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GENETIC DETERMINANTS OF VITAMIN D METABOLISM DISORDERS IN METABOLIC SYNDROME

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Abstract. Metabolic syndrome is a complex combination of metabolic changes, including insulin resistance, and dyslipidemia, that can lead to various chronic diseases. Vitamin D has been identified as a crucial regulator of metabolic processes, and its deficiency is frequently observed in patients with metabolic syndrome. The genetic determinants that affect vitamin D metabolism represent an essential aspect that necessitates further in-depth study. The present study investigates the impact of diverse genetic polymorphisms associated with vitamin D metabolism on serum vitamin D levels and their correlation with the components of metabolic syndrome. A particular focus is placed on genes implicated in vitamin D synthesis, transport, and activation and their interaction with other factors such as diet and climatic conditions. The study of genetic factors affecting vitamin D metabolism may facilitate the development of individualized approaches to the prevention and treatment of metabolic syndrome, as well as enhance the understanding of the mechanisms of its pathogenesis.

Keywords: metabolic syndrome, gene polymorphism, vitamin D, 25(OH)D, vitamin D receptor, type 2 diabetes

Метаболикалық синдром кезінде Д3 алмасуы бұзылыстарының генетикалық детерминанттары

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Аңдатпа. Метаболикалық синдром-бұл әртүрлі созылмалы ауруларға әкелуі мүмкін инсулинге төзімділік пен дислипидемияны қоса, метаболикалық өзгерістердің күрделі комбинациясы. Д витамині метаболикалық процестердің маңызды реттеушісі ретінде анықталды және оның жетіспеушілігі метаболикалық синдромы бар науқастарда жиі байқалады. Д витаминінің метаболизміне әсер ететін генетикалық детерминанттар әрі қарай терең зерттеуді қажет ететін маңызды аспект болып табылады. Бұл зерттеу D дәрумені алмасуымен байланысты әртүрлі генетикалық полиморфизмдердің сарысудағы D дәрумені деңгейіне әсерін және олардың метаболикалық синдром компоненттерімен байланысын зерттейді. Д витаминінің синтезіне, тасымалдануына және белсендірілуіне, сондай-ақ олардың диета және қоршаған орта сияқты басқа факторлармен өзара әрекеттесуіне қатысатын гендерге ерекше назар аударылады. Д витаминінің метаболизміне әсер ететін генетикалық факторларды зерттеу метаболикалық синдромның алдын алу мен емдеуге жекелендірілген медицинаның дамуына ықпал етуі мүмкін, сонымен қатар оның патогенезінің механизмдерін түсінуді күшейтуі мүмкін.

Түйін сөздер: метаболикалық синдром, гендік полиморфизм, D дәрумені, 25(OH)D, D дәрумені рецепторы, 2 типті қант диабет

Генетические детерминанты нарушений метаболизма витамина D при метаболическом синдроме

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Аннотация. Метаболический синдром представляет собой сложное сочетание метаболических изменений, включая инсулинорезистентность и дислипидемию, которые могут приводить к различным хроническим заболеваниям. Витамин D был определен как важнейший регулятор метаболических процессов, и его дефицит часто наблюдается у пациентов с метаболическим синдромом. Генетические детерминанты, влияющие на метаболизм витамина D, представляют собой важный аспект, требующий дальнейшего углубленного изучения. В настоящем исследовании изучается влияние различных генетических полиморфизмов, связанных с метаболизмом витамина D, на уровень витамина D в сыворотке крови и его корреляцию с компонентами метаболического синдрома. Особое внимание уделено генам, участвующим в синтезе, транспорте и активации витамина D, а также их взаимодействию с другими факторами, такими как диета и климатические условия. Изучение генетических факторов, влияющих на метаболизм витамина D, может способствовать разработке индивидуализированных подходов к профилактике и лечению метаболического синдрома, а также углубить понимание механизмов его патогенеза.

Ключевые слова: метаболический синдром, полиморфизм генов, витамин D, 25(OH)D, рецептор витамина D, диабет 2-го типа

Introduction. Metabolic syndrome (MetS) is a pathological condition associated with abdominal obesity, insulin resistance (IR), hypertension, and dyslipidemia. The diagnosis of MetS is made through the measurement of waist circumference, low-density lipoprotein (LDLP) levels, triglycerides (TG), total cholesterol, and blood pressure (BP) [1].

