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STUDYING OF THE ROLE OF THE PREDICTOR GENES POLYMORPHISM IN THE DEVELOPMENT OF METABOLIC SYNDROME IN PERSONALIZED PREVENTION OF TYPE 2 DIABETES MELLITUS (LITERATURE REVIEW)

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Key words: metabolic syndrome, diabetes mellitus, obesity, gene polymorphism, FTO, TCF7L2-2, GNB3, ADRB3.

Annotation. Insulin resistance, dyslipidemia are determined by genetic and environmental factors. The aim of the study was to analyze modern domestic and foreign literature in the eLibrary and PubMed systems in order to study single nucleotide polymorphisms (SNP) of genes that predict the development of metabolic syndrome FTO, TCF7L2-2, GNB3, ADRB3 in personified prevention of type 2 diabetes mellitus (T2DM). Depending on their expression and function, gene variants can influence insulin action or other metabolic features. Currently, a preventive approach is considered as a promising direction in the treatment of DM-2, which allows to prevent and/or slow down the progression of the diabetic process and its redoubtable macro- and microvascular complications. Nutrition also plays an important role in the development and progression of these conditions. Due to the complex nature of genetic and environmental interactions, dietary therapy requires a “personalized” approach to nutrition.

Introduction. Metabolic syndrome (MS) in the modern world remains as one of the most complicated issues in the healthcare system, acquiring a scale of the 21st century’s epidemic. More than 1,9 billion people around the would have excessive weight, 650 million of them have obesity [1-3]. Metabolic syndrome in whole, alongside with its components: hyperglycemia, obesity, insulin resistance, arterial hypertension (AH), dyslipidemia play a significant role in occurrence of cardiovascular diseases (CVS) and type 2 diabetes mellitus (T2DM) in adult population. According to data given by the International Diabetes Federation, 8,5% of the world’s population suffer from T2DM, in the development of which the key role is given to the interaction of environmental factors and genetic features [1].

Within the genome-wide association study, many single nucleotide polymorphisms (SNP) of genes involved in the regulation of energy processes were

identified, as well as their relation to obesity, increased body mass index (BMI) and the risk of T2DM development [4-5]. That is why the search for genetic markers, related to MS, which would allow us to reveal mechanisms of eating behavior regulation, connected with the excessive lipopexia, would help in selecting patients from the high risk group and evaluate qualitative and quantitative changes of metabolites in case of dietary therapy in contrast with different genotypes. It would allow not only treating, but also implementing effective prevention measures for MS and its complications [5].

It is known that overeating, a tendency for an energy-enriched food, a desire to eat when the hunger is absent and the AH are associated with SNP, which serve as markers of metabolic disruptions. However, no gene responsible for MS was found. It was proven long ago, that the disruption in the carbohydrate metabolism lies in the base of metabolic syndrome [6]. This is why special attention should be given to FTO (Fat mass and obesity-associated protein, or the ketoglutarate dependent dioxygenase) genes, that is the rs9939609 polymorphism, the rs12255372 polymorphism of the TCF7L2 (transcription factor 7-like 2) gene, the nucleotide-binding protein beta polypeptide 3 (GNB3) and the β3-adrenergic receptor (ADRB3) as markers of the disruption in the carbohydrate metabolism in people with MS components [7-10].

The aim of this study was to analyze modern domestic and foreign literature in the eLibrary and PubMed systems in order to study single nucleotide polymorphisms (SNP) of genes that predict the development of metabolic syndrome FTO, TCF7L2-2, GNB3, ADRB3 in personified prevention of type 2 diabetes mellitus (T2DM).

Methods and organization. Databases eLibrary, PubMed and Google Scholar for 2015-2021 were analyzed.

Results and discussion. The FTO (rs9939609) gene polymorphism. The FTO gene is expressed in different tissues: liver, muscle tissue, adipocytes, β-cells of the pancreas and, mostly, in the hypothalamus [11, 12]. The most studied SNP of the FTO gene is rs9939609. The first intron of the gene (16th chromosome, position 53820527) can include either thiamine (T) or adenine (A). Recent population-based studies have shown that people, who are homozygous on the A allele (the polymorphous marker rs9939609) of the FTO gene have higher values of the body mass index and waist girth in comparison with homozygous people on the T allele, who have a lower MS incidence (loss of the hypothalamus's control over the appetite) [12].

This association is universal and is registered among different populations, such as Asian, European and middle Eastern. When studying SNP FTO in several Russian cities (Kaliningrad, Kursk, Saint-Petersburg), the following genotype

distribution was revealed: TT – 36,1%, AT – 46,4%, AA – 17,5%. Almost same numbers are recorded among residents of Moscow and Sverdlovsk Oblast. Moreover, the highest number of homozygous hosts on the T allele are women [7, 13].

