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Genetic factors of vitamin D3 deficiency and their clinical significance

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Objective: to analyze the available literature data on genetic polymorphisms that affect the metabolism of vitamin D3 and its concentration in blood serum, with an emphasis on the latest experimental and clinical data.

Material and methods. A search and analysis of scientific papers and review articles on the effect of genetic polymorphisms in genes (GC, CYP2R1, CYP27A1, DHCR7, VDR) on the metabolism of vitamin D3 and on the subsequent realization of its pleiotropic effects was carried out.

Results. The role of hereditary factors in changes in serum indices of vitamin D3 is 23-80%, along with indicators such as the UV index, skin insolation, nutritional route of administration, or with drugs. The review analyzed data on the genetic polymorphisms of the GC (DBP), CYP24A1, CYP2R1, CYP27B1, VDR, NADSYN1 / DHCR7 genes, which are involved in the metabolism of vitamin D3 and their association with blood vitamin D3, and analyzed the relationship between vitamin D3 and genetic polymorphisms. The very state of hypovitaminosis D3 increases the likelihood of developing diseases such as type 2 diabetes mellitus, cardiovascular disease, and hypertension.

Conclusion. Knowledge of hereditary risk factors for low levels of vitamin D3 can be of great practical importance for the personalization of therapeutic and preventive measures.

Keywords: Genetic polymorphisms, vitamin 25 (OH)D, diabetes mellitus, cardiovascular diseases.

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Vitamin D3 and its role in various pathological processes are currently being actively studied. According to the latest clinical recommendations of the Endocrinological Society, in 40-60% of the world's population, the level of provision with vitamin D3 is regarded as insufficient [1].

Vitamin D3 - cholecalciferol - is synthesized in the malpigian and basal layers of the epidermis of the skin with the active participation of 7-dehydrocholesterol as a result of the non-enzymatic, ultraviolet-dependent photolysis reaction. The activity of vitamin D3 formation directly depends on the ultraviolet index and is inversely related to the degree of skin pigmentation. In the epidermis of the skin, cholecalciterol binds to vitamin D-binding protein transports (VDBP), and 70% of it passes from the bloodstream to the liver, and the other part enters the fat cells, where the formation of a vitamin D3 depot occurs [2].

In Kupffer liver cells, under the influence of the membrane enzyme of the cytochrome P450 family, 25-hydroxylase, the gene-controlled (CYP3A4) cholecalciferol and ergocalciferol are hydroxylated and an

active metabolite of 25(OH)D (25-hydroxyvitamin D – calcidiol). Recent studies of the pleiotropic effects of vitamin D3 show that P-450 isoenzymes: CYP2C9 and CYP2D6 are involved in this reaction [3]. More than 90% of vitamin D3 is bound to VDBP, which in turn is bound to serum albumin. A person has studied 3 main variants of VDBP (Gc1F, C2, and Gc1S), which differ in their affinity for vitamin D3.

Polymorphism of the above options differs in persons of different nationalities and ethnic groups. For example, the Gc1F variant is more common in individuals with an African genealogy, the predominance of a high affinity Gc1F phenotype with a high affinity is revealed, and with a homozygous genotype, the VDBP level was only half its level in whites, in which the variant prevailed Gc1S. At the second stage of metabolism, transport proteins 25(OH)D are transported to the kidneys. The D3/VDBP complex interacts with proximal tubule cell receptors - megaline and cubilin, which reabsorb vitamin D3 from glomerular filtrate, D3 hydroxylation occurs with the participation of the mitochondrial cytochrome P450, 1a-hydroxylase enzyme, which is controlled by CYP27B1 and 24-hydroxylase, which forms a biologically highly active metabolite D3 - calcitriol (1.25(OH)2D [4, 5].

At the gene level, active metabolites of vitamin D3 bind to specific receptor proteins - vitamin D receptor (VDR). The complex D3(VDR) has a specific deoxyribonucleic acid (DNA) binding domain. During the interaction of the active form of vitamin D3(VDR) complex with the chromatin of regulatory DNA regions, a VDR-DNA compound is formed, as a result of which DNA transcription is selectively stimulated. This process leads to the biosynthesis of new mRNA molecules and the translation of specific proteins that are involved in the formation of a physiological response [9-12].

Studies of the pleiotropic effects of vitamin D3 indicate the inverse correlation between low levels of vitamin D3 and the prevalence of cardiovascular diseases (CVD), as well as the development of certain cardiometabolic risk factors such as diabetes mellitus, dyslipidemia, hypertension and metabolic syndrome [13].