The prevalence of MetS is increasing rapidly on a global scale. According to the International Diabetes Federation, approximately one-quarter of the global adult population is affected by MetS, which results in significant medical, social, and economic challenges [2]. MetS has been observed in 25% of the global population, with notable variations in prevalence attributed to factors such as gender, age, ethnicity, and geographical location[3].

The number of patients with MetS in Kazakhstan is increasing. According to the findings of nationally representative studies conducted in the Republic of Kazakhstan, the prevalence of MetS components among adults was 53.1%. In 2012, the Kazakh Academy of Nutrition conducted a survey that revealed an average incidence of excess body weight of 30.6% among women and 36.8% among men. The survey also documented an average prevalence of obesity of 27.6% among women and 15.9% among men[5].

It has been demonstrated that MetS increases the risk of developing long-term microvascular and macrovascular damage-related diabetes and diseases of the cardiovascular system diseases (CVSD) [6]. CVSD is a major cause of disability and mortality around the globe [7]. Atherosclerosis, a chronic inflammatory disease, constitutes the primary etiology of CVSD. A body of research has indicated that diminished antioxidant levels, alongside heightened inflammation and oxidative stress biomarkers, may play a role in the pathophysiology of T2DM complications [9] and the development of CVSD [10]. The inflammatory process can be triggered by metabolic disorders, such as atherogenic dyslipidemia (characterized by elevated levels of triglycerides and apolipoproteins, small particles of LDLP, and diminished concentrations of high-density lipoproteins (HDLP)) and increased levels of T2DM and inflammatory cytokines [11].

Vitamin D has been identified as a significant antioxidant and a potential risk factor for developing CVSD in patients with vitamin D deficiency [12]. Vitamin D deficiency has been

demonstrated to influence insulin secretion and sensitivity, thus playing a pivotal role in the development of MetS [13]. In addition, a study found that vitamin D intake positively affects lipid profile, insulin resistance, hyperglycemia, obesity, hypertension, and the treatment of MetS-associated disorders [14].

In recent years, there has been a growing interest in research on vitamin D. This hormone plays a pivotal role in regulating calcium and phosphorus levels, inflammatory responses, insulin resistance, and obesity. The two primary forms of vitamin D, cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are converted into the active form (1,25-dihydroxy vitamin D) by two hydroxylases found in the liver, kidneys, pancreas, and immune cells. Research has shown that vitamin D elevates the production of some anti-inflammatory cytokines but reduces other anti-inflammatory cytokines[15].

Vitamin D is a fat-soluble vitamin, which means it is stored in adipose tissue. However, studies have shown that the bioavailability and circulatory levels of vitamin D are lower in individuals with central obesity compared to those who are healthy. Vitamin D plays an essential role in regulating the expression of the insulin receptor. Therefore, an increase in insulin receptor substrate (IR) in glucose transport is directly related to low serum levels of vitamin D. Additionally, vitamin D deficiency has been observed to induce hypertension, as it functions as an antihypertensive agent by inhibiting the renin-angiotensin-aldosterone system at physiological concentrations. A growing body of research has identified a link between vitamin D deficiency and an increase in lipogenesis, a process which involves the accumulation of fat within adipocytes. This phenomenon is thought to occur due to the suppression of lipolysis, where adipocytes break down fat for energy. The underlying mechanism appears to involve elevated parathyroid hormone and calcium flux within adipocytes, suggesting a potential role for vitamin D in modulating energy metabolism in these cells[16].

In recent years, the prevalence of hypovitaminosis D has increased in developed countries due to lifestyle changes and the emergence of harmful habits. Vitamin D deficiency has been linked to various diseases, including MetS, which is clinically defined by a combination of metabolic and vascular disorders. A substantial body of research has documented the beneficial effects of vitamin D supplementation on outcomes for individuals with MetS. Concurrently, there is an ongoing exploration of measures aimed at maintaining optimal vitamin D levels as a potential preventive strategy against the progression of MetS. Assessing the vitamin D level influencing insulin resistance and glucose metabolism, which presents a risk for developing insulin resistance-related disorders, is a significant issue today. While recent studies have shown a biological connection between vitamin D and insulin resistance, more research is needed to validate these findings with specific molecular evidence. Evaluating serum D levels in relation to the pathogenesis of the exchange process that occurs in the early stages of MetS is crucial for both the patient and the doctor [17]. This is mainly because it facilitates the prediction of subsequent changes in MetS and the implementation of a personalized therapeutic and preventive strategy for each individual patient. Interventions for early diagnosis and timely prevention are essential steps in the optimal path to reducing the incidence of MetS, to study of early laboratory predictors of MetS and gene polymorphism was conducted for early diagnosis.

