converting them into ATP. Among the 720 currently known magnesium-dependent proteins of the human proteome, more than 310 are involved in ATP metabolism. In particular, magnesium is necessary for the transmission of a signal from insulin receptors and for the effective breakdown of glucose [22]. This paper presents the results of a systematic analysis of the molecular mechanisms of the relationship between magnesium deficiency, pyridoxine and MS.

It is known that reproductive disorders are associated with metabolic disorders, dietary and lifestyle characteristics, and therefore the use of various vitamins and vitamin-like substances, including inositol, has been actively studied recently [23].

In patients aged 18-30 years with reproductive health problems on the background of overweight (BMI>26 kg/m2) and high stress levels on the IDIX scale, myoinositol levels in the blood are significantly lower (less than 24 mmol/l, on average 16 mmol/l) [24].

Inositol therapy (either myoinositol + folic acid or myoinositol + D-chiroinositol + folic acid) significantly improved tissue sensitivity to insulin, reduced levels of glycosylated hemoglobin, HC and TG, as well as blood pressure (when used for more than 3 months) [25].

Based on the above, it can be concluded that reducing or eliminating refined sugar and simple carbohydrates, increasing the consumption of complex carbohydrates and whole grain products (oatmeal, barley, wheat) 3-4 times a week, other dietary and lifestyle changes that favorably affect glucose and insulin levels can positively affect life expectancy and reduce the risk of developing chronic diseases in women of fertile age. In addition, regular (daily) 40-minute walking per day:

-burns approximately 100-120 kcal per day;
-has a vasodilating effect;
-helps to reduce weight and reduce insulin resistance;
-has a positive effect on the brain and nervous system;
-contributes to the prevention of GB.

Vitamin D deficiency and deficiency correlate with the main pathological changes in metabolic syndrome, such as dyslipidemia, insulin resistance, and obesity. From a practical

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point of view, in patients with metabolic syndrome, it is advisable to determine the level of vitamin D in the blood serum and, accordingly, to carry out correction in case of its deficiency. In addition, cholecalciferol therapy at a dose of 4000 IU / day. Within three months, it was associated with normalization of glycemic control in women with MS.

Magnesium is also one of the most important nutritional factors determining the efficiency of fat and carbohydrate metabolism, the normal physiological course of which is an essential component of MS prevention. According to clinical and epidemiological studies, adequate provision of magnesium to the population significantly reduces the risk of developing MS. Clinical trials within the framework of evidence-based medicine show the promising use of oral preparations of organic magnesium and its synergist pyridoxine, organic magnesium salts (lactate, magnesium citrate) in the treatment and prevention of overweight and MS in women.

Inositols in combination with metformin can work as synergists, which makes it possible to use a reduction in the dose of metformin, especially in patients with poor tolerance. The effectiveness of D-chiroinositol in the treatment of women with metabolic syndrome is associated with an improvement in tissue sensitivity to insulin and an improvement in ovulatory function, a decrease in the concentration of androgens in blood serum, a decrease in blood pressure and TG concentrations.

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