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# ASSESSMENT OF VITAMIN D STATUS AND RESPIRATORY DISEASE RISK FACTORS IN CHILDREN

The diversity of the effect of vitamin D on the body is determined by the discovery of vitamin D receptors on a variety of tissues (40 tissues or more) (Wimalawansa S.J., 2018). However, to date, the diversity of the effect of vitamin D on the body in childhood with diabetes mellitus, cardiac pathologies, the effect on immune processes, malignant formations has not been fully investigated. The importance of vitamin D in the formation of the immune system and anti-infective protection in a child is being studied. Indications for diagnosis and correction are being developed, therapeutic and preventive effective doses of vitamin D for children are calculated (Zakharova I.N., 2017). Therefore, the problem of vitamin D deficiency in children with respiratory diseases has determined the purpose of the study to date.To study risk factors, vitamin D availability in children, the effect of hypovitaminosis on the course and severity of respiratory diseases.

Prospective study of patients of the Department of pulmonology of the DGKB No. 2. 75 patients aged from 1 month to 5 years. I (main) group – 50 children with a low content of vitamin D (25-hydroxyvitamin D) in the blood and II group (control) - 25 children with a level of vitamin D (25-hydroxyvitamin D) in the blood within the normal range.

In the study of vitamin D availability in children with respiratory pathology in 40% of children under the age of 1 year of the main group, vitamin D was determined at a deficiency level of 15.63±1.71 ng/ml. In breastfed children without additional vitamin D supplementation, 40% of children were deficient. In the patients of the main group, 40% of mothers suffered from chronic diseases of the gastrointestinal tract. In the control group, only 8% of mothers were found to have morbidity.

**Key words**: children, pneumonia, bronchitis, vitamin D, risk factors.

## Introduction

It has been shown over the past decade that a sufficient amount of vitamin D maintains healthy bones and muscles, and is also important for various diseases prevention [1, 2].

According to the large-scale researches conducted in the Russian Federation, RODNICHOK-1 and RODNICHOK-2 34% and 42% of the surveyed young children, respectively, were deficient in the vitamin D supply, with 18% that were deficient badly, and only 34% children under study had normal levels of vitamin D [3].

It has been proven that the physiological effects of vitamin D are divided in two types, genomic and non-genomic. The genomic type is an effect on a genome (mitosis, DNA repair, chromosome rearrangement), an impact upon polypeptide chain biosynthesis, immunity, embryo formation and development, and upon metabolism. The non-genomic type of vitamin D effects is identified by its impact onVD-binding proteins. 1,25(OH)2D3 has important immunomodulatory effects, namely strengthening of innate immune system and inhibition of adaptive immune responses related to increased synthesis of interleukin IL-4 by T-helper-2 lymphocytes and upregulation of regulatory T lymphocytes.

In fact, different types of immune cells (dendritic cells, macrophages, T- and B-lymphocytes) express VDR, and most of them are able to synthesise calcitriol through an independent regulatory pathway, reacting to a range of pro-inflammatory agents, such as bacterial lipopolysaccharides and tumour necrosis factor alpha [4,5].

This variety of biological effects demostrates the potential to prevent and treat various child- hood diseases. So far, the discovery of calcitriol receptors on the cells of the human immune sys- tem and the ability of mononuclear phagocytes to generate 1,25 (OH)2 D3 has been a great con- tribution to the study of the effects of vitamin Don immunity [6]. For long, vitamin D has been considered to be essential for stimulating mono- cyte differentiation, activating phagocytosis in macrophages and increasing the production of antimicrobial peptides. But later it was proven that the interconnected activity of the other cells was also related to vitamin D; the immunomodu- latory effects were identified, which normalised the Th1/Th2 ratio in healthy newborn infants [6]. It has also been found that vitamin D supplemen- tation in babies in their first year of life increases cellular immunity options. However, the vitaminD levels impact on the seve- rity of respiratory disease remains underesearched. Gombart A.F., Borregaard N., Koeffler H.P. (2005) conclud-ed that the group of children with low levels of 25(OH) D had more frequent ve- nipuncture, ven- tilator use and antibiotic therapy than the group with higher vitamin D levels [7]. Patients with vitamin D levels lower than 30 ng/ml were more vulnerable to severe illnesses caused by respi- ratory infections, and had an increased need in reducing hypoxemia [8,9,10,11].