A number of studies show that homozygotes on the A allele in people, who suffer from excessive weight and obesity, have various biochemical disruptions, for example hyperglycemia and hyperinsulinemia in the fasted state, increase in the level of triglycerides, C-reactive protein, decrease in the concentration of high-density lipoproteins, increase in the functional activity of β-cells, which in whole contribute to the development of metabolic syndrome and T2DM [11, 14]. A sustainable association between the FTO polymorphism and constitution features, variation and topography of the subcutaneous fat was revealed. High values of the "waist girth/hip girth" and the more pronounced lipopexia with the preferred localization in the stomach area are registered in men with the AA genotype. A presence of the T protective allele (heterozygote AT) increases the lipolytic activity of adipocytes, which leads to the decrease of fatty tissues [15-16].

The GNB3 gene polymorphism (rs5443). Proteins connecting guanine nucleotides (G-proteins) are transferring signals from many hormones, neurotransmitters and chemokines. Because of their main role in the functioning of many types of cells, genetic anomalies in the G-protein subunits can potentially serve as an etiologic factor of the wide spectrum of clinical states [8, 17].

The C825TGNB3genetic polymorphism is related to obesity, hypertension, depression and cardiovascular diseases. The GNB3 gene, located in the 12p13 chromosome, consists of 11 exons and 10 introns. The GNB3 gene has C → T (rs5443) polymorphism with the nucleotide number 825 in the exon of the tenth subunit of the Gi-type b3 protein [18]. In vivo studies have demonstrated an increased vascular reactivity in case of stimulating coronary α1-adrenoreceptors in GNB3825T hosts. Some ethnic groups with the given polymorphism have a very strong connection with hypertonia, when at the same time this effect is not registered in other groups. For example, the GNB3(C825T) polymorphism was not related to the arterial hypertension in Asian population, the other meta analytic study has revealed a significant association of the AH with the GNB3 (C825T) polymorphism in the Caucasian race [8, 18].

The ADRB3 (rs4994) gene polymorphism. It was proven more than 20 years ago, that rs4994 (T/C) SNP in the ADRB3 gene (also known as the Trp64Arg) is associated with obesity. The ADRB3 gene belongs to the family of adrenergic receptors, which plays an important role in the regulation of energy homeostasis and thermogenesis in fatty tissue [10]. Studies in several populations have shown that hosting the C-allele (CC + CT) is related to a lesser weight loss after life style

intervention in comparison with patients with the TT-genotype [10, 19].

The TCF7L2-1 (rs7903146) gene polymorphism. It was proven that the transcriptional factor 7, similar to the second one (TCF7L2), impacts the lipid metabolism: is the effector of the Wnt signaling pathway, participates in adipocytes differentiation, adipokine regulation and the β-cells functioning in the pancreas [20]. TCF7L2 polymorphisms were identified as one of the most important genetic predictors of the type 2 diabetes in genome-wide association studies [21].

The TCF7L2 rs7903146 (C/T) gene's allele (T), located in the intron 4 of the TCF7L2 gene, was related with the increased risk of the type 2 diabetes development and is a most common variant of disposition to the type 2 diabetes in the whole world [22]. This variant is connected with the increased expression of the mRNA TCF7L2 in the pancreas [23]. It increases the risk of type 2 diabetes development, influencing the insulin secretion, increasing the gluconeogenesis and insulin resistance [24].

The personified treatment and MS prevention. Based on the aforementioned data, it can be concluded that SNP can influence a response to diet, physical exercises for weight loss, increase of the insulin sensitivity and lipid profile, as well as blood pressure. It is assumed that data, based on studies presented in this review, are needed for general practitioners, kinesiologists and dietitians to develop personalized diet and pharmaceutical therapy in order to improve results of MS treatment.

A change from sensible nutrition to the non-balanced nutrition contributes to the activation of "silent" genetic factors, predicting T2DM development. It was revealed that the manifestation of polymorphism of genes that affect the metabolism of carbohydrates and lipids depends on the amount of carbohydrates and fats in food [25]. However, the patient's genetic status predetermines coordination of gene system, which is the personalized diet. For example, in people predisposed to the lipoprotein abnormality an excessive fat intake contributes to the development of visceral obesity and disruption in the carbohydrate metabolism. Following principles of the Mediterranean diet and intake of a sufficient amount of unsaturated fats is the most preferable. Realization of unfavorable polymorphism is usually noted in case of following hyper-calorie died by people with high risk of T2DM development [3, 26, 27].