It was found that a decrease in vitamin D3 levels already in childhood is associated with high risks of CVD, including high blood pressure, a decrease in high density lipoproteins, and an increase in the concentration of parathyroid hormone. The above changes can potentiate the development of CVD in young people [14]. Vitamin D3 deficiency contributes to the development of atherosclerosis, which contributes to endothelial dysfunction, the formation of foam cells and the proliferation of smooth muscle cells.

The antihypertensive properties of vitamin D3 include suppression of the renin-angiotensin-aldosterone system, renoprotective effects, direct effects on endothelial cells and calcium metabolism, inhibition of vascular smooth fiber cell growth, prevention of secondary hyperparathyroidism and a beneficial effect on cardiovascular risk factors.

Vitamin D3 also affects the glycemic profile, lipid metabolism, and insulin secretion, which allows us to believe that there is a relationship between vitamin D3 deficiency and metabolic syndrome. In deficit correction, other indicators should also be taken into account, such as the level of phosphates, parathyroid hormone, renin, and fibroblasts [15]. The active metabolite of vitamin D3, calcitriol, realizes its endocrine, paracrine, and autocrine biological effects by binding to the VDR [16, 17]. Vitamin D receptors are located: endothelial, pancreatic islet cells, hematopoietic cells, cardiac and skeletal muscle cells, monocytes, neurons, T-lymphocytes, placental cells, etc., which confirms the pleiotropic effects of vitamin D3 [18].

According to the results of the study using genome-wide association study (GWAS), genes were identified, mutations in which can affect the concentration of vitamin D3: GC (VDBP) – a gene that encodes a protein that binds to Vitamin D3; CYP2R1 is a gene that controls the activity of microsomal enzymes, CYP27A1 is a gene that encodes mitochondria 25-hydroxylase, DHCR7 is a gene that controls the activity of 7 dehydrocholesterol

reductase [19]. Genomic effects of vitamin D3 are realized through the corresponding receptors VDR, the detection of polymorphism of which affects the realization of biological effects of vitamin D3 [20, 21]. According to various estimates, the role of inherited factors in the change in serum D3 indices is from 23-80% [22-24].

In one of the meta-analyzes of data from 15 GWAS studies, among 733 996 studied Europeans (USA, Canada and European countries) and studied the effect of mutations of 3 genes (GC, DHCR7 / NADSYN1 and CYP2R1), on the level of vitamin D3 with reliability fluctuations (from $p = 4.99 \times 10^{-9}$ to $p = 1.9 \times 10^{-10}$), an association of serum vitamin D3 values with 18 single nucleotide polymorphisms (SNP) in regions with above-mentioned genes (rs2282679, rs3755967, rs17467825, rs1155563, rs2298850, rs7041 for GC gene; rs12785878, rs7944926, rs12800438, rs3794060, rs4945008, rs4944957 for gene DHCR7 / NADSYN1 and rs10741657, rs2060793, rs1993116, rs12794714, rs10500804, rs7116978 for CYP2R1 gene) [25]. In another meta-analysis of data from 21 studies, a significant dependence of circulating vitamin D3 indices on polymorphisms was revealed: rs4588 and rs7041 in the GC gene, rs10735810 of the VDR gene and rs10877012 of the CYP27B1 gene [26].

In a Danish study that examined the effect of genetic polymorphisms on serum levels of vitamin D3 among children (n = 344) and adults (n = 414), an association of vitamin levels with a number of polymorphisms in the genes CYP2R1, CYP24A1, DHCR7 / NADSYN1, was revealed. GC, VDR. The largest number of genetic polymorphisms was found in the GC gene. A significant ($p = 0.01$ - $p < 0.0001$) decrease in the concentrations of vitamin 25(OH)D (by 9.1-24.4%) was detected in children and adults with rs16846876 polymorphism (haplo- type TT), rs12512631 (haplotype TT), rs17467825 (haplotype GG), rs2282679 (haplotype CC), rs842999 (haplotype CC), rs4588 (haplotype AA), rs222020 (haplotype CC). Similar results were obtained in the analysis of polymorphisms and the CYP2R1 gene [27].

A survey of 1605 Latin American women found that two polymorphisms of the GC gene (rs7041 and rs2282679) and one of the CYP2R1 gene (rs2060793) have a significant effect on vitamin 25(OH)D levels. Each of the above polymorphisms influenced from 0.6–3.5% on fluctuations in the concentrations of vitamin 25(OH)D [28].

