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### RESEARCH ARTICLE

## THE SIGNIFICANCE OF THE QUALITY OF CONSUMED FATS AND HYPOTHERMAL STIMULATION IN ANTI-INFLAMMATORY MECHANISMS AND IN THE PREVENTION OF OBESITY

Vasile Fedash

Postdoctoral Fellowship, Institute of Physiology and Sanocreatology, Chisinau, Republic of Moldova.

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### Abstract

An overview analysis highlighting the possibilities of solving the problem of preventing the formation of an obeso- and diabetogenic environment, preventing inflammatory processes in adipose tissue, imbalance in the mechanisms of neuroendocrine interactions of relationships based on an integrated approach, characterized by a harmonious combination of individualized correction of the applied diet with hypothermic stimulation.

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### Introduction:-

The unambiguity of the statement that consumed fats is a promoter of obesity is questioned. The problem of revealing the fundamental mechanisms underlying the etiology of obesity requires further solution [18]. Currently, the term "obesogenic environment" is increasingly used, which means the availability of high-calorie food and an increased amount of its consumption due to technologically enhanced hedonic properties, social conditions characterized by sedentary lifestyle and psycho-emotional stress development, etc. [28]. Experts argue that technological innovations in the processing of raw materials and the production of food products contribute to the formation of a dehumidified environment and way of life. Lifestyle changes remain the cornerstone, both in primary and secondary prevention, as well as in the correction of lipid and lipoprotein metabolic disorders, and the treatment of obesity. Lifestyle changes recommended for people with high cholesterol level include diet characterized by low content of saturated and trans fatty acids, functional foods rich in biologically active substances such as fiber, antioxidants, plant sterols and stanols in combination with regular exercise, and maintenance of healthy body mass index. Modernization of technologies used in the food industry and an increase in the level of income of the population in economically developed countries have made a number of food products readily available without any significant seasonal fluctuations [6]. It is known that the usual approach in the prevention of obesity is, first of all, to limit the consumption of foods with a high lipid and carbohydrate index. However, some weight loss is often achieved only in the short term, while there is little evidence that such losses persist in the long term [50]. Of all the food groups, it has been shown that meat consumed in large quantities, especially, promotes weight gain due to its high energy density and/or increased fat content [2, 16, 41, 43, 54]. It is obvious that the amount of food eaten has a significant effect on the initiation and maintenance of the development of obesity [20]. The constant consumption of a large amount of meat and meat products determines the formation of a positive nitrogen balance on the background of insufficient, but excessive satisfaction of the body's need for the supply of proteins, fats and carbohydrates, exerting an obesogenic effect on the body [61]. The lipids circulating in the bloodstream are highly dynamic interactive biological molecules that make up the majority of cellular components as well as signaling molecules. Circulating lipids and fatty acids of various compositions act as key regulators in the anabolic and catabolic pathways and are influenced by dietary [9, 17, 22, 36], pharmacological [25], hormonal [57] and

**Corresponding Author:- Vasile Fedash**

Address:- Postdoctoral Fellowship, Institute of Physiology and Sanocreatology, Chisinau, Republic of Moldova.

environmental triggers [26]. Using modern analytical approaches in the quantitative assessment of complex lipid structures, several plasma lipid metabolites have been identified. These metabolites can serve as diagnostic indicators, both in the early and late stages of the metabolic syndrome. Improvement of methods for determining the fatty acid composition of complex lipid compounds in various tissues and biofluids has great potential in fundamental studies of the mechanistic interaction of metabolic phenotype. For example, an increase in the total concentration of free fatty acids in plasma and, in particular, palmitic acid [30], appears to be associated with metabolic syndrome due to the induction of lipotoxicity in peripheral tissues, including skeletal muscles, liver, and pancreas [29]. Epidemiological studies have shown that impaired glucose tolerance, as well as type 2 diabetes, are associated with increased plasma cholesterol, palmitate and palmitoleate concentrations [42]. A positive relationship was found between changes in the concentration of phospholipid of stearic acid in plasma and the manifestation of the incidence of diabetes mellitus [21, 56]. Obviously, lipid metabolism is reflected in fluctuations in the concentration of lipids circulating in the bloodstream, which makes it possible to describe the metabolic phenotype [48].

