

**L.R. Shostakovych-Koretskaya¹,
M.A. Nikolaychuk¹,
I.V. Budayeva¹,
O.P. Shevchenko-Makarenko¹,
K.Yu. Lytvyn¹
S.V. Biletska^{1,2}** **COMPARATIVE ANALYSIS
OF VITAMIN D CONTENTS
IN PATIENTS WITH CHRONIC
VIRAL HEPATITIS C AND HEALTHY**

SE «Dnipropetrovsk medical academy of Health Ministry of Ukraine»¹

Department of Infectious Diseases

V. Vernadsky str., 9, Dnipro, 49044, Ukraine

Medical Center «Unimed»²

Młodej Polski str., 7, Krakow, 30-131, Poland

ДЗ «Дніпропетровська медична академія МОЗ України»¹

кафедра інфекційних хвороб

(зав. – д. мед. н., проф. Л.Р. Шостакович-Корецька)

вул. В. Вернадського, 9, Дніпро, 49044, Україна

Медичний центр «Unimed»²

вул. Молодої Польщі, 7, Краків, 30-131, Польща

e-mail: nk.miroslava@gmail.com

e-mail: biletskasv@gmail.com

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Ключевые слова: хронический гепатит С, дефицит витамина D

Abstract. Comparative analysis of vitamin D contents in patients with chronic viral hepatitis C and healthy. Shostakovych-Koretskaya L.R., Nikolaychuk M.A., Budayeva I.V., Shevchenko-Makarenko O.P., Lytvyn K.Yu., Biletska S.V. From scientific literature it is known that vitamin D helps maintain the most important functions of the immune system, there is evidence of its role in inflammatory and metabolic diseases of the liver, including infection with hepatitis C. Aim – to study vitamin D status in patients with chronic viral hepatitis C compared to the healthy ones. We examined 100 patients with chronic viral hepatitis C (main group) and 30 patients without hepatitis C virus (control group). Level of 25 (OH) D in serum was studied by immunochemical method with electrochemiluminescent detection. To verify the diagnosis of vitamin D deficiency and insufficiency, a classification (M.F. Holick, 2011), adopted by the International Institute of Medicine and the Committee of Endocrinologists for clinical practice guidelines, was used. Vitamin D deficiency was found in 44% of people with chronic viral hepatitis C in the main group (mean hydroxycalciferol – 14.36±4.12 ng/ml). Vitamin D deficiency was found in 6,6% in the control group (mean 17,5±8,52 ng/ml). The average vitamin D deficiency in the main group was slightly lower than that in the control group. Factors that affect the metabolism of vitamin D in patients with chronic viral hepatitis C include a lack of vitamin D in blood serum.

Реферат. Сравнительный анализ содержания витамина D у больных хроническим вирусным гепатитом С и здоровых. Шостакович-Корецкая Л.Р., Николайчук М.А., Будаева И.В., Шевченко-Макаренко О.П., Литвин К.Ю., Белецкая С.В. Из научных литературных источников известно, что витамин D помогает поддерживать важнейшие функции иммунной системы, есть данные о его роли в воспалительных и метаболических заболеваниях печени, в том числе при инфицировании вирусом гепатита С. Цель – выявить витамин D – статус у больных с хроническим вирусным гепатитом С по сравнению со здоровыми. В обследовании приняли участие 100 больных хроническим вирусным гепатитом С (основная группа) и 30 практически здоровых лиц с отсутствием вируса гепатита С (контрольная группа). Уровень 25(OH)D в сыворотке крови изучали с помощью иммунохимического метода с электрохемилюминесцентной детекцией. Для верификации диагноза дефицита и недостаточности витамина D использовали классификацию (M.F. Holick, 2011), принятую международным институтом медицины и комитетом эндокринологов по созданию установок по клинической практике. Дефицит витамина D обнаружен у 44% лиц с хроническим вирусным гепатитом С основной группы (средний показатель гидроксикальциферола – 14,36±4,12 нг/мл). В контрольной группе дефицит витамина D установлен в 6,6% (средний показатель – 17,5±8,52 нг/мл). Средний показатель дефицита витамина D в основной группе был несколько ниже соответствующего показателя в контрольной группе. К факторам, которые влияют на метаболизм витамина D у больных хроническим вирусным гепатитом С, относится недостаточный уровень витамина D в сыворотке крови.

