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## Vitamin D and chronic spontaneous urticaria: searching for algorithms of personalized therapy

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Today, we can see a great interest in vitamin D because it participates in the regulation of many metabolic processes, and its deficiency is associated with the development of various diseases. Chronic spontaneous urticaria (CSU) is the disease that affects the quality of patient's life, and the existing strategy of patient management is not always sufficiently effective. Nowadays, there is enough information about the role of vitamin D deficiency and the severity of CSU. That is why it is important to study not only therapeutic schemes, but also a role of genetic variability that may have an impact on vitamin D levels.

Such studies will help to personalize the treatment schemes for patients with CSU. At the same time, the focus of these studies should be not only on the receptor and vitamin D binding protein, but also on P450 system, which plays a key role in the vitamin D metabolism.

**Keywords:** vitamin D, chronic spontaneous urticaria, personalized medicine, vitamin D deficiency, polymorphisms, CYP, P450, cholecalciferol, allergic diseases, pharmacogenetics

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## Витамин D при хронической спонтанной крапивнице: поиск алгоритмов для персонализированной терапии

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В настоящее время большой интерес к витамину D объясняется его участием в регуляции многих метаболических процессов, а его дефицит ассоциирован с развитием различных заболеваний. Хроническая спонтанная крапивница (ХСК) – сложное заболевание, существенно снижающее качество жизни пациентов. Несмотря на существующую стратегию медикаментозного контроля заболевания, лечение не всегда бывает достаточно эффективным. На сегодняшний день существует много данных о влиянии дефицита витамина D на тяжесть течения ХСК. В связи с этим перспективным направлением для лечения ХСК является не только изучение терапевтических схем применения витамина D, но и изучение генетической вариабельности участников метаболизма витамина D, влияющих на колебания его уровня в организме.

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Поиск новых алгоритмов поможет индивидуализировать лечение пациентов с ХСК путем персонализации терапевтических схем у пациентов. При этом внимание должно уделяться не только рецептору и белку, связывающему витамин D, но и изоферментам системы P450, играющим ключевую роль в его метаболизме.

**Ключевые слова:** витамин D, хроническая спонтанная крапивница, персонализированная медицина, дефицит витамина D, полиморфизмы, CYP, P450, колекальциферол, аллергические заболевания, фармакогенетика

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## Introduction

Chronic Spontaneous Urticaria (CSU) is the heterogeneous disease characterized by daily (daily round or nearly so) appearance of transitory skin blisters (typically <24 hr) and / or angioedema for >6 weeks due to known or unknown reasons [1].

It was found out that in 33–67% of patients with CSU it manifests with urticarial rash and angioedema, while 29–65% of patients have only manifestations of urticaria, and 1–13% of patients have only angioedema [1]. The number of patients in Russia requires the studies in a large-scale epidemiological research.

In December 2016, at the Charite University during the Third GA<sup>2</sup>LEN World Urticaria Forum (GUF2016), with the participation of over 300 specialists from more than 50 countries of the world, there were revised clinical guidelines on the diagnosis and treatment of urticaria. According to this guidelines, non-sedative antihistamines should be used in standard (1<sup>st</sup> line) as well as high doses (2<sup>nd</sup> line); therapy with monoclonal anti-IgE antibodies (3<sup>rd</sup> line), with the ineffectiveness of which the use of cyclosporin (4<sup>th</sup> line) is recommended [1]. As in the previous version of these guidelines, a short-term use of glucocorticoids (GCS) is allowed for 7–10 days at any stage of therapy. Stepwise therapy of CSU is also presented in the last version of Russian guidelines of the Russian Association of Allergists and Clinical Immunologists (RAAKI), the Russian Society of Dermatovenereologists and Cosmetologists and the Union of Pediatricians of Russia [2].

Despite significant advances in the treatment of CSU over the past decade, some questions remain unresolved. Firstly, it seems relevant to study the predictors of the efficacy and safety of antihistamines in the doses exceeding those specified in instructions for medical use of these drugs. Secondly, an important issue remains a search for predictors of the effectiveness of therapy for genetically engineered biological drugs (GMBDs), for example, omalizumab in patients with CSU.

In addition, the toxicity of cyclosporine dictates the need to search for safer therapeutic agents. Also, with the implementation of high-tech and expensive therapy with GMBD in CSU, the pharmacoeconomic aspects of therapy have acquired relevance due to the high economic

costs of both patients and the healthcare system. Solving these issues will make it possible to personalize therapy for CSU patients, optimize the effectiveness of therapy and use of health care resources.