It is important that lipids are involved in the formation and implementation of various intercellular signaling molecular mechanisms of anti-inflammatory action. Eicosanoids, fatty acids, sphingolipids, and phosphoinositides mediate the regulation of critical cellular processes, including cell metabolism, proliferation, and apoptosis. Fatty acids affect inflammatory processes both through their interactions with extracellular receptors and through intracellular signaling mediators. It is important that obesity is at the intersection of the mechanisms of development of inflammatory processes and metabolic disorders that cause aberration of the immune defense, an increased risk of type 2 diabetes, atherosclerosis, liver obesity and pneumonia, to name just a few of the dire consequences. An increase in the percentage of deaths and morbidity in inflammation induced by the pathogenesis of obesity has led to an increased interest of researchers in the study of various lipid-mediated neuroendocrine molecular mechanisms. It is obvious that in situations where the absorption of energy exceeds its consumption, a violation of cellular functions occurs, an insufficiency of the mechanisms of appetite regulation (appetate) is formed, and the likelihood of developing pathogenetic transformations increases [19]. Obesity is characterized by an imbalance in the metabolic carbohydrate, insulin-dependent, and lipid pathways, which contributes to meta-inflammation affecting key tissues and organs and negatively affecting the maintenance of homeostasis. Obesity in combination with metabolic syndrome, inducing inflammation, contributes to the pathogenesis of cardiovascular diseases, asthma, Alzheimer's disease and carcinogenesis, in special, due to excessive and prolonged inflammatory reactions [35, 45]. At the same time, special attention of researchers is paid to omega-6 and omega-3 fatty acids, which are known to regulate the action of inflammatory mediators in hepatocytes and adipocytes through the cyclooxygenase and lipoxygenase pathways. They also have a strong effect on the production of eicosanoids [35]. The inflammatory cyclooxygenase pathway, which originates from arachidonic acid, is a critical stage in the development of inflammatory reactions. As is known, cyclooxygenases catalyze the conversion of arachidonic acid to prostaglandin H<sub>2</sub> (PGH<sub>2</sub>, the precursor of other prostaglandins, prostacyclin and thromboxane A<sub>2</sub>). New oxygenated products of omega-3 metabolism, namely resolvins and protectins, act as endogenous mediators, exhibiting potent anti-inflammatory and immunoregulatory effects. Short-term and long-term inflammatory stimulation along the cyclooxygenase pathway (COX) can cause a shift towards less inflammatory cyclooxygenase pathways (involving prostaglandins of the PG 3 series and thromboxanes of the TX 3 series). The result of the implementation of these pathways is the formation of lipoxins and resolvins, which are capable of stopping the development of the inflammatory process. In addition, the dissolution of the LOX (LT5) lipoxygenase pathway by long-chain polyunsaturated fatty acids (LC PUFAs), namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), mediates the inflammatory protection mechanism. A high content of EPA is found, namely, in fish oil [24]. Recent studies show that a decrease in the proportion of adipose tissue in obese individuals, as well as their rehabilitation with exogenous means, using an appropriate type of diet with the inclusion in the diet of foods enriched with omega-3 polyunsaturated acids, contribute to the elimination of metabolic dysfunction and inflammatory processes in adipose tissue [52]. However, according to some authors, the role of docosapentaenoic acid in the lipoxygenase pathway requires revision in the context of anti-inflammatory action [34]. It is also important that the use of a diet based on the rich content of polyunsaturated fatty acids in fish oil can increase the secretion of adiponectin and improve the response of skeletal muscle cells to insulin. This is the key difference between consuming a diet enriched with saturated fat, which, on the contrary, leads to the formation of insulin resistance [51]. LC PUFAs also regulate gene expression through transcription factors PPAR and nuclear factor kappa B (NF- $\kappa$ B), as well as through the production of eicosanoids, reducing the production of proinflammatory cytokines from various cells, including macrophages. Infiltrated macrophages are an integral part of the stromal vascular fraction of adipose tissue and are involved in the production of proinflammatory monocytic chemoattractant protein-1, tumor necrosis factor-alpha (TNF $\alpha$ ) and interleukin-6 (IL-6). This anti-

inflammatory property of omega-3 fatty acids can be strategically used to reduce obesity-induced insulin resistance [38].

### **Inflammatory processes, remodeling in adipose tissue and hypothermic stimulation:**

In the mechanisms of regulation of lipid metabolism and inflammatory processes in white adipose tissue, the endocrine function of adipose tissue provides the implementation of one of the main links. This link includes, as you know, the basic metabolic processes: lipogenesis, based on cell proliferation and the absorption of circulating free fatty acids; lipolysis based on triglyceride hydrolysis to glycerol and free fatty acids; as well as oxidation of fatty acids inside mitochondria [33]. When a negative energy balance is formed with an excess of energy expenditure over its consumption, for example, during an exercise program in combination with fasting, reserved lipids are mobilized through lipolysis. The released fatty acids and glycerol are then used by actively functioning other tissues and organs [63]. A positive energy balance, obviously, is established when energy consumption, on the contrary, exceeds its consumption, for example, when using a diet with a high lipid or carbohydrate index in combination with an inactive sedentary lifestyle. With a positive energy balance, the unused energy substrate is reserved mainly in the form of lipids, which accumulate in white adipose tissue due to increased absorption of fatty acids and de novo initiation of lipogenesis [4, 7, 10, 55].

