International Journal of Innovative Research and Advanced Studies (IJIRAS)
Volume 7 Issue 4, April 2020

ISSN: 2394-4404

General Aspects Of Metabolism, Functions Of Vitamin D And Its Role In Liver Pathologies

Dr. Lipov Andrey, M.D.

Dr. Lipov Andrey, M.D.

Assistant Professor, Department of Hospital Therapy,
Stavropol State Medical University, Stavropol, Russia

Dr. Geyvandova Natalya M.D., Ph.D., D.Sc.

Professor, Department of Hospital Therapy,
Stavropol State Medical University, Stavropol, Russia

Dr. Sarithala Vijaya Jawahar M.D., Ph.D.

Assistant Professor, Department of Hospital Therapy,
Stavropol State Medical University, Stavropol, Russia

Khabichev Kerim

Urchukova Larisa

Junior Research Assistant, Department of Hospital Therapy,
Stavropol State Medical University, Stavropol, Russia

Abstract: ***Despite the recent advances in molecular and genetic mechanisms of liver pathologies, the role and metabolism of vitamin D in the liver pathologies still remain unexplored. This article gives a modern view on the role of vitamin D in normal and in pathologies of liver and provides a brief description and discussion on the correlation of vitamin D with the fibrosis of liver and results of treatment of patients with chronic viral hepatitis C.***

Keywords: ***vitamin D, VDR gene, hepatic fibrosis, chronic hepatitis C, antiviral therapy.***

I. GENERAL CONCEPT AND NORMAL RANGE OF VITAMIN D

Interest in vitamin D that has grown in recent years is associated not only with its ability to form and maintain a healthy skeletal system to prevent osteopenic conditions, but also with the ability to exert other effects in the human body. For a long time, bone manifestations of vitamin D deficiency were perceived as the only ones, however, up to date there is evidence that vitamin D not only affects calcium and phosphorus metabolism, but is also associated with the secretion and biological effects of other hormones, neurotrophic factors, and cytokines.

The problem of vitamin D deficiency is relevant, since at least 30-50% of the world's population is characterized by low supply of vitamin D. Elderly age, winter season, high body mass index, ethnicity, and an increase in the concentration of parathyroid hormone cause a decrease in the mediator level in the body. Vitamin D deficiency is associated with an increased risk of diabetes mellitus, cardiovascular pathology, including arterial hypertension and myocardial infarction, oncopathology, immunosuppressive, autoimmune and inflammatory diseases.

Up to date, the optimal vitamin D content in the body has not been determined. It was previously thought that vitamin deficiency develops in cases where blood concentrations are less than 8 ng/ml. However, only at a concentration of 25 (OH) D from 30 to 40 ng/ml, a balance is reached in between the amount of 25 (OH) D and the level of parathyroid hormone (PTH). With a decrease in the content of 25 (OH) D below 20 ng/ml, a significant increase in PTH production is observed, reaching a plateau with vitamin D values of 30-40 ng/ml, which block the excessive synthesis of PTH.

According to experts, the lower threshold of 25 (OH) D in the blood is defined as 75 nmol/l or 30 ng/ml. Vitamin D deficiency is recommended to be diagnosed at a level of 25 (OH) D below 20 ng/ml, borderline insufficiency in cases of values of 21-29 ng/ml, and the normal content of vitamin D ranges from 30 to 100 ng/ml.

The physiological need for vitamin D for children and adults is 10 μg/day (400 IU/day), for people over 60 years old - 15 μg/day (600 IU/day).

ISSN: 2394-4404

II. METABOLISM AND FUNCTIONS OF VITAMIN D

Vitamin D exists in two forms: ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), which differ slightly in chemical structure and have similar metabolic stages. Vitamin D2 is found in foods of plant origin (cereals, bread, mushrooms), cholecalciferol is rich in oily fish, caviar, liver, butter, egg yolks.

Vitamin D is absorbed in the duodenum and jejunum in the presence of bile acids and is transported by the intestinal lymphatic system as part of chylomicrons. The formation of vitamin D also occurs in the skin under the influence of ultraviolet radiation of spectrum "B", which decreases with insufficient radiation intensity, the presence of dark skin color, poor environmental conditions, the use of sunscreen lotions, physical inactivity, etc. Using vitamin D-binding protein (VDBP) Vitamin D is transported to the liver (where the first stage of transformation occurs), and to the depot (adipose and muscle tissue).