Today, the problem of vitamin D deficiency is extremely urgent, with almost one billion people worldwide characteristically exhibit low availability of this vitamin [8]. There is evidence that vitamin D helps maintain the most important functions of the immune system, it takes on the role in inflammatory and metabolic diseases of the liver, including the infection with hepatitis C virus [16]. However, the association between vitamin D metabolism and chronic hepatitis remains insufficiently known and is therefore the focus of our study.

In addition to insufficient sun exposure, seasonality, habitat, diet and skin pigmentation affecting the bioavailability of vitamin D, hepatitis C and B, the major causes of liver cirrhosis (LC) and hepatocellular carcinoma (HCC) also contribute to vitamin D deficiency.

Vitamin D plays an important role in the pathogenesis of infectious and cardiovascular diseases, diabetes mellitus and oncopathology [2]. Plasma levels of 1,25 (OH)₂D are reduced in tuberculosis, HIV, respiratory infections and viral hepatitis [6, 15, 18]. Scientists claim that the level of 25-hydroxyvitamin D₃ inhibits the replication of hepatitis C virus [14]. Some clinical evidence suggests the prevalence and risk of vitamin D deficiency in patients with chronic hepatitis C, so researchers point to the benefits of vitamin D supplementation in chronic hepatitis C [11]. Today it is proved that in many immunocompetent cells there is vitamin D₃-hydroxylase activity, which testifies to the possibility of synthesis of hormone-active form of vitamin D by cells of different organs and tissues [1, 7]. The level of activity of D₃-hydroxylase is directly dependent on the dose of dioxymetabolite and is enhanced under the influence of gamma-interferon [3]. Receptors for hormone-active forms of vitamin D in active, capable of proliferation T and B-lymphocytes, macrophages and monocytes have been found. The same receptors are found in cells of the thymus, bone marrow and in the monocyte-macrophage line of the lungs [4, 13]. It should also be noted the effect of vitamin D on the proliferation, differentiation and activity of cells of the monocyte-macrophage row according to functional intent - at any stage of maturation [9, 10, 12, 17].

Analyzing data from various scientific sources, we can say that vitamin D is of great importance for the health of the body and affects all organs and systems. Since vitamin D is actively involved in immune processes, it is natural that it also affects the pathogenesis of infectious diseases. Vitamin D receptors are found in many organs and synthesis occurs in almost all cells. Vitamin D metabolites act as an integral system that plays an important role in

maintaining the normal functioning of the whole organism, its individual organs and systems. The presence of vitamin D in the liver and kidneys is extremely important. However, the effect of vitamin D on the human body, in particular its role in the pathophysiology of liver disease, needs further study.

The aim of the study was to investigate the level of vitamin in patients with chronic viral hepatitis C and in healthy subjects.

MATERIALS AND METHODS OF RESEARCH

Vitamin D content in serum was screened in 100 patients with chronic viral hepatitis C (CVHC) who were enrolled in the registry of patients with chronic hepatitis in the Dnipropetrovsk region and had not received antiviral therapy before. Diagnosis of chronic viral hepatitis C was performed in accordance with the instructions for diagnosis, clinical classification and treatment of these diseases in accordance with the order N 729 of 18.07.2016 "On approval and implementation of medical and technological documents for standardization of care in viral hepatitis C". The etiological verification of the diagnosis was confirmed by the detection of RNA-HCV in the serum of patients by PCR using the test system "CFX96" (BioRad, USA); "Vector-Best-Ukraine" with detection of amplification products in "real-time" regimen at automatic station "NucleiSENS easyMAG" for RNA/ DNA isolation and system "Amplicor HCV test, v2.0" (Roche Molecular Systems, California). Defining 25 (OH)₂D was performed using electrochemiluminescent method on an Eclia apparatus (Roche Diagnostics, Switzerland) using the analyzer and test systems Cobas 6000/Cobas 8000, Roche Diagnostics (Switzerland) in an independent laboratory in Dnipro city. To verify the diagnosis of vitamin D deficiency and insufficiency, a classification (M.F. Holick, 2011), adopted by the International Institute of Medicine and the Committee of Endocrinologists was used. According to this classification, the level of 25 (OH)₂D in serum from 30-85 ng/ml corresponds to the norms, the level of 25-hydroxycalciferol from 29-20 ng/ml in the blood is considered to be an insufficiency of vitamin, the figure less than 20 ng/ml corresponds to a deficiency of vitamin D [5]. Laboratory reference values were identical: for adults (18 years and older): deficiency: <20.0 ng/ml; insufficiency: 20.0 – <30.0 ng/ml; optimum level (norm): ≥30.0 ng/ml.

