POLYMORPHISM OF THE VITAMIN D RECEPTOR GENE AND THE CYTOKINE GENES IL-6 AND TNF-A AND THE RISK OF DEVELOPING TYPE 1 DIABETES

Raimova F.S
Samarkand State University named after Sharof Rashidov

Vitamin D (VD) is a group of biologically active fat-soluble compounds, including more than 50 metabolites, which are formed under the influence of ultraviolet irradiation in the tissues of animals and plants from sterols [14]. From an evolutionary point of view, VD is considered the most ancient hormone currently known. Its extremely important importance for the human body is due to its numerous effects on various organs and tissues through the regulation of about 2000 genes [13]. VD acquires the biological activity of the hormone only after a series of transformations that occur step by step in the liver and kidneys [3,7]. Supplied with food (D2), or synthesized in the skin under the influence of ultraviolet radiation (D3), VD enters the liver. UV-induced synthesis of vitamin D3 in the skin from 7-dehydrocholesterol is catalyzed by DHCR7 (NADP-dependent 7-dehydrocholesterol reductase). In the liver, under the influence of the enzyme 25hydroxylase of mitochondria (CYP27A1) and microsomes (CYP2R1), VD is converted into its prohormonal forms 25(OH)D3 (calcidiol) and 25(OH)D2 (ergocalcidol). The latter are the main circulating forms of VD, which enter the kidneys through the bloodstream.

It is important to note that the determination by laboratory methods of the serum level of the prohormone 25(OH)D is the most acceptable, reliable and clinically significant for assessing the VD saturation of the human body [5]. Of all the vitamin metabolites, it is 25(OH)D that best correlates with bone mineral density, serum calcium levels, and the intensity of parathyroid hormone secretion. In addition, the half-life of 25(OH)D is quite long and is about 15 days, which also makes it preferable for assessing VD status. In circulation, only 0.2-0.6% of 25(OH)D molecules are in a free state [10], while the vast majority of them are associated with DBP - vitamin D binding protein (80-90%) and albumin (10 -20%). In the cells of the proximal tubules of the renal cortex and some other tissues, from the incoming 25(OH)D molecules, as a result of a reaction catalyzed by the mitochondrial enzyme 1α-hydroxylase (CYP27B1), active hormonal forms VD are formed - 1,25(OH)2D: calcitriol (1 ,25-dihydrovitamin D3) and ergocalcitriol (1,25-dihydrovitamin D2). To prevent excessive synthesis, 1,25(OH)2D induces 24-hydroxylase (CYP24A1) activity. 24-hydroxylase is involved in the conversion of 1,25(OH)2D to biologically inactive calcitroic acid 24,25-(OH)2D3, which is the end product of VD metabolism and is excreted in bile [6].

The genomic effects of 1,25(OH)2D are realized through the corresponding receptors, the nuclear vitamin D receptors (VDR). The main function of VD is to

stimulate the absorption of calcium and phosphorus by small intestinal epithelial cells that possess the above receptors [16]. In addition, by now there is no doubt that VD is also directly involved in the metabolism of bone tissue, directly affecting its cellular elements through the VDR receptors present in chondrocytes, osteoblasts, osteocytes and osteoclasts [8].

Thus, the results of numerous studies conducted since the discovery of VD emphasize its key role in regulating calcium and phosphorus metabolism and ensuring healthy bone metabolism [15]. To date, there is no doubt that deficiency of this vitamin is the most important factor in the pathogenesis of diseases of the skeletal system such as rickets and osteoporosis. This is confirmed by the established associations of risk indicators for developing the above diseases with the presence of mutations in genes involved in VD metabolism [14]. In this regard, VD (1,25(OH)2D) is rightly called calciotropic hormone, and the administration of its drugs is widely used in medical practice for the prevention and treatment of corresponding bone pathologies. Along with the above, it must be emphasized that the biological role of VD is not limited only to the regulation of bone metabolism. Scientific research over the past two decades has significantly expanded our understanding of the role of VD in the human body. The first and important prerequisite for judging the wide extraskeletal spectrum of effects of the vitamin was that VDRs were found in almost all human tissues. The expression of VDR by almost all nucleated cells suggests an important role for VD in various physiological processes. In addition, it was found that the enzyme 1αhydroxylase, which provides the synthesis of 1,25(OH)2D, is present not only in the renal tubules, intestines, bone and cartilage tissues, but also in the cells of the skin, nervous system, placenta, testicles, spleen, lymph nodes, skeletal muscles, lungs, liver, in monocytes, macrophages and stem cells [4]. This indicates the presence of sources of the hormone other than the kidneys

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