



The Role of Vitamin D in Respiratory Viral Infections and Other Infectious Diseases

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Abstract

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BACKGROUND: Clinical studies and meta-analyses have shown that reduced levels of 25-hydroxyvitamin D in the blood contribute to impaired immunity and stimulate excessive inflammation that adversely affects the health of children: The risk of developing bronchial asthma, obstructive bronchitis, and allergic rhinitis increases.

AIM: The main purpose of this review is to summarize the present literature data on the relationship between Vitamin D, VRI, and other infectious diseases with a clinical example.

MATERIALS AND METHODS: A comprehensive analysis was carried out under Vitamin D in respiratory viral infection and other diseases.

RESULTS: The results of fundamental research allow us to assert that Vitamin D is fundamentally necessary for maintaining the normal physiological functioning of the immune system.

CONCLUSION: Clinical studies and meta-analyses have shown that reduced levels of 25 (OH) E in the blood contribute to impaired immunity and stimulate excessive inflammation, which adversely affects the health of children: The risk of developing bronchial asthma, obstructive bronchitis, and allergic rhinitis increases.

Introduction

At present, there are more than 7,200 publications in the databases of scientific publications on biomedicine (such as PUBMED and ELIBRARY), which present the results of fundamental and clinical studies on the role of Vitamin D in supporting anti-infectious immunity [1], [2], [3], [4]. The results of fundamental research allow us to assert that Vitamin D is fundamentally necessary to maintain the norm of the physiological functioning of the immune system: Activation of antibacterial and antiviral defense, reduction of excessive inflammation, etc. [5]. Vitamin D belongs to the group of fat-soluble vitamins, but due to its characteristics, the active form of the vitamin, or calcitriol, is called the D-hormone. Vitamin D is naturally present in a very limited amount of food and synthesis in the human body is only possible under certain conditions, when the UV rays of sunlight hit the skin. Vitamin D, obtained from food and in the form of dietary supplements, as well as formed by exposure to the sun, is biologically inert; two hydroxylation processes must

occur in the body to activate and convert to D-hormone. Vitamin D plays an important role in many metabolic processes in the human body. In recent years, interest in the extraosseous effects of Vitamin D has increased, since a number of studies have revealed an association of its low values with an increased risk of some extraskeletal pathologies, including certain types of cancer, infections, autoimmune diseases, cardiovascular diseases, mental disorders, and kidney disease. Receptors to active metabolites of Vitamin D are present in most cells and tissues of the body, which also indicates the participation of Vitamin D in the regulation of various biological functions [6].

Vitamin D, obtained from food and in the form of dietary supplements, as well as formed by exposure to the sun, is biologically inert. To activate and convert the hormone (1, 25-hydroxyvitamin D [25 (OH) 2D]) into the active form D, the body must undergo two hydroxylation processes. The first stage of hydroxylation occurs in the liver and converts Vitamin D to 25 (OH) D, also known as calcidiol. The second stage of hydroxylation occurs mainly in the kidneys (with the participation of the enzyme

CYP27B1 - 1 α -hydroxylase), and its result is the synthesis of the physiologically active D-hormone, 1, 25 (OH) 2D [7]. Blood levels of calcitriol are mainly determined by the activity of CYP27B1 in the kidney, under the control of parathyroid hormone, and tightly regulated by negative feedback, which is closed by inhibition of CYP27B1 by high concentrations of calcitriol itself and fibroblast growth factor 23 (FGF23). The limitation of the formation of the active form of the vitamin is facilitated by the stimulation of the enzyme CYP24A1 (24-hydroxylase), which converts calcitriol into an inactive, water-soluble form of calcitric acid, which is subsequently excreted from the body with bile. FGF23, secreted primarily by osteocytes, that is, bone tissue, promotes the activation of 24-hydroxylase in response to high concentrations of Vitamin D hormone and an increase in the concentration of phosphorus in the blood [8], [9], [10].