Chronic dysregulation of the energy balance due to the excess of energy consumption over its expenditure leads to excessive accumulation of lipids in the white adipose tissue, which leads to obesity. A number of environmental factors associated with individual activity and lifestyle, called the Western lifestyle, characterized by the use of a high-calorie diet, hypokinesia in combination with psycho-emotional stress, together contribute to the imbalance of energy homeostasis and the development of obesity [31]. Due to the global pandemic nature of the increase in obesity and associated metabolic diseases, it is very important to continue to discover the mechanisms underlying the regulation of lipid metabolism, the endocrine function of adipose tissue and its involvement in neuroendocrine regulatory pathways of interaction between nerve and glandular structures. These neuroendocrine interactions play an important role in the coordination of numerous processes in white, brown, and beige adipose tissue (WAT, BAT, and BeAT, respectively), including lipid reservation, WAT mobilization, fatty acid oxidation and thermogenesis in BAT, and WAT darkening to BeAT, which ultimately provide energy homeostasis in the internal environment of the body. Brown adipose tissue is a thermogenic tissue, the structural and functional units of which consume a significant amount of glucose and fatty acids as an energy substrate for thermogenesis and energy production [5, 8, 14]. The efforts of researchers in this direction provided the discovery of a number of humoral factors synthesized and secreted in adipose tissue, which are incorporated into the nerve regulatory circuits that go beyond the brain. Due to their heterogeneity and plasticity, white and brown adipocytes change their morphology and function in accordance with fluctuations in energy demand under certain physiological or pharmacological conditions.

For example, in conditions of increased energy consumption observed when exposed to cold, i.e. with hypothermic stimulation [64]. A targeted influence on metabolism by changing the physical parameters of the environment, in particular, reducing the temperature of the air or the aquatic environment, is a physiologically and evolutionarily determined means for inducing adaptive structural and functional remodeling of the system. It is assumed that a decrease in air temperature in residential premises contributes to a decrease in body weight and a decrease in the likelihood of concomitant metabolic disorders and even obesity due to an increase in the proportion of brown adipose tissue in the body composition and functional activity [27, 53, 60]. The effect of low temperatures on the body can presumably lead to an increase in metabolic rate by almost two times.

However, moderate doses of hypothermic stimulation may not affect changes in body weight or obesity, since food intake increases with a decrease in ambient temperature, which fully compensates for the increase in energy expenditure caused by cold [40]. An effective combination of physical exercise with hypothermic stimulation, which significantly alters the metabolism in BAT, induces the biosynthesis and release of batokins, factors that act in an autocrine, paracrine or endocrine manner, providing protection against metabolic syndrome. Exercise reduces insulin-mediated glucose uptake in BAT, suppresses the reservation of triglycerides (TG) and mitochondrial lipids such as cardiolipin (CL) and lysophosphatidylglycerol (LPG). These mitochondrial lipids affect the thermogenic capacity of BAT. However, exercise-based training stimulates the activity of epoxide hydrolase 1 and 2 (Ephx1/2) and promotes lipokine biosynthesis 12,13-diHOME. 12,13-diHOME is a lipokine, the biosynthesis and release of which is induced by physical training, and the effect is aimed at increasing the uptake of fatty acids by cells of active skeletal muscle. In contrast to exercise, hypothermic stimulation increases insulin-mediated glucose uptake in BAT, synthesis of cardiolipin, and lysophosphatidylglycerol, as well as the secretion of batokins: fibroblast growth factor

21 (FGF21) and vascular endothelial growth factor A (VEGF A). Factors FGF21 and VEGF are known to increase tissue sensitivity to insulin and the degree of its vascularization. Moreover, hypothermic stimulation, namely by increasing the biosynthesis of 12,13-diHOME, acting autocrine, promotes the absorption of fatty acids by brown adipocytes, which ultimately leads to an increase in thermogenesis mediated by TAG and UCP1 [12].