There is data on the dependence of the efficacy of prescribing Vitamin D3 preparations on the presence of genetic polymorphisms. In 1787 examined US residents aged 45-75 years, it was found that an increase in vitamin D3 levels with vitamin D3 intake of 1000 IU / day and calcium carbonate (1200 mg / day) depended on rs10766197 polymorphisms (CYP2R1 gene), rs6013897 (CYP24A1 gene) and rs7968585 (VDR gene) [29].

People with genetic risk factors for vitamin D3 deficiency need higher doses of vitamin supplements. According to the study, among women over 70 who took vitamin D3 at a dose of 800 IU / day for whom there were genetic risk factors, only 50% reached an adequate level of vitamin D3 in the blood serum, then among people with a more favorable genetic background - in 77% of cases, an increase in the level of vitamin D3 was achieved ($p < 0.05$) [30].

A correlation was revealed between the rs2228570 polymorphism located in exon 2 of the VDR gene and containing 2 alleles, C and T, with the level of vitamin D3 in the blood among Europeans (Great Britain) [31, 32]. According to another study conducted in Tehran, it was revealed that rs2228570 polymorphism is associated with vitamin D3 deficiency in patients who had cardiovascular diseases [33]. In another study, genetic characteristics were revealed among the inhabitants of the Russian Arctic compared with Europeans. Among the population of the Arctic region, the frequency of occurrence of the C allele rs2228570 of the VDR gene was higher than that of the newcomer population, and amounted to 71.1%, while the frequency of occurrence in Europeans was 57.8%. An analysis of the results revealed a statistically significant relationship between the C allele of the rs2228570 polymorphism of the VDR gene and vitamin D3 deficiency [34]. A similar association between the

presence of a dominant T allele and vitamin D3 level was found during examination of other groups of healthy and sick individuals [35–39].

According to a study in Southeast China, it was found that polymorphisms in the genes (GC, CYP3A4, CYP24A1 and NADSYN1 / DHCR7) involved in the metabolism of vitamin D3 have associations with levels of vitamin D3 in blood serum among pregnant women [40].

In another genome study (GWAS), among 4501 among the European population taken from 5 cohorts, SNP in the genes were identified. An analysis of polymorphisms of 3 genes revealed that with SNP levels 25 there were significant associations of SNP rs2282679, rs7041, rs1155563 (GC gene), rs3829251, rs1790349,11234027 (DHCR7 / NADSYN1 gene), rs206079 and rs1993116 (CYP2R1 gene). The polymorphism rs2282679 of the GC gene ($p = 1.8 \times 10^{-49}$) had a pronounced relationship with indices 25(OH)D. With all this, the presence of its allele was interrelated with a low level of vitamin 25(OH)D.

The set of differences between the average levels of 25(OH)D between the carriers of two copies of the minor allele (genotype CC) and the rest (genotypes AC and AA) ranged from -6.4% to -34.4% (median -18.3%). When compared with the normal type (AA) of the GC gene, heterozygous individuals (AS) had an almost 2 times higher risk (odds ratio = 1.83) of vitamin D3 deficiency (level 25(OH)D <25 nmol / L). It was found that the rs11234027 polymorphism in the DHCR7 / NADSYN1 gene also affects the concentration of D3. The minor hapotype (AA) of this polymorphism reduced the levels of vitamin D3 by 7.3-24.9% (on average - by 9.5%). In this case, the haplotype AA rs1993116 of the CYP2R1 gene (frequency of the A allele in the population is 0.39) increased the concentration of 25(OH)D by 12.7–20.0% [30].

Conclusion

The role of hereditary factors in changing the serum indices of vitamin D3 is 23-80%, along with indicators such as the UV index, insolation of the skin, nutritional route or with drugs. The review analyzed data on the genetic polymorphisms of the GC (DBP), CYP24A1, CYP2R1, CYP27B1, VDR, NADSYN1 / DHCR7 genes, which are involved in the metabolism of vitamin D3 and their associations with blood vitamin D3 level, and analyzed the relationship between vitamin D3 deficiency and genetic polymorphisms. The very state of D3 hypovitaminosis increases the likelihood of developing diseases such as type 2 diabetes mellitus, cardiovascular disease, and hypertension. Knowledge of hereditary risk factors for low levels of vitamin D3 can be of great practical importance for the personalization of therapeutic and prophylactic measures**.**

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