The aim of the study: Conduct a literature review of the relationship between serum vitamin D levels and gene polymorphism in metabolic syndrome.

Search strategy: The literature review analyzed articles published from the scientific databases PubMed, Medline, Google Scholar, Embase, and Web of Science from 2019 to 2024. The keywords "metabolic syndrome", "gene polymorphism", "vitamin D", "25(OH)D", "T2DM", "VDR" were used for the search.

For the literature review, articles were considered that meet the following criteria:

1. full-text articles;
2. relationship between MetS and vitamin D;
3. articles that publish the research results focused on identifying gene polymorphisms responsible for vitamin D metabolism.

The relationship between vitamin D and metabolic syndrome and its components.

The relationship between visceral obesity and vitamin D metabolism. The impact of vitamin D on the biology and modulation of adipose tissue in visceral obesity is a topic of significant interest and has been extensively studied. Both preclinical and clinical studies have demonstrated that the anti-inflammatory effects of vitamin D are evident and consistent in human adipose tissue [18]. Most studies conducted on 3T3-L1 (pre-mouse adipocytes) cells have reported that 1.25(OH) 2D3 inhibits adipocyte differentiation (18). However, contradictory findings have emerged from studies involving mesenchymal stem cells from pigs [19] and mice derived from bone marrow, revealing a role for 1.25(OH) 2D3 in promoting adipocyte differentiation. Several studies on human primary fat stem cells and primary subcutaneous preadipocytes have shown that vitamin D enhances adipocyte differentiation and lipid accumulation [20].

Insulin resistance and vitamin D metabolism. The relationship between insulin resistance and vitamin D metabolism involves molecular mechanisms related to the pathophysiological hypothesis of a possible link between hypovitaminosis D and insulin resistance. These mechanisms are primarily associated with insulin receptor expression, as well as the formation of inflammatory cytokines and the polymorphism of vitamin D receptors (VDR) expressed in pancreatic β cells. Notably, vitamin D influences gene transcription through both genomic and non-genomic mechanisms. The evidence suggests a genetic interrelation between hypovitaminosis D and insulin resistance[21].

Dyslipidemia and vitamin D metabolism. Both genetic and non-genetic mechanisms influence vitamin D and lipids. A primary function of vitamin D is to regulate calcium metabolism. In this capacity, vitamin D affects lipid metabolism through the following mechanisms: Enhanced calcium absorption in the intestinal tract may modulate the microsomal protein of triglyceride transport, thereby reducing triglyceride synthesis and secretion[22]; increased calcium levels in the intestine decrease the absorption of fatty acids due to the formation of insoluble calcium-fat complexes; calcium promotes the conversion of cholesterol into bile acids, which leads to lower cholesterol levels. Furthermore, 25-OH-D regulates parathyroid hormone (PTG) levels. Previous research on rat tails has shown a correlation between hyperparathyroidism and elevated triglyceride levels[23]. Consequently, vitamin 25-OH-D, a regulator of PTG, may also modulate triglyceride levels. Vitamin D influences beta cell function and insulin resistance, impacting lipoprotein metabolism and increasing triglyceride levels while simultaneously reducing TSLP concentrations [24].

Diseases of the cardiovascular system and vitamin D metabolism. Vitamin D has been demonstrated to play a role in calcium homeostasis; however, recent studies have identified its deficiency as a novel risk factor in the development of CVSD. Specifically, epidemiological and clinical studies have reported a close relationship between low vitamin D levels and CVSD, which encompasses coronary heart disease, heart failure, and cardiac arrhythmias [23]. The pathophysiological mechanisms through which vitamin D deficiency may function as a risk factor for the development of CVSD are postulated to include the following: activation of the renin-angiotensin-aldosterone system, abnormal regulation of nitric oxide, oxidative stress, or changes in inflammatory pathways[25].