The control group included 30 relatively healthy individuals. Selection of patients in this group was conducted in a targeted manner, the main condition of which was the absence of any chronic or acute diseases that could lead to impaired vitamin D metabolism.

Statistical processing of the obtained results was carried out using the methods of variation statistics implemented in the package of applications "STATISTICA 6.1" using parametric and non-parametric methods of estimation of the obtained results. The study was performed within the framework of the research work of the Department "Immunogenetic predictors of the development of diseases associated with latent infections in adults and children" (state registration number 0115U001214).

RESULTS AND DISCUSSION

Study of vitamin D content in patients with CVHC. The initial content of vitamin D in the serum of patients with CVHC, as well as the content of vitamin D depending on the age and sex of patients was analyzed.

We analyzed and divided the patients into groups according to the content of 25 (OH)D in the serum.

Table 1 presents the distribution of patients by groups depending on the content of 25 (OH)D in the serum: only 18 (18.0%) patients had sufficient vitamin D level, 38 patients (38.0%) had vitamin D

insufficiency and in most patients, n=44 (44%) – deficiency.

The analysis of the presented data (Table 1) shows the presence of a significant difference in the content of vitamin D in patients in the group with vitamin D deficiency and in the group with vitamin D insufficiency compared with the group with normal vitamin D content (p 1-2 <0.05, g 1-3 <0.05). There was also a significant difference (p 2-3 <0.05) between vitamin D findings in the second and third groups (vitamin D insufficiency and deficiency), indicating impaired metabolism of this vitamin.

Analysis of frequency of vitamin D insufficiency or deficiency showed that the proportion of patients in the second and third groups significantly exceeds the group with normal vitamin D levels: the frequency of vitamin D insufficiency or deficiency compared with the group with normal vitamin D level is 2-2.4 times higher, and when summing the number of both groups (2 and 3) – by 4.5 times. This fact indicates the negative effect of chronic hepatitis C on the metabolism of vitamin D in most patients with this disease.

Table 1

Distribution of patients by groups depending on 25 (OH)D content in serum

Group number	Number of patients, (n,%)	Ratio of vitamin D content registration rate	Serum content of 25 (OH)D - ng/ml (M ± m)	Confidence factor - p
Group 1 (normal vitamin D level)	n=18 (18%)	1 group: 2 group = 1:2.1	41.53±1.99	p 1-2<0.05 p 1-3<0.05
Group 2 (vitamin D insufficiency)	n=38 (38%)	1 group: 3 group = 1:2.4	25.29±0.50	p 2-3<0.05
Group 3 (Vitamin D deficiency)	n=44 (44%)	1 group: 2+3 groups = 1:4.5	14.30±0.61	

We also analyzed the content of vitamin D in patients with CVHC, taking into account gender characteristics (Table 2).

The analysis showed that the gender of patients with CVHC did not affect the content of vitamin D in this disease in any group. The findings of vitamin D content in different groups in both males and females are close (p>0.05). Almost equally, there was a registration of relative vitamin D insufficiency or its absolute deficiency in the majority of patients regardless of gender (Table 2).

Table 3 presents the analysis of vitamin D content in serum in patients with CVHC and healthy individuals (Table 3, Fig.).

Study of vitamin D content in the control group.

The study of vitamin D content in the group of healthy individuals revealed that in most of the surveyed - 63.3% – violations of this indicator were not observed, insufficiency was registered in 30%, and vitamin D deficiency – only in 6.67% of the surveyed.

