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The Content Of Vitamin D Metabolites In Rachit In Children Of Early Age Who Received Specific Prevention

Rasuljon Mamasiddikovich Shermatov
Candidate Of Medical Sciences, Head Of The Department Of Pediatrics, Fergana Medical Institute Of Public Health, Uzbekistan

Zebo Xamroevna Nishanova
Assistant Of The Department Of "Pediatrics" Of The Fergana Medical Institute Of Public Health, Uzbekistan

Mavlonjon Ziemiddinovich Nasirdinov
Assistant Of The Department Of "Normal And Pathological Physiology" Of