## Vitamin D of the patients with chronic urticaria

Currently, international clinical guidelines contain information about vitamin D as a component of basic drug therapy for CSU. This is due to the results of some studies that have been published in recent years, demonstrating the effectiveness of vitamin D in CSU, with a high safety profile of such therapy [3]. Considering the new challenges for the world healthcare system, it seems especially urgent to analyze critically the evidence of the effectiveness of the vitamin D therapy in CSU.

In the world, it is assumed that 1 billion people are deficient in vitamin D, which indicates the relevance of vitamin D deficiency as a public health problem [4]. Vitamin D deficiency is common in patients with CSU, which may ultimately affect to clinical symptoms of this disease.

The study of the effect and algorithms for correcting vitamin D deficiency opens prospects for the implementation of principles of predictive medicine in treatment patients with CSU. Several international studies demonstrated clinical efficacy of various courses of vitamin D pharmacotherapy, not only with the recommended dosage regimen.

Thus, 20 patients with CSU and vitamin D deficiency (below 10 ng/ml) received an 8-week course of 50,000 IU of vitamin D per week, after a preliminary three-month course of antihistamines [5]. The result was an improvement of the patients' symptoms at 55% according to the international standardized rating scale – the urticaria severity score (USS).

In the other study [6], the therapy of 300,000 IU of vitamin D per month was added to the standard pharmacotherapy for 12 months, if the baseline plasma level of vitamin D was less than 30 mg/L (98% of patients was noted with deficiency of vitamin D). As a result, while taking vitamin D, according to the UAS4 scale, an improvement of symptoms was noted from 21 to 6 points, and on the CU-Q2oL scale from 38 to 10.8 points.

A dose-dependent efficacy of vitamin D course was noticed in patients' clinical case. Thus, a 58-year-old patient with CSU for 4 months had severe acute disease [7]. He was prescribed fexofenadine and vitamin D<sub>3</sub> at a dosage of 400 IU per day, with a baseline plasma vitamin D level of 4.7 ng/ml. 2 months later CSU symptoms persisted, and therefore the dosage was increased up to 2000 IU per day. At the end of the 4<sup>th</sup> month of treatment, the vitamin D level was increased to 65 ng/ml, and the symptoms of CSU during this time did not appear anymore.

In addition to this clinical case, a similar effect was demonstrated in a study of 42 patients with CSU, who were randomized into 2 groups, where in the first group vitamin D administrated at 4000 IU per day, and in the second group it was administrated at 600 IU per day [8]. The duration of treatment in both groups was 12 weeks, and the baseline therapy in both groups consisted of cetirizine, ranitidine and montelukast. The efficacy of that treatment was evaluated by the 12<sup>th</sup> week using the USS scale. It was found, within the first week of the therapy, that both groups of patients showed an improvement of 33% on the USS scale, and by the 12<sup>th</sup> week there was an improvement of another 40% on the USS scale, but only in the first group. These studies indicate benefits and high relevance of combining vitamin D with standard pharmacotherapy for patients with CSU.

Some studies have evaluated the comparative efficacy of vitamin D treatment as monotherapy and in combination with antihistamines and corticosteroids, as well as these drugs, but without vitamin D. Thus, 192 patients with moderate and severe CSU were randomized into three groups, depending on the described scheme of the pharmacotherapy. The assessment of treatment result was carried out on several scales – VAS, 5D-Score [9]. Baseline and post-treatment vitamin D levels were also assessed. Vitamin D<sub>3</sub> was given at 60,000 IU per week for 4 weeks, and the group with combined treatment received additionally hydroxyzine 25 mg/day and deflazacort 6 mg/day for 6 weeks. The same drugs were prescribed in the vitamin D-free group.

As a result of the treatment, vitamin D levels were increased more with vitamin D monotherapy than with combination of antihistamines and corticosteroids. However, clinical efficacy was higher in the group with combined treatment: by the VAS scale the improvement was from 6.7 to 5.2 points in patients with vitamin D monotherapy compared to 6.6 to 1.9 points in patients with combined treatment. And by the 5D-Score scale from 14.5 to 12.06 points vs from 13.9 to 5.0 points, respectively. The researchers noted a greater clinical efficacy of combination vitamin D compared to treatment without it. By VAS it was demonstrated changes from 6.6 to 3.3 points, and by 5D-Score from 13.9 to 8.1 points.