It should be noted that in healthy individuals with vitamin D deficiency all cases of this type of disorder were observed only in men. In fact, we cannot explain this fact of by gender influence on impaired vitamin D metabolism.



Table 2

Distribution of patients by groups depending on 25 (OH)D content in serum and by gender

Level of 25(OH)D	Males n=49		Females n=51			Confidence factor – p	
	absolute number	%	25(OH)D level in serum (M ± m)	absolute number	%		25(OH)D level in serum (M±m)
Normal level of vitamin D - 1 group	10	20.4%	44.3±2.98	8	15.6%	38.18±1.79	p m-f>0.05
Insufficiency of vitamin D – 2 group	16	32.6%	25.87±0.81	21	41.3%	24.86±0.67	p m-f>0.05
Deficiency of vitamin D – 3 group	23	47.3%	13.62±1.84	22	43.1%	15.11±0.86	p m-f>0.05

When comparing the frequency of registration of different forms of vitamin D metabolism disorders in the group of patients with CVHC and in the control group (Table 3), it was found that vitamin D deficiency is almost 6.5 times more often occurs in patients with CVHC, which clearly confirms the fact of negative impact of chronic liver damage caused by hepatitis C virus on vitamin D metabolism.

However, the relative insufficiency of vitamin D was observed almost equally often in both groups (in patients with CVHC and in the control group),

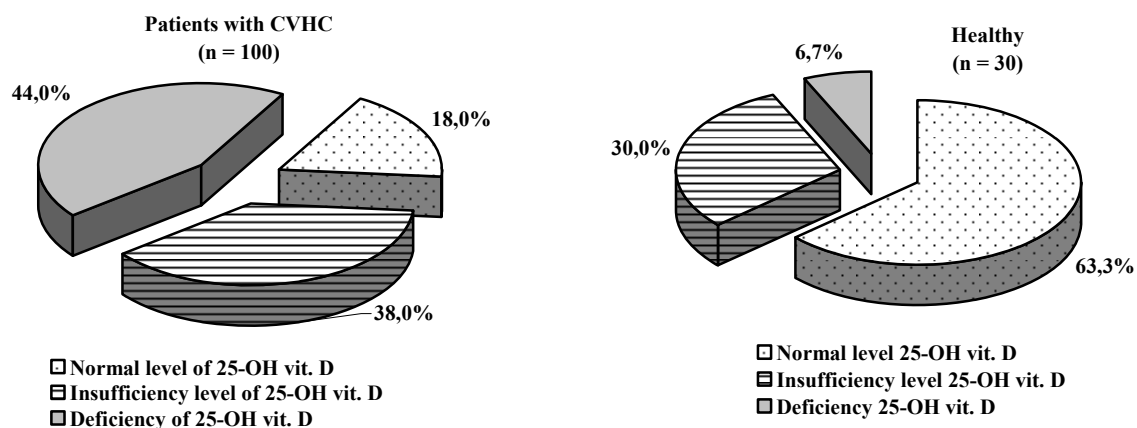
approximately in one-third of those surveyed in both groups. This fact indicates that one third of healthy individuals have a primary relative vitamin D insufficiency, which, when any chronic disease overlays, can cause the development of vitamin D deficiency, as we show in our study through an example of CVHC patients.

Normal vitamin D level in the healthy group is recorded 3.5 times more often, being an expected fact which again confirms the negative impact of CVHC on vitamin D metabolism.

Table 3

Distribution of patients with chronic viral hepatitis C and healthy individuals relative to vitamin D content in serum

	Frequency of registration of patients depending on the content of vitamin D		Content of vitamin D M±m (ng/ml) Frequency of registration of patients depending on the content of vitamin D	Frequency of registration of patients depending on the content of vitamin D		Vitamin D content M±m (ng/ml) Frequency of registration of patients depending on the content of vitamin D	Ratio of frequency of registration between groups CVHC / healthy
	males, n=49	females, n=51	All CVHC patients	males, n=15	Females, n=15	healthy	
Normal content is 25-OH vitamin D ₃	10- 20.4%	8 15.7%	41.59±1.9 n=18 18%	9- 60.0%	10- 66.7%	37.67±1.3 n=19 63.3%	1:3.5
Insufficient content of 25-OH vitamin D ₃	16- 32,6%	21 41.2%	25.21±0.5 n=38 38%	4- 26.6%	5- 33.4%	26.63±0.3 n=9 30%	1:1.2
Deficient content of 25-OH vitamin D ₃	23 47%	22 43.1%	14.36±0.7 n=43 43%	2 11.8%	0	17.5±1.5 n=2 6,67%	1:6.44