Obviously, functionally brown adipose tissue has a different purpose than white adipose tissue: it is extremely important for heat production under hypothermic stimulation, ensuring the conversion of chemical energy, reserved in lipids, into heat. Whereas, white adipose tissue serves as a place for saving one of the main energy substrates (lipids) to maintain energy metabolism, and an uncontrolled increase in the proportion of white adipose tissue in the case of a positive energy balance induces the development of overweight and obesity. A third type of adipose tissue, called beige, identified as distinct from white adipose tissue, exhibits characteristics of brown adipose tissue in response to a variety of stimuli, including cold, dietary variation, and medication [1, 13, 15, 23]. Like adipocytes in classic brown adipose tissue, beige adipocytes can also burn fat for heat production through the classic thermogenin-dependent mechanism [46]. Unlike brown adipose tissue, which is derived from the clone of the myogenic factor 5 (Myf5) [44], beige adipocytes are derived from the clones of the myogenic factors: Myf5<sup>+</sup> and Myf5<sup>-</sup>. In beige adipocytes, several specific markers of the cell membrane surface are unambiguously expressed, such as transmembrane protein 26 (Tmem26) and CD137 [23, 32, 58].

Brown and beige adipocytes contain the potential thermogenic ability to increase energy expenditure, therefore brown and beige adipose tissue is considered a promising therapeutic agent in the prevention and treatment of obesity associated with metabolic syndrome [3, 11]. A decrease in ambient temperature or a hypothermic stimulus is not only a serious stressor factor, but also an adaptogenic effect that triggers plastic remodeling of adipose tissue, maintains the functional activity of brown adipose tissue and the formation of beige adipocytes ("darkening of white adipose tissue") is associated with the induction of gene expression and biosynthesis of mitochondrial uncoupling protein 1 (UCP1, thermogenin) [47, 53]. Fundamental studies using mass spectrometry and RNA sequencing (RNA-seq) have shown that three-day hypothermic stimulation can induce profound changes in transcriptional activity underlying the mechanisms of lipid metabolism regulation and homeostatic maintenance of body temperature (thermostasis) [59]. It is known that brown adipose tissue has a number of advantages: a high degree of vascularization and innervation, a high rate of fatty acid oxidation and glucose absorption, and its structural and functional units (brown adipocytes) include multiple lipid droplets, and are also rich in mitochondria. So, it is obvious that brown adipose tissue is involved in providing the mechanisms of thermostasis by inducing and ensuring thermogenesis, which are realized due to the protein thermogenin [37]. Thermogenin uncouples cellular respiration and oxidative phosphorylation, reducing the proton gradient, and also ensures the use of  $\beta$ -oxidation of fatty acids released from triacylglycerol (TAG) in lipid drops, and also stimulates biogenesis of the mitochondrial apparatus, an increase in the density of cristae. The increased activity of brown adipose tissue and the "darkening" of other tissues, such as white adipose tissue, can increase the consumption of excess reserved energy and, in turn, reduce the likelihood of pathogenesis of metabolic diseases. Brown adipocytes represent an important target in the reduction of ectopic lipid accumulation caused by metabolic syndrome through several identified transcriptional regulation pathways that coordinate lipid metabolism in brown adipocytes. Proteins associated with lipid droplets act as regulators of lipid retention and release. Most likely, lipid droplets of brown adipocytes possess a unique proteome that is dynamic in nature and responds to physical stimuli such as cold, facilitating the release of stored energy [62].

Recently, there has been great interest in identifying new circulating endocrine factors that mediate the beneficial effects of exercise on health. Particular attention is paid to factors derived from skeletal muscle, known as myokines [39], our team of authors and, as well as other researchers [49] are inclined to the hypothesis that endocrine interactions, realized, for example, through adipokines, can be stimulated exercises that provide certain advantages of adaptation and rehabilitation programs in health-forming technologies.

Thus, the harmonious combination of a fundamentally substantiated individualized diet with the inclusion of foods rich in omega-3, omega-6 and omega-9 polyunsaturated acids after their sparing technological processing with hypothermic stimulation contains the potential of a beneficial effect on the plasticity of adipose tissue, its endocrine functions and prevention of inflammatory processes in it. Recently, there has been great interest in identifying new circulating endocrine factors that mediate the beneficial effects of exercise on health. Particular attention is paid to factors derived from skeletal muscle, known as myokines [39], our team of authors and, as well as other researchers [49] are inclined to the hypothesis that endocrine interactions, realized, for example, through adipokines, can be

stimulated exercises that provide certain advantages of adaptation and rehabilitation programs in health-forming technologies.

### Conclusion:-

The harmonious combination of a fundamentally substantiated individualized diet with the inclusion in the diet of foods rich in omega-3, omega-6 and omega-9 polyunsaturated acids after their sparing technological processing with hypothermic stimulation contains the potential of a beneficial effect on the plasticity of adipose tissue, its endocrine functions and prevention of inflammatory processes in it.

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