## Vitamin D correction and unresolved issues in patients with CSU

The results of the described studies demonstrate the high importance of assessing of vitamin D biotransformation pathways status in patients with CSU. On one hand, it is important for the influence of some metabolites of vitamin D to immune responses, and on the other hand, it is important for the potency to some drugs which are also metabolized with the cytochrome P450 system.

According to the Russian clinical guidelines [2], the screening studies to identify vitamin D deficiency are only recommended for the patients with bone diseases, age >60 years, obesity (BMI 30 kg/m<sup>2</sup>), pregnancy and breastfeeding, gestational diabetes, minimal time of sun exposure, children and adults with dark skin, chronic kidney disease, liver failure, malabsorption syndromes, granulomatous diseases, taking certain medications (glucocorticosteroids, antiretrovirals, antifungals, anti-epileptic drugs, cholestyramine) [10].

In Russia, colecalciferol (D<sub>3</sub>) is recommended for the treatment of vitamin D deficiency, while colecalciferol (D<sub>3</sub>) and ergocalciferol (D<sub>2</sub>) are recommended for the prevention of vitamin D deficiency. For the treatment of vitamin D deficiency in adults (25(OH)D levels less than 20 ng/ml) it is recommended to use calciferol with a total saturating dose 400,000 IU [11].

The recommended daily dose of vitamin D for prophylaxis depending on patient's age, level of vitamin D deficiency, comorbidity, and pregnancy. For the prevention of vitamin D deficiency, patients between 18 and 50 years old are recommended at least 600–800 IU per day, while for patients over 50 years old, at least 800–1000 IU per day. For the prevention of vitamin D deficiency during pregnancy or lactation, at least 800–1200 IU per day is recommended. To maintain a 25(OH)D level above 30 ng/ml it is recommended 1500–2000 daily [10].

For the patients with CSU, the feasibility of biochemical screening of vitamin D levels requires further data from a large-scale study, including Russia. The correction of vitamin D deficiency in patients with CSU is carried out according to Russian local clinical guidelines.

## Vitamin D metabolism and impact of genetic variability to it

An important role in the metabolism of various forms of vitamin D plays by receptors (VDR), specialized proteins (VDBP), as well as isoenzymes of the P450 system: CYP2R1, CYP27A1 and CYP27B1, catabolic cytochrome P450 CYP24A1, which seriously influence on the metabolism of 25-hydroxyvitamin D<sub>3</sub> [25(OH)D<sub>3</sub>] and 1β, 25(OH)<sub>2</sub>D<sub>3</sub> via side chain hydroxylation [12].

Quite recently, a possible alternative pathway of vitamin D metabolism through the cytochrome P450 system was discovered due to CYP11A [13]. CYP11A1 can hydroxylate the side chain of vitamin D<sub>3</sub> at carbons atoms 17, 20, 22 and 23 to produce at least 10 metabo-

lites – 20(OH) $D_3$ , 20, 23(OH) $_2D_3$ , 20, 22(OH) $_2D_3$ , 17, 20(OH) $_2D_3$  and 17, 20, 23(OH) $_3D_3$ , which are the main active metabolites. However, it is important to consider that CYP11A1 is not associated with the metabolism of the clinically significant 25(OH) $D_3$ . A diagram of the vitamin D metabolism cascade is shown in Figure 1.

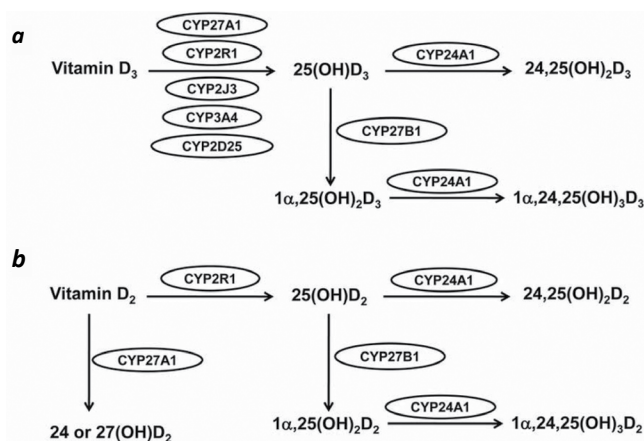


Figure 1. (Vitamin D<sub>3</sub> (a) and D<sub>2</sub> (b) metabolism with the participation of various cytochrome P450 (CYP) enzymes)

Genetic variability can influence on both lengthening and shortening the half-life of vitamin D [14–18]. At the same time, the half-life is not affected by the duration of taking active metabolites of vitamin D.