Serum 25 (OH) D concentration is the best indicator of Vitamin D status, as it reflects the total amount of Vitamin D produced in the skin and obtained from food and nutritional supplements (Vitamin D as a single drug or multivitamin and vitamin-mineral complexes), and has a fairly long half-life in blood - about 15 days [11]. Vitamin D deficiency, as defined by 25 (OH) D levels of <30 ng/ml and <20 ng/ml, is widespread throughout the world.

At present, the deficiency, and to a greater extent the deficiency of 25 (OH) D, is a pandemic, affecting the majority of the general population, including children and adolescents [12]. The Vitamin D receptor is the main mediator of the biological action of Vitamin D. Vitamin D receptors are present in almost all tissues of the human body, which suggests that the functions of all cells are impossible without Vitamin D.

Materials and Methods

There have been many studies that studied not the effect of Vitamin D on phosphorus-calcium metabolism, but extrasosseous processes with the participation of Vitamin D. Today, many processes are associated with the metabolism of Vitamin D. Vitamin D has crossed the boundaries of Ca and phosphate metabolism and has become a factor in providing the most important physiological functions. It can be considered as a steroid hormone with endocrine, paracrine, and autocrine effects.

Vitamin D acts through its membrane receptor, which is found in cells of a wide variety of human organs and tissues, in particular, in most cells of the immune system and epithelial cells lining the mucous membranes. By binding to this receptor, Vitamin D goes into the cytoplasm, where it forms a complex with Vitamin A and its receptor. This complex either inhibits or enhances the transcription of hundreds of genes in nuclear DNA, including those that control cell growth, differentiation, apoptosis, and prevent malignant growth and angiogenesis.

The following effects of Vitamin D on the immune system have been established: It weakens the presentation of antigen by dendritic cells, inhibits Th1 cell differentiation and production of Th1 cytokines, shifts the balance of Th1/Th2 cell responses toward the Th2 response, has an inhibitory effect on Th17 cells, and promotes development of Treg-cells and an increase in their activity. In addition, Vitamin D enhances the production of "endogenous antibiotics" that can have potent effects on Gram-positive and Gram-negative bacteria, fungi, and viruses. It turns out that Vitamin D is very important for the prevention of autoimmune and atopic diseases: Multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes, Crohn's disease, and ulcerative colitis; prevents the development of asthma in children, turns out to be an effective means of preventing and symptomatic treatment of chronic obstructive pulmonary diseases, protects against a wide range of infections, including tuberculosis, leprosy, and respiratory infections; and prevents the development of tumors in a number of organs.

Hypovitaminosis D, often hidden and undiagnosed, is present in almost half of the population of various countries and is one of the leading causes of weakened immunity and increased morbidity. Its identification, prevention, and treatment should be among the most important tasks of public health [13]. The incidence of acute respiratory infections (ARI) in the world is one of the highest [14], [15], [16], [17], [18], [19], [20], [21], [22], [23]. Observational studies indicate a strong correlation between low levels of 25-hydroxycalciferol, the main active metabolite of Vitamin D, and susceptibility to ARI [2], [3], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37]. Vitamin D has many biological effects due to its effect on the Vitamin D receptor, which is present in most body tissues. The possible role of Vitamin D in infections is explained by its influence on the mechanisms of innate and acquired immune responses. An important effect of Vitamin D is also its suppression of inflammatory processes.

Since Vitamin D deficiency belongs to the so-called "seasonal stimulants" of the development of ARVI by many scientists, the possibilities of preventive and therapeutic use of Vitamin D during the ARVI and influenza season are of particular interest.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the ongoing pandemic coronavirus disease 2019 (COVID-19), affects cells in the lower respiratory tract, leading to a cytokine storm in a significant number of patients, resulting in severe pneumonia, shortness of breath, respiratory, and organ failure. Extensive research has shown the role of Vitamin D in suppressing the cytokine storm in COVID-19 and reducing viral infection; however, the exact molecular mechanism is not yet known. In 2020, a study was published that used transcriptome

data and identified 108 differentially expressed host genes (DEHG) in normal human bronchial epithelium cells infected with SARS-CoV-2, compared to controls. DEHGs were then integrated with human protein-protein interactions to create a SARS-CoV-2 (SiHgrn)-induced regulatory host gene network.