A number of studies showed that the effect of AA genotype of the FTO gene can be weakened in physically active people [28]. The effect of interaction between FTO (rs9939609) and physical activity on BMI and waist girth was studied. Thus, association of polymorphism and physical activity can change the nature of the mRNA methylation and expression of the FTO gene in muscle and fatty tissue. Moreover, physical exercises increase thermogenesis in the subcutaneous adipose tissue, when at the same time variations in the FTO gene suppress the mitochondrial

thermogenesis, which is why physical activity is the most effective way to control body mass in people with genetic predisposition to obesity [28, 29].

The effect of the AA genotype of the FTO (rs9939609) gene on appetite was studied. Hosts of the FTO risk allele consume more food, but it gives less satiation in comparison with hosts of the joint allele, without any effect on energy consumption [30]. Thus, shortening of everyday calorie intake within the program of weight loss serves as an additional motivation for weight loss in people with the FTO risk allele. It was proven that in case of reducing diet therapy the nucleotide transversion mutation (A→T) takes place by the appropriate site (23525) of the intron mutation (rs9939609), which gives way to wider prospects for further research [31].

Different mechanisms of increasing the risk of T2DM related to the rs7903146 allele of the TCF7L2 were suggested. Most studies suggest that TCF7L2 plays a key role in β-cell functioning. The progressing loss of insulin secretion can be the main mechanism, which the help of which people with the T risk allele are predisposed to the T2DM development. However, precise molecular mechanisms are still unknown [32].

TCF7L2 is a transcription factor, which plays a leading role in the Wnt signaling pathway influencing the insulin secretion, induced by incretin, from the pancreas [33]. It was also proven that TT homozygotes for two SNP in TCF7L2, rs12255372 (G/T) and rs7903146 (C/T) had lower insulin secretion and higher sensitivity to insulin on the initial level comparing to hosts with any SNP allele. Physical loads increase methylation in TCF7L2 and decreases the TCF7L2 gene expression in fatty tissues. Therefore, it is possible that improving the insulin secretion in hosts of "risk" genotypes comparing to ordinary genotypes after addition of physical activity will increase the speed of weight loss [34].

Metformin is the most frequently used medication in T2DM treatment. However, there is a significant individual variability of therapeutic response to metformin. The most common variant of the TCF7L2 rs7903146 is the strongest genetic risk factor related to T2D to this date. Various mechanisms, which lie in the basis of this association, including the effect on β-cell proliferation, insulin synthesis, processing and secretion, as well as the disruption of the incretin response, were suggested [35]. Most studies show that the rs7903146 variant influences β-cells and insulin secretion. Merformin inhibits the mitochondrial complex I in hepatocytes, which leads to a decrease in the Adenosine triphosphate (ATP) level and an increase in the Adenosine monophosphate (AMP) level, which leads to the gluconeogenesis inhibition using suggested mechanisms [36-37]. Changes in the ATP/AMP ratio also activate the 5' AMP activated protein kinase (AMPK), which leads to a decrease in lipid synthesis and an increase of sensitivity to insulin. Thus,

it is possible, that various mechanisms are responsible for the gluconeogenesis inhibition, induced by metformin, and its effect on lipid metabolism and sensitivity to insulin. Researches proved that the T TCF7L2 allele (rs7903146) is related to the lower resistance to insulin and better glycemic response in recently diagnosed patients during the first year of metformin treatment [36-38].

When examining people with SNP in the ADRB3 gene, it was revealed that hosts of CC or CT genotypes lost significantly more weight than people with the TT genotype. Despite the fact that it is different to approve contradictory data, it is notable that the TT genotype (or the Trp64 genotype) possesses a higher reactivity (lipolysis) to the selective agonist beta-3 adrenergic receptors of a human in comparison with CT and TT genotypes in adipocytes of the human's omentum [10, 19].

Conclusion. When prescribing dietary therapy to patients with obesity, it is recommended to conduct molecular genetic testing, which can increase effectiveness of therapeutic events. Thanks to genetic testing, it is possible to reveal people with an increased necessity to personalize dietary therapy and prevent the development of a number of obesity's complications. Knowing features of the metabolic status in case of different polymorphous variants of appropriate genes, as well as the patient's genotype, it is possible to suggest an individual diet, which would allow achieving good results as soon as possible. Conducting molecular genetic testing will allow determining qualitative and quantitative changes of metabolites when exposed to different diets associated with a certain genotype, which will support not only treatment of obesity, but also its prevention. A transition from diagnosis to disease prevention, and then – to the selection of individual therapy is a foundation of personalized medicine today.

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