The following polymorphisms are distinguished: CYP2R1, DHCR7, CYP3A4, CYP27A1, DBP, LRP2, CUB, CYP27B1, CYP24A1, VDR and RXRA. A level of the metabolite 25(OH) is associated with DBP, CYP2R1, and DHCR7 polymorphisms [18].

Two large-scale genomic studies (GWAS) confirmed the association of genetic variants of CYP21R1, 7-DHCR, CYP24A1 and vitamin D-binding protein (GC) genes with the level of 25(OH) D metabolite in the peripheral blood. The results of a meta-analysis demonstrated the relationship of 25(OH)-hydroxyvitamin D levels with loci near genes encoding vitamin-D binding protein (GC), 7-dehydrocholesterol reductase (DHCR7), 25 hydrolase (CYP2R1), and 24-hydrolase (CYP24A1). It is important to note that results of some studies conflicting with each other in loci located near genes encoding the hormonal activation enzyme vitamin D (CYP27B1). That is why the variability in levels of 25(OH)D metabolite is explained by the genetic variability [19].

Since vitamin D is a product of biotransformation by cytochrome P450 system, it is necessary to consider the pathway of vitamin D metabolism, which consists of two isoforms – vitamin D<sub>2</sub> and vitamin D<sub>3</sub>.

Although 25OHD<sub>3</sub> is the main circulating form of vitamin D<sub>3</sub>, it must be further oxidized at position 1 $\alpha$  by CYP27B1 to 1 $\alpha$ , 25-dihydroxyvitamin D<sub>3</sub> (1 $\alpha$ , 25(OH) $_2D_3$ ) to become fully active for influence to gene transcription and cell function.

1 $\alpha$ , 25(OH) $_2D_3$  initiates or suppresses a gene transcription by binding to the vitamin D receptor (VDR). Binding to VDR induces heterodimerization of VDR with the retinoid X receptor (RXR). The heterodimer is then translocated into the nucleus, where the complex binds to the vitamin D response elements and alters gene transcription. In addition to this classical pathway for controlling cell function, several “non-genomic” cell regulation pathways have been proposed involving extra-nuclear 1 $\alpha$ , 25(OH) $_2D_3$ , and multiple growth factors.

CYP3A4 is the most important cytochrome in P450 family of enzymes that metabolize a variety of drugs, which greatly contributes to their clearance and metabolic biotransformation. CYP3A4 is mainly expressed in the liver and small intestine, and several transcription factors regulate its expression. CYP3A4 transcription is induced by 1 $\alpha$ , 25(OH) $_2D_3$  by binding of the VDR-RXR ligand heterodimer to the same proximal ER6 (–169/–152), distal DR3 (–7733/–7719) and DR4 (–7618/–7603), to which the ligand-PXR-RXR complex is attached.

Looking forward it seems relevant to develop some personalized approaches to correcting vitamin D deficiency in patients with CSU, considering the individual characteristics of metabolism. To develop the principles of personalized correction of vitamin D in patients with CSU it is necessary not only to select the optimal dosage regimen of vitamin D, but also to assess the role of genetic variability of individual pathways of vitamin D biotransformation. These pathways may affect in accumulation and further maintenance of vitamin D levels in patients and may influence on local and systemic inflammation in patients with CSU.

A first studies on the role of single-nucleotide polymorphisms of vitamin D receptor and its binding protein in patients with CSU showed that the homozygous AA genotype of VDR rs1544410 was significantly associated with the progression of symptoms in such patients when compared with GA genotype (OR 4.34, 95% CI (1.7331–10.8852)) [20].

However, there is still no clear data about isoenzymes gene polymorphisms role in patients with CSU. This determines the relevance of further research, especially in the Russian population.

Thus, genetic and biochemical studies of the pathways of vitamin D biotransformation in patients with CSU are necessary, both to assess the role of each vitamin D metabolites in the immunological processes underlying pathogenesis of CSU, and to study its impact in potency other drugs that are also metabolized through P450 system.

## Conclusion

Current data indicate a high incidence of vitamin D deficiency in patients with CSU, although the exact mechanisms of this relationship remain unclear.

Correction of vitamin D deficiency in patients with CSU may favorably influence on severity of the disease,

however, large-scale randomized trials are required to obtain evidence how vitamin D effect on symptoms and biomarkers of inflammation in patients with CSU.

In clinical practice, the personalization of treatment schemes for patients with CSU should be based on individual characteristics of biotransformation pathways. In addition, this may improve quality of life of such patients, effectiveness of treatment and optimize its costs.

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