An in-depth analysis and study of the literature showed that Vitamin D binds to its receptor and can act in two different ways: (i) It suppresses the expression of pro-inflammatory cytokines by blocking the TNF-induced signaling pathway NFkB1; and (ii) it initiates the expression of genes that stimulate interferon (IFN). This comprehensive study has identified pathways associated with the cytokine storm in SARS-CoV-2 infection. The proposed mechanism underlying Vitamin D may hold promise in suppressing the cytokine storm and inducing a robust antiviral response in patients with severe COVID-19. The findings of this study urgently require further experimental testing of the suitability of Vitamin D in combination with IFN- α to combat severe COVID-19 [5].

According to the WHO website, at the end of November, there are 130 thousand cases. The number of cases is growing every day. The country has had two major waves of morbidity. The first one began on July 1; they began to register cases together with pneumonia, since pneumonia is the main complication of CVI. For July 1, 2020, 18,757 cases were registered. In the city of Nur-Sultan, 15,989 cases have been identified for the entire time. It was detected 11,077 cases in Karaganda region.

Results and Discussion

The main target in the body for SARS-CoV-2 is the lungs. In Kazakhstan, only 14 cases of children with Kawasaki syndrome have been registered. At the moment, the only case of children with Kawasaki syndrome has been registered in the Karaganda region.

Let's take a clinical case as an example

A child M. born in 2010 was admitted to the children's hospital. Complaints on admission from the mother's words: Vomiting, loose stools up to 10 times a day, anxiety, rash on the body, hyperemia of the conjunctiva of the eyes, swelling of the eyelids, redness of the palms, pain in the abdomen, weakness, fever up to febrile numbers, and decreased appetite. The next time a skin rash appeared, then conjunctival hyperemia, and then redness of the palms took: Antibacterial therapy,

rehydron, smecta, activated carbon, paracetamol, ibufen - no effect.

Allergic history

Skin rash with this disease for the 1st time.

On objective examination

BH 22/min, heart rate 100/min, T 37.5C, blood pressure 90/60 mm Hg, and Art. Blood saturation 96%. The condition is closer to severe due to symptoms of intoxication and dyspeptic syndrome. Consciousness is clear. Pale skin, maculopapular rash on the trunk, limbs. The palms are hyperemic. Hyperemia and edema of the eyes, conjunctiva is markedly hyperemic. Anterior cervical lymph nodes are up to 1 cm in diameter, in other groups - up to 0.5 cm. They are painless, mobile. Patients breathe freely through the nose. Pharynx - moderate hyperemia of the mucous membranes, the mucous membrane of the lips is hyperemic, dry. There is no shortness of breath. Heart sounds are loud; the rhythm is correct, tachycardia, short systolic murmur at the apex and at the 5th point, without irradiation. The abdomen is soft on palpation, rumbling along the intestines, painful on palpation, more in the umbilical region. No symptom of peritoneal irritation. Peristalsis is not heard; the anus is closed. The stool is frequent and liquid. Meningeal symptoms are negative.

Laboratory diagnostic tests

ESR - 10 mm/h; complete blood count without pathological changes.

Biochemical blood test

Total protein 57.0 g/l; ALAT - 80.00 IU/l; Vitamin D <10 ng/ml; ACaT - 80.00 IU/l; albumin 33 g/l, urea 18.7 mmol/l, creatinine 243 mmol/l, glucose 5.1 mmol/l, calcium 2.0 mmol/l, potassium 3.9 mmol/l, sodium 128 mmol/l, bilirubin 5.0 mmol/l, thymol test 3.0, alkaline phosphatase 173 IU/l, amylase 39 U/l, CPK 45, cholesterol 2.17 mmol/l, triglycerides 2.33 mmol/l, CRP 407.9 mg/l, rheumatoid factor +, troponin I 4.9 mg/ml, BNP - natriuretic peptide <0.05 ng/ml, and ferritin 368.4 ng/ml. Further, an additional study was carried out: Procalcitonin 17.9 ng/ml, interleukin 842.5 pg/ml, and PCR detection of RNA virus COVID-19 coronavirus COVID-19 - negative.

ELISA IgM to SARS-COV-2 coronavirus Result 0.65, ELISA IgG to SARS-COV-2 coronavirus Result 8.7.

Coagulogram analyzer showed D-dimer 2202.20ng/ml. Blood gases and electrolytes without pathology. General urine analysis have no pathology.

Instrumental research

Ultrasound of the hepatobiliopancreatic region, conclusion: Hepatosplenomegaly. Diffuse changes in the parenchyma of the liver and pancreas. ECG conclusion: Sinus tachycardia. Metabolic disorders in the myocardium. Incomplete right bundle branch block.

X-ray survey of the chest organs (1 projection): X-ray pathology in the lungs was not revealed. Plain X-ray of the abdominal organs conclusion: No pathology was revealed.

Cardiac echo

Bicuspid aortic valve, partially undivided commissure between the right and left coronary cusps, mild aortic regurgitation, dilation of the ascending aorta. Diffuse enlargement of the lumen of the right coronary artery typical for Kawasaki disease, mild hydropericardium. Hypokinesia of the basal lower segment of the left ventricular myocardium; in the study of regional deformity, contractility disorders were not confirmed.

Cardiologist's conclusion

Multisystem inflammatory syndrome (Kawasaki-like syndrome) associated with COVID-19.

As part of this syndrome, acute renal injury can be occurred. Conclusion by a nephrologist was the following: An increase in urea and creatinine are noted the next day after admission to the outpatient clinic. Feature - preserved diuresis. At the moment, in urine tests - no features. BBA - increased transaminases, hyponatremia, normal potassium, creatinine 243 $\mu\text{mol/L}$, and urea 18.7 mmol/L . Ultrasound of the kidneys - the size is increased. Glomerular filtration rate (GFR) according to the Schwartz formula 24.7 ml/min . Diagnosis: Acute renal injury (prerenal), non-oliguric form. GFR 24.7 ml/min - as part of Multisystem Inflammatory Syndrome.

Treatment was performed

Prescribed medications: Antibiotics, antihistamines - Loratal® (10 mg, Tablets * 2 times), Paracetamol (200 mg, Tablets) Rehydron (18.9 g, 4 r/d. 1 d.) Cef III2 r/d 2 days.

Prescribed OARIT medications

IV kiovig 2 g/kg - 80 g in 24 h 08.19-20.08.2020. IV methylprednisolone 750 mg + 0.9% NaCl solution 200 ml from day 3, followed by oral administration of metiprednisolone at a dose of 1 mg/kg (according to prednisolone) IV cep32g * 2 times a day, by mouth: Acetylsalicylic acid 500 mg * 3 times 2 days after admission, s/c heparin 200 units/kg per day in 4 injections 2 days after admission, 300 units/kg per day in 4 injections from the 3rd day after admission; IV kvamatel 20 mg once a day.

Conclusion

The results of fundamental research allow us to assert that Vitamin D is fundamentally necessary for maintaining the normal physiological functioning of the immune system: Activating antibacterial and antiviral defenses, reducing excessive inflammation, etc. Clinical studies and meta-analyses have shown that reduced levels of 25 (OH) E in the blood contribute to impaired immunity and stimulate excessive inflammation, which adversely affects the health of children: The risk of developing bronchial asthma, obstructive bronchitis, and allergic rhinitis increases.

With COVID-19 in children, complications are given, cytokine and bradykinin storms, when the immune system overreacts to the introduction of the virus. Everything is very individual and depends on immunity. The susceptibility of the organism, the source of infection, transmission factors, and the amount of the virus play a role in the development of multisystem inflammatory syndrome. This is all individual, it is difficult to predict. "Young children" are more seriously ill - decompensation of the body against the background of a viral infection.

For further treatment, he is transferred to the SECMR in Nur-Sultan for biological therapy due to the persistence of inflammatory activity in the blood and changes in echocardiography. It is good that Kawasaki syndrome is rare in children. The available evidence points to the promise of using drugs and Vitamin D supplements for the treatment and prevention of respiratory tract infections, incl. caused by the respiratory syncytial virus RSV and influenza A.

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