In Kupffer cells, under the influence of cytochrome P-450 enzymes (CYP2R1, CYP2C9 and CYP2D6), cholecalciferol is converted by hydroxylation to the first intermediate metabolite, 25-hydroxyvitamin D (25 (OH) D) or calcidiol). In the proximal convoluted tubules of the kidneys, the second stage of vitamin D transformation is carried out: from the hydroxycholecalciferol under the action of hydroxylases (CYP27B1, CYP24A1, CYP93E1), the formation of the hormone-active form of vitamin D - calcitriol (1,25-dihydroxyvitamin D - 1.25 (OH) 2D) or forms an alternative metabolite is 24.25 (OH) 2D. The active form of the vitamin transported by the VDBP transporter protein reaches targeted tissues whose cells contain the vitamin D receptor (VDR).

III. VITAMIN D RECEPTOR AND GENE

VDR consists of three regions: N-terminal DNA-binding domain, the C-terminal ligand-binding domain and the extensive non-structural region that binds the functional domains of the protein. Three main receptor variants (Gc1F, C2, Gc1S) are distinguished, which differ in their affinity for 25 (OH) D. The prevalence of receptor variants depends on ethnic characteristics. Thus, the Gc1F variant is more common among representatives of the Negroid race.

The VDR receptor gene is expressed in all body tissues and is located on the 12th chromosome (q13-14 segment), and its structure includes 11 exons. Several gene polymorphisms have been identified: TaqI (rs731236), BsmI (rs1544410), EcoRV, ApaI (rs7975232) and FokI (rs10735810). They are located between exons 8 and 9, except for FokI, located in exon 2. The restriction enzyme sites ApaI and BsmI are located in intron 8 (non-coding region) near exon 9 and do not affect the structure of the receptor. Two alleles were found in the VDR gene cluster in each locus: ApaI (a and A), BsmL (b and B), TaqI (t and T), FokI (f and F). There are evidences confirming the connection of variants of nucleotide polymorphisms of the VDR gene with the formation of a number of pathologies.

By binding to VDR, active forms of vitamin D exert physiological effects primarily through genomic mechanisms. The effect of vitamin D on the expression of more than 200 genes has been proven , it is assumed that it is able to alter the expression of more than 5000 genes. The genomic roles of vitamin D include maintaining the stability of the genome (cell division cycle, DNA repair, chromosome restructuring), controlling protein synthesis and degradation, regulating embryogenesis, blood coagulation, apoptosis, and inflammation. Given the expression of VDR on cells of the immune system (monocytes, macrophages, lymphocytes, thymus cells), it is obvious that a change in the functioning of immunoregulatory substances depending on the genetic polymorphism of VDR affects the formation of the body's immune response.

IV. VITAMIN D AS AN IMMUNOMODULATOR

Much attention is paid to the immunomodulatory and anti-inflammatory effects of calcitriol. The presence of receptors on the cells of the immune system, as well as the ability of mononuclear phagocytes to synthesize calcitriol confirms the participation of vitamin in the functioning of the immune system. Vitamin D receptors are found on activated T-lymphocytes, macrophages, immature thymus lymphocytes and mature CD8 cells, while B-lymphocytes express a small number of receptors. Calcitriol interacts with receptors on antigen-presenting cells, T- and B-lymphocytes and suppresses the maturation of dendritic cells, the expression of antigens of the main histocompatibility complex of class II, blocks the synthesis of pro-inflammatory cytokines, and inhibits the secretion of interleukin-12 by macrophages, which ensures differentiation of "naive" T- helper cells in T-helper cells of the 1st type.

Influencing activated T-lymphocytes, calcitriol reduces the production of pro-inflammatory cytokines (IL-2), IFN-α, granulocyte-macrophage colony-stimulating factor. Calcitriol reduces the proliferation of cytotoxic T-lymphocytes and natural killer cells, stimulates the activity of T-suppressors, maintaining the body's resistance to its own antigens. Vitamin D does not have a direct effect on B-lymphocytes, however, interacting with T-helpers, levels their activating effects on antibody production by B-cells and stimulates apoptosis of B-lymphocytes.

Antigen-presenting cells also produce 1.25 (OH) D after immune stimulation. Dendritic cells are not only the site of extrarenal formation of 1.25 (OH) D, but also represent the primary target for the immunomodulatory activity of vitamin D, which inhibits the differentiation and maturation of dendritic cells. As a result, dendritic cells have tolerogenic properties, respond less to proinflammatory cytokines, inhibit the inflammatory response, and stop tissue damage. In addition, vitamin D induces apoptosis and promotes a shift in the cellular response towards Th2.

The immunomodulatory effect of vitamin D is expressed in its ability to prevent the development and reduce the severity of manifestations of immune diseases, such as multiple sclerosis, systemic lupus erythematosus, type 1 diabetes mellitus, rheumatoid arthritis, reduce inflammation in the liver parenchyma, suppress hepatitis C virus replication.