The relationship between vitamin D receptor polymorphisms and the risk of developing MS:

The vitamin D receptor (VDR) gene has been demonstrated to influence lipid and glucose metabolism in humans. In humans, the VDR gene is located on chromosome 12q13.11. Among its many single-nucleotide polymorphisms (SNPs), five variants have been previously described: TaqI (rs731236 T > C), ApaI (rs7975232 C > A), BsmI (rs1544410 G > A), FokI (rs2228570 G > A), and Cdx2 (rs11568820 G > A). Numerous studies have demonstrated a correlation between polymorphisms in the VDR gene and vitamin D deficiency, obesity, and glucose intolerance in children and adolescents [26].

A thorough analysis of the relationship between genetic variants of VDR and parameters such as glycemia, body mass index, fat mass, and lipid levels can deepen our understanding of the pathogenesis of T2DM, MS, overweight, and obesity. A solid understanding of this association can provide individuals with essential information for preventing these diseases.

The association between vitamin D receptor polymorphisms, T2DM*, and glycemic status*. In a study by Xu et al., individuals with the A/A genotype of the polymorphism rs2189480 (G>A, C, T) in the VDR gene exhibited a lower incidence of T2D development compared to those with the G/A and G/G genotypes [27]. This polymorphism is known to influence the function of regulatory T cells within the 4th intron, thereby modulating inflammatory activity. It is hypothesized that by affecting the inflammatory response, this polymorphism may provide a protective effect against the development of T2DM [28].

The connection between vitamin D receptor polymorphisms and metabolic syndrome. In a study of Brazilian adolescents aged 10-19 years, rs7975232 was not associated with an increased risk of developing CVSD. However, the C/C genotype in the recessive model was consistently associated with arterial hypertension. In the case of other VDR polymorphisms, no significant associations with the components MetS and MetS were observed. Researchers emphasize the importance of identifying genetic markers associated with vitamin D metabolism in overweight or obese children and adolescents. Identifying these genetic markers is imperative for determining the risk of developing MetS at an early age. Consequently, this facilitates a more expeditious diagnosis of the disease and enables effective coping strategies for individuals affected by it [29].

In a study by Tong Zhao et al., the CA+AA genotypes of the rs4588 gene and AC carriers of the rs2282679 genotype were shown to be prone to decreased susceptibility to metabolic syndrome in rural Chinese populations. Concurrently, the analysis of MetS components revealed significant negative correlations between the AA genotype of the rs4588 gene and the SS genotype of the rs2282679 gene of the GC gene and the levels of TG and HDLP in blood plasma [30].

Concurrently, recent findings have indicated that genetic polymorphisms of VDR may be associated with components of MS, including abdominal obesity, BMI ≥30, prediabetes, diabetes, increased LDLP levels, high blood pressure, or hypertension [31].

The association between vitamin D receptor polymorphisms and obesity. The findings, which have emerged from recent studies, suggest a potential link between genetic variations in the VDR and the presence of MetS. The relationship between vitamin D receptor polymorphisms and obesity focuses on the correlation between these polymorphisms and body mass index (BMI). A study examined the association between polymorphisms of the DVR gene rs731236, rs7975232, and rs1544410 and the risk of obesity. The results of an Iranian study indicated that the rs7975232 allele and the A/A genotype may be predictors of obesity. A notable finding was the observation of elevated mean oral glucose levels and fasting glucose concentrations in individuals bearing the A/a genotype. The polymorphism rs7975232 may predict an elevated risk of obesity and could facilitate the development of novel therapeutic interventions for this metabolic disorder [32].

Conclusion. Polymorphisms in the VDR gene have been shown to influence the development of MetS, obesity and insulin sensitivity. A comprehensive analysis of the potential interplay between the genetic basis of VDR and critical parameters such as glycaemia, adipose tissue condition and lipid metabolism promises to deepen our current understanding of the multifaceted pathogenesis of CD, MetS, overweight and obesity. Confirmation of the influence of specific VDR genetic polymorphisms on the parameters associated with these pathological conditions and diseases will facilitate the development of personalized therapeutic interventions for patients in the future. In addition, this knowledge will provide individuals with valuable information to help prevent the development of cardiometabolic disorders.

Conflict of interest. The authors declare no conflict of interest.

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