Comparative data of patients with chronic viral hepatitis C and healthy individuals with regard to their vitamin D-status

To more accurately study the effect of CVHC on the impairment of vitamin D metabolism compared to the control group of healthy individuals, we used the definition of relative risk and odds ratios (Table 4, Table 5).

In our study, we obtained a relative risk greater than 1 (RR=2.236). This indicates that the factor of

CVHC presence in a human is a predictor of the direct suppressive effect of this disease on the negative metabolism of vitamin D in patients. This correlation is statistically significant ($p < 0.05$), as indicated by the lower limit and upper limit values of 95% CI (CI) > 1 .

Table 4

Calculation of indicators of relative risk of vitamin D deficiency (insufficiency) in CVHC compared with the control group of healthy individuals

Absolute risk of vitamin D deficiency (or insufficiency) in patients with CVHC (EER)	0.820
Absolute risk of vitamin D deficiency (or insufficiency) in control group (CER)	0.367
Relative risk (RR)	2.236
Standard Relative Risk Error (S)	0.244
The lower limit of 95% CI (CI)	1.385
95% CI (CI) upper limit	3.611
Relative Risk Reduction (RRR)	1.236
Risk Difference (RD)	0.453
The number of patients requiring therapeutic adjuvant correction of vitamin D (NNT)	2.206
Method sensitivity (Se)	0.882
Specificity of the method (Sp)	0.514

Similar results on the direct negative impact of the chronic process on vitamin D metabolism (deficiency and insufficiency) in liver damage due to hepatitis virus C were obtained when calculating odds (Table 5).

The odds ratio of 4.556 indicates that the presence of CVHC in humans has a direct and close relationship between the presence of this disease and the occurrence of vitamin D metabolism (deficiency or insufficiency) with a probability of $p < 0.05$.

Table 5

Calculation of indicators of a chance of occurrence of deficiency (insufficiency) of vitamin D in CVHC compared with control group of healthy individuals

Chance to find risk factor for vitamin D deficiency or insufficiency in group of patients with CVHC	4.556
Chance to find risk factor for vitamin D deficiency or insufficiency in healthy controls	0.587
Odds Ratio (OR)	7.757
Standard odds ratio error (S)	0.333
The lower limit of 95% CI (CI)	4.041
95% CI (CI) upper limit	14.888

Thus, the study showed that the chances vitamin D deficiency or insufficiency in the group of CVHC patients is by 4.5 times higher than in healthy individuals. The detected dependence is statistically significant ($p < 0.05$).

Summarizing the above, it is safe to assume that vitamin D deficiency in the serum of patients with liver disease is another factor that may to some extent affect the final development of chronic viral hepatitis C.

CONCLUSIONS

1. Our results have shown that in CVHC patients there is vitamin D deficiency and insufficiency which needs some therapeutic correction.

2. One-third of healthy individuals have an initial insufficiency of vitamin D, which, if any chronic disease develops, can lead to an absolute deficit of this vitamin, as confirmed by this study of CVHC patients.

3. The study showed that CVHC causes a risk of vitamin D deficiency or insufficiency ($p < 0.05$), therefore with the chances of vitamin D deficiency or insufficiency in the group of patients with CVHC are 4.5 times higher than in healthy individuals. The detected dependence was statistically significant ($p < 0.05$).

Prospects for further research. In the future, it is necessary to conduct research on the effect of vitamin D on the effectiveness of antiviral therapy in chronic viral hepatitis C and determine the dose of vitamin D to achieve normal levels in the serum of such patients. There should be research in the medical institutions to determine the level of vitamin D in the serum of people with chronic liver disease.

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

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