Despite the proven effect of vitamin D on inflammatory and immune responses, the mediator levels required for immunomodulatory function remain unknown, and the data obtained in *in vitro* studies are controversial.

V. VITAMIN D AND CHRONIC LIVER DISEASE

Vitamin D plays an important role in the pathogenesis of infectious and cardiovascular diseases, diabetes mellitus and oncological pathology. Plasma levels of 1.25 (OH) D were reduced in tuberculosis, HIV, respiratory infections, and viral hepatitis. Vitamin D deficiency and polymorphism of its receptor are associated with the development of autoimmune diseases and tumors, which is reflected in the use of vitamin or its agonists as adjunctive therapy.

The association of vitamin D with chronic liver pathology has been demonstrated by a decrease in its levels in various liver diseases. The frequency of vitamin D deficiency or its deficiency in chronic liver diseases is increased compared to the general population and varies from 64 to 92%. Vitamin D deficiency is not only a characteristic feature of cholestatic liver disease. Thus, the blood vitamin D content in alcoholic liver cirrhosis was lower than in case of primary biliary cirrhosis. Reduced concentrations of vitamin D and its active metabolites in the blood were determined in patients with HCV infection. Decreased vitamin D levels were observed in cases of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

The severity of vitamin D deficiency is exacerbated with the progression of liver pathology. Thus, reduced levels of vitamin D in patients with cirrhosis of the liver were more likely to occur in Child-Pugh class C. There is evidence of the effect of vitamin D on mortality in chronic liver disease, including cirrhosis and hepatocellular carcinoma. The relationship of low levels of vitamin D with the development of liver failure supports the thesis of the use of the mediator as a prognostic marker in patients with cirrhosis.

Vitamin D deficiency in liver pathology is associated with reduced intake and intestinal absorption of the vitamin, decreased exposure to the sun, and reduced content of transport proteins. In addition, in liver diseases, hepatic hydroxylation of vitamin D is impaired, which leads to a decrease in the production of active forms of the hormone.

VI. THE ROLE OF VITAMIN D IN THE DEVELOPMENT OF LIVER FIBROSIS

A number of studies have demonstrated a negative relationship between vitamin D and the stage of liver fibrosis, which can be explained by its anti-inflammatory effects, taking into account the contribution of inflammatory cells to the formation of liver fibrosis. It has been established that 1.25 (OH) 2D inhibits the proliferation of stellate cells and their transformation into a profibrogenic phenotype and reduces the degree of liver fibrosis. In a model of obstructive nephropathy, vitamin D analogues reduced renal fibrosis [Tacke, F.]. These results suggest that vitamin D deficiency promotes liver fibrosis, while the addition of the hormone had an antifibrotic effect in patients with HCV infection.

[41] VDR expression in hepatocytes, Kupffer and stellate cells correlates with suppression of fibrogenesis, and the development of liver fibrosis is independently associated with genetic variants of VDR and low levels of 25 (OH) D in plasma. Deficiency of 25 (OH) D and unfavorable VDR gene polymorphisms (bat [CCA] - haplotype, ApaI rs7975232 CC genotype) increase the risk of progression of hepatic fibrosis in patients with chronic viral hepatitis (CVH) C.

The serum vitamin D content was found to negatively correlate with the stages of fibrosis in chronic liver pathology, and the homozygous carriage of the DHCR7 allele or CYP2R1 allele is associated with low levels of vitamin D. Genetic polymorphism of rs12785878 gene at the DHCR7 locus correlated with liver elasticity. According to the authors, vitamin D affects initiation rather than progression of liver fibrosis. The GG genotype of the DHCR7 gene was an independent factor in severe liver fibrosis in cases of HCV infection and was associated with vitamin D deficiency.

According to other sources, there is no correlation between the content of 25 (OH) D in the blood and the presence or absence of liver cirrhosis, as the dynamics of vitamin D with a deterioration in the severity of cirrhosis according to Child-Pugh were not revealed. The thesis that there is no connection between vitamin D and the stage of liver fibrosis is postulated. Thus, the average serum values of vitamin D did not significantly change with increased liver fibrosis and depended more on seasonal, racial and geographical differences.

VII. VITAMIN D AND HEPATOCELLULAR CARCINOMA

VDR expression in hepatocellular and cholangiocellular carcinoma cells of the liver was increased compared to normal cells, and activation of VDR in tumor cells reduced cell proliferation and prevented tumor growth. Vitamin D, having anti-apoptotic, anti-inflammatory and anti-angiogenic effects, inhibits the proliferation of tumor cells. The inhibitory effect of vitamin D on hepatocellular and cholangiocellular carcinoma cells was noted.