Currently, there are recommendations from various countries for a prophylactic dose of vi- tamin D in children: 1000 IU/day, with 1500 IU recommended especially to children from one to three years of age, while the dose of 1000 IU/day is recommended to 1-6 months infants from the Euro- pean North, while 1500 IU is a recommendation to those from 6 months to 18 years old [12,13].

Thus, nowadays there is a growing interest in the diverse functions of vitamin D, particularly in its positive effect on anti-infective immunity thanks to the activation of antimicrobial peptides.

The purpose of study is to research the risk fac- tors, vitamin D status in children and the hypovita- minosis impact on the course and severity of respi- ratory diseases[14].

The present study was approved (Minutes № 8 of December 5, 2019) at a meeting of the Local Eth- ical Committee of JSC «Kazakh Medical University of Continuing Education».

**Materials and Methods**

A prospective analysis were carried out during the study. The children were included in the study by the criteria of being the pulmonology department patients in Children’s City Clinical Hospital #2 regardless of gen- der. The study exclusion criteria were as follows: intake of vitamin D in any form during the last six months be- fore the study as well as genetic syndromes, mental de- velopment disorders, active rickets, hepatic and/or renal dysfunction, intrauterine development delay, malnutri- tion of grade 2-3, and malabsorption syndrome.

The study was conducted in two phases. The first phase involved a retrospective analysis of the patient records, and the second phase was a pro- spective study of the patients in the pulmonology department of CCCH#2. In a prospective study, 75 patients between 1 month and 5 years of age were selected according to the inclusion and exclusion criteria (Table 1). The patients were split in groups, where Group I (main group) was of 50 children with low blood levels of vitamin D (25-hydroxyvitamin D) whereas Group II (control group) had 25 children with blood levels of vitamin D (25-hydroxyvitamin D) within normal limits.

**Table 1 –** Age distribution of children included in the study

| Age group | Number of surveyed children | | | |
|---|---|---|---|---|
| | Main group | | Control group | |
| | abs. | % | abs | % |
| 1-12 months | 20 | 40 | 10 | 40 |
| 1-3 years | 18 | 36 | 8 | 32 |
| 3-5 years | 12 | 24 | 7 | 28 |
| Total | 50 | 100 | 25 | 100 |

As is shown in Table 1, 76% of children in the main group and 72% of children in the control group were under 3 years of age, being the most vulnerable group for respiratory disease.

The ratio of boys to girls in the main group was 24 (48%) and 26 (52%) respectively. There were 11 (44%) boys and 14 (56%) girls in the control group. The informed consent form to participate voluntarily in the study was obtained from the guardians/legal representatives of the surveyed children.

The 25(OH) D in the blood was found in order to study the blood levels of vitamin D in the children. Blood samples for vitamin D were taken once in 75 patients (of both main and control groups).

We examined vitamin D status in children with respiratory disease (table 2).

**Table 2 –** Nosological forms of children in the main and control groups

| Nosological form | Value | Surveyed group | |
|---|---|---|---|
| | | Main | Control |
| Acute bronchitis | abs. number | 9 | 11 |
| | % | 18,0% | 44,0% |
| Acute obstructive bronchitis | abs. number | 13 | 6 |
| | % | 26,0% | 24,0% |
| Acute tracheitis | abs. number | 1 | 1 |
| | % | 2,0% | 4,0% |
| Acute bronchiolitis | abs. number | 1 | 0 |
| | % | 2,0% | 0,0% |
| Unilateral focal pneumonia | abs. number | 12 | 5 |
| | % | 24,0% | 20,0% |
| Unilateral focal-drainage pneumonia | abs. number | 5 | 0 |
| | % | 10,0% | 0,0% |
| Bilateral focal pneumonia | abs. number | 5 | 2 |
| | % | 10,0% | 8,0% |
| Bilateral focal-sprain pneumonia | abs. number | 2 | 0 |
| | % | 4,0% | 0,0% |
| Destructive pneumonia | abs. number | 2 | 0 |
| | % | 4,0% | 0,0% |

Children in the main group were found to have more severe forms of respiratory pathology. Thus, in the main group the destructive pneumonia made 4%, while in the control group no such cases were registered. Focal pneumonias were more frequently diagnosed in the main group, whereas no such forms of pneumonia were detected in the control group (with normal vitamin D content). No cases of acute bronchiolitis were detected in this group either, while in the main group patients with acute bronchiolitis accounted for 2%. Focal pneumonias were more common in the main group: bilateral 10%, unilateral 24%. Focal pneumonias in the control group were detected in 8% and 20%, respectively, and all the cases were uncomplicated.

After identifying the vitamin D level, cholecalciferol preparations were prescribed to the patients with low vitamin D level (the main group). The dosing of vitamin D preparations for the low blood levels correctoion was carried out according to the National Programme «Vitamin D insufficiency in children and adolescents in the Russian Federation: current approaches to correction».

The children with vitamin D blood levels lower than 10 ng/ml were given 4000 IU/day, those with less vitamin D than 10-20 ng/ml got 3000 IU/day, and the ones with 20-30 ng/ml had 2000 IU a day [14]. In a second step, a blood test was performed a month later in the main group, and the efficacy of the selected dose of vitamin D was assessed.

The statistical data were processed using the Microsoft Excel 2010 and IBM SPSS Statistics. The Mann-Whitney test was used to determine the reliability of differences. The data were plotted as error of arithmetic mean (±). Pearson's $\chi^2$ test was also used to analyse the trait prevalence within the groups.

The Shapiro-Wilk's test for small samples was used to identify a normality of the distribu- tion.

## Results and Discussion

We examined an average vitamin D levels in the blood in different age groups of children (table 3).

**Table 3** – Average vitamin D levels in the blood in different age groups

| | Age group | | | | | |
|---|---|---|---|---|---|---|
| | 0-1 year | | 1-3 years | | 3-5 years | |
| Average value of calcidiol, (ng/ml) Group I, n=50 | 15,63±1,71 | | 20,17±1,42 | | 20,93±1,39 | |
| | n=20 | 40% | n=18 | 36% | n=12 | 24% |
| Average value of calcidiol, (ng/ml) Group II, n=25 | 40,79±3,105 | | 40,12±2,16 | | 43±2,45 | |
| | n=10 | 40% | n=8 | 32% | n=7 | 28% |

Table 3 shows that 40% of patients (n=20), children under 1 year of age in the main group had vitamin D deficiency (15.63±1.71 ng/ml). In children aged 1-3 years, vitamin D level was (20.17±1.42 ng/ml), and those aged 3-5 years (n=12) had 20.93±1.39 ng/ml. In the control group, vitamin D levels were within the normal limits.

We studied the vitamin D status in the breastfed and formula-fed infants considering the vitamin D fortification of infant formula.

In 60% of breastfed infants without a vitamin D supplementation, the average vitamin D blood level was 11.5 ng/ml, which is deficient (n=12). Sixty per cent of artificially fed children had a vitamin D value of 25 ng/ml (deficiency). However, this is not the normal level. A similar difference between the breastfed and formula-fed groups was observed in the other age subgroups. The mean vitamin D blood levels in the breastfed and formula-fed children aged 1-3 years were 12.62ng/ml and 22.49 ng/ml, respectively whereas in those of 3-5 years it was 14.9 ng/ml for the breast- fed and 23.30 ng/ml for the formula-fed patients. These data lead to the conclusion that the type of feeding among the surveyed children had an ef-fect on vitamin D supply. The formula fed patients got a prophylactic dose with their formula, never- theless there were also no children with normal blood levels of vitamin D, indicating the need for additional supplementation with cholecalciferolpreparations.

A maternal morbidity was analysed to examine the factors influencing vitamin D availability in the children with respiratory pathology (figure 1).

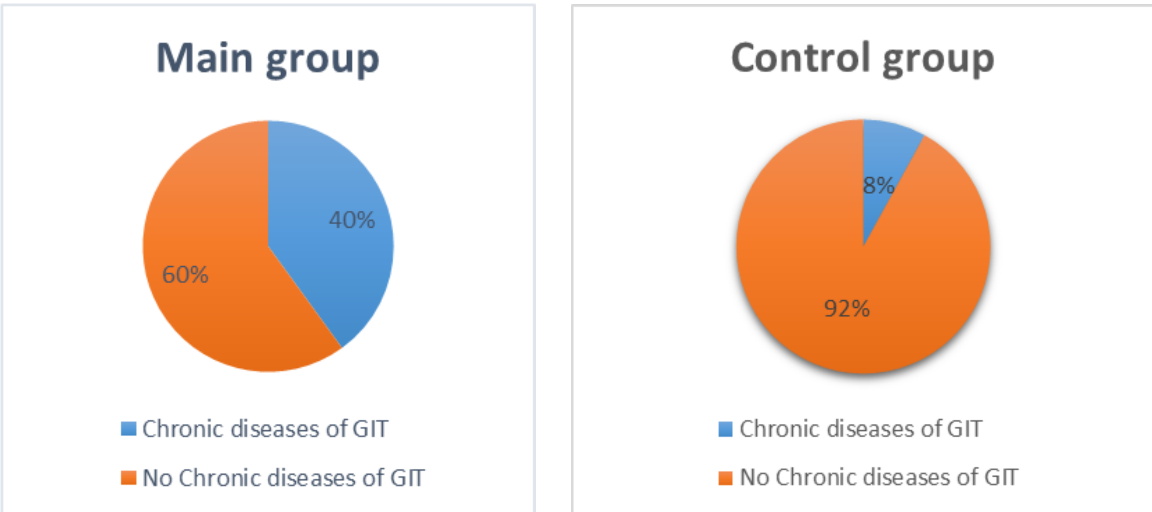


**Figure 1** – Chronic diseases of gastrointestinal tract/GIT in the patients' mothers

The mothers in the main group had a higher incidence of chronic gastrointestinal disease (40%). In the control group, only 8% of mothers were found to have the disease.

We focused on the months of birth of children in the main and control groups in order to identify the dependence of vitamin D supply on the season of birth (table 4).

**Table 4** – Months of birth of the children in the main and control groups

| Month of birth | I group (main) | | II group (control) | |
|---|---|---|---|---|
| | abs. | % | abs. | % |
| December | 4 | 8 | 4 | 16 |
| January | 5 | 10 | 2 | 8 |
| February | 1 | 10 | 0 | 0 |
| March | 3 | 6 | 3 | 12 |
| April | 9 | 18 | 2 | 8 |
| May | 8 | 16 | 0 | 0 |
| June | 6 | 12 | 2 | 8 |
| July | 3 | 6 | 2 | 8 |
| August | 2 | 4 | 2 | 8 |
| September | 3 | 6 | 1 | 4 |
| October | 3 | 6 | 3 | 12 |
| November | 4 | 8 | 4 | 16 |

40% of children born in spring and 28% of those born in winter have low vitamin D levels. This might indicate the effect of the sunshine duration during the last trimester of pregnancy on the vitamin D status of a child. In other words, patients born in spring and winter are more likely to have low vitamin D levels.

The next stage of our research was to analyse the effect of sunlight on children's vitamin D supply. The patients under study were permanent resi- dents of Almaty. Information about the insolation in Almaty was taken from the official website . According to these official data, the average duration of sunshine in Almaty is 2392 hours per year (99.7 days per year), which is higher than the same exponent in European countries.

The City of Almaty is known to be located at 43.2567 north latitude and 76.9286 east longitude, 787 metres above sea level, in a low insolation zone.

The highest number of sunny days in Almaty is recorded in June, August and July. The least number of sunny days is recorded in February, January, March according to the data.

The city insolation importance is quite low given the low blood levels of vitamin D in the surveyed patients. Consequently, the main source of vitamin D is the dietary intake route.

The statistical accuracy of differences be- tween the main and control groups was found bythe U-Mann-Whitney test for independent samples, according to which the null hypothesis of equal categories of observation groups was re- jected.

We see evidence of a high level of accuracy in the differences between the groups at p=0.05.

Table 5 shows the mean vitamin D levels in the main and control groups.

**Table 5 –** Mean vitamin D levels in the main and control groups.

| Surveyed group | abs.n | % | Mean vitamin D blood levels |
|---|---|---|---|
| Main group | 50 | 66,67 | 18,54±0,97 |
| Control group | 25 | 33,33 | 41,43±1,56 |

The mean value of vitamin D in blood was fixed in the main group at a deficiency level of 18.54 ng/ml, while in the control group it was 41.43 ng/ml.

The ranking of vitamin D status in different nosological forms is shown in Table 6.

**Table 6 –** Vitamin D levels in the children with different nosological forms

| Diagnoses | Main group | | | Control group |
|---|---|---|---|---|
| | under 10 ng/ml | 10-20 ng/ml | 20-30 ng/ml | over 30 ng/ml |
| Acute bronchitis | n=1(2%) | n=2(4%) | n=6 (12%) | n=11 (44%) |
| Acute obstructive bronchitis DN of 0-I stages | - | - | n=5 (10%) | n=6(12%) |
| Acute obstructive bronchitis DN of II-III stages | n=4 (8%) | n=4 (8%) | - | - |
| Acute bronchiolitis | - | n=1(2%) | - | - |
| Tracheitis | - | - | n=1(2%) | n=1(2%) |
| Unilateral focal pneumonia | n=3 (6%) | n=3 (6%) | n=6 (12%) | n=5 (10%) |
| Unilateral focal-drainage pneumonia | - | n=1(2%) | n=4 (8%) | - |
| Bilateral focal pneumonia | n=2 (4%) | n=2 (4%) | n=1(2%) | n=2(4%) |
| Bilateral focal-sprain pneumonia | - | n=1(2%) | n=1(2%) | - |
| Destructive pneumonia | n=1 (2%) | - | n=1 (2%) | - |

The data in Table 6 indicate low vitamin D availability among patients with more severe nosological forms of respiratory pathology.

Vitamin D levels after correction with cholecalciferol are shown in table 7.

**Table 7 –** 25(OH)D levels in children after vitamin D correction

| Index 25(OH)D | Before correction | | After correction | |
|---|---|---|---|---|
| | abs. | % | abs. | % |
| under 10 ng/ml | 11 | 22 | 0 | 0 |
| 10-20 ng/ml | 13 | 26 | 3 | 6 |
| 20-30 ng/ml | 26 | 52 | 33 | 66 |
| over 30 ng/ml | 0 | 0 | 14 | 28 |
| Total | 50 | 100 | 50 | 100 |

Table 7 shows the results between cholecalciferol and 25(OH)D gain after one month of vitamin D supplementation in 50 children in the main group. The baseline 25(OH)D level in the main group children was up to 10 ng/ml in 22% of children, 10-20 ng/ml in 26% of children and 20-30 ng/ml in 52% of children.

In this group of children cholecalciferol was administered according to the following scheme: with 25(OH)D level less than 10 ng/ml - 4000 IU/day; 25(OH)D level 10-20 ng/ml - 3000 IU/day; 25(OH) D level 20-30 ng/ml - 2000 IU/day for a month. After the therapy, normal vitamin D levels were found in 28% of children, 66% showed an increase in 25(OH)D levels from 10-20 ng/ml to more than 20 ng/ml, and no patient had a deficiency.

It is obvious that this simple dosing scheme can make the task of correcting vitamin D deficiency in children much easier for public health practitioners.

## Conclusion

In a study of vitamin D status in children with respiratory pathology, 40% of children under 1 year of age in the main group showed a vitaminD deficiency of 15.63±1.71 ng/ml. A deficiency was observed in 40% of the breastfed children without additional vitamin D supplementation. One month therapy with cholecalciferol prepara- tions was accompanied by normalization of vita- min D level in 28% of children, in 66% there wasan increase in 25(OH)D level from 10-20 ng/mlto more than 20 ng/ml, and deficiency was not observed in any patient. Drug treatment of vita-min D deficiency and insufficiency will signifi- cantly reduce the incidence of hypovitaminosis and vitamin D-dependent conditions, as well as the frequency and severity of respiratory diseas-es in children.

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