VIII. THE EFFECT OF VITAMIN D ON ANTIVIRAL THERAPY OUTCOMES IN LIVER DISEASE

Patients with different genotypes of CVH C do not respond equally to treatment, which depends on many factors. Regulators of connective tissue homeostasis, components of the hemostasis system (protein C, fibrinolysis indicators, etc.), markers of endothelial dysfunction and soluble adhesion molecules can be considered as predictors of the effectiveness of antiviral therapy for CVH C from the microorganic view. It is of interest to study the polymorphisms of the VDR gene, the content of vitamin D in the blood in comparison with the results of antiviral therapy.

The presence of low levels of vitamin D in the blood was associated with negative results of treatment of CVH C

regardless of genotype, while the addition of oral forms of vitamin D improved response to therapy and reduced the frequency of relapses. In patients with CVH C who had a number of VDR polymorphisms and were treated with interferon-α (IFN-α), ribavirin, and vitamin D, a higher frequency of achieving a sustained virologic response (SVR) was observed.

High serum levels of 25 (OH) D can act as predictors of SVR during treatment with pegylated interferon and ribavirin. So, serum values of vitamin D 12 ng/ml were characterized by a high negative predictive value (87.5%), and vitamin indices with a cut-off point of 38 ng/ml had a positive predictive value of 69.6% in predicting SVR with the 4th HCV genotype.

The increased content of vitamin 25 (OH) D in the blood was a favorable predictor in achieving SVR in patients with CVH C with no severe liver fibrosis, while hepatic fibrosis combined with low levels of vitamin D in the blood led to a decrease in the frequency of stable virological clearance. A correlation was found between reduced levels of vitamin D and unsatisfactory results of antiviral therapy.

It is suggested that the addition of vitamin D to standard therapy can increase the frequency of achieving rapid (RVR), early (EVR), and sustained virological responses in untreated patients with HCV genotype 1. Thus, the combination of vitamin D with standard therapy contributed to an increase in the frequency of RVR, EVR, SVR and a decrease in the risk of relapse. The use of vitamin D improved the results of antiviral therapy in patients with HCV infection after liver transplantation. The beneficial effects of vitamin D were confirmed by a negative correlation of its content with the inflammatory response and liver fibrosis.

Polymorphisms of the CYP2R1 and VDR genes can affect the results of antiviral therapy. However, in cases of the HCV infection of 1st genotype, the CYP2R1 gene polymorphism did not have predictor ability.

VDR cross-interacts with the Jak-STAT system by altering the expression of interferon-stimulated genes (ISG), resulting in a calcitriol-induced increase in the hepatocellular response to IFN-α. Thanks to the introduction of exogenous IFN-α, the modified expression of ISG provides an antiviral effect against HCV through interferon receptors and the Jak-STAT system. Genetic polymorphisms of ISG influenced the results of antiviral therapy for HCV genotype 1.

The association of polymorphisms of the interleukin-28B (rs12979870), CYP2R1 (rs10741657 A/G) and VDR (rs 2228570 A/G, rs 1544410 C/T) gene polymorphisms was studied with treatment results in patients with the HCV 4th genotype. When prescribing standard therapy, carriage of the A allele in the VDR (rs2228570) and CYP2R1 (rs10741657) genes increased the chance of achieving SVR, and its combination with the CC genotype of the interleukin-28B gene (rs12979870) increased the frequency of stable aviremia to 100%. There was no correlation between CT genotype of the VDR gene (rs1544410) and the results of antiviral therapy. Carriage of the AA genotype of the VDR gene (rs2228570) and the CC genotype of the interleukin-28B gene increases the SVR frequency to 100% in patients without liver cirrhosis. Carriage of the A allele of the CYP2R1 gene is associated with a higher content of vitamin D in the blood and is an independent predictor of achieving SVR. The data obtained can be extrapolated for patients with the HCV of 1st genotype.

The vitamin D content in the body, AA genotype of the VDR gene (rs2228570), the CC genotype of the interleukin-28B gene (rs12979860), the carriage of the A allele of the CYP2R1 gene are favorable predictors of SVR in patients without cirrhosis. The relationship between VDR and ISGs suggests an important role for vitamin D in improving the effectiveness of antiviral therapy with IFN-α. The possibility of using vitamin D drugs to improve SVR in the treatment of CVH is being debated.

Thus, vitamin D plays an important role in the immune response, inflammatory responses, tissue remodeling and carcinogenesis, including in case of chronic viral liver diseases. At the same time, it is still not clear: liver damage enhances the violation of vitamin D homeostasis or, conversely, an imbalance of vitamin D affects liver damage.

It is assumed that the existing relationship of vitamin D with chronic HCV-associated liver pathology, including liver function, fibrosis stage, and antiviral therapy results, is characterized by great potential for the clinical use of the mediator as a diagnostic and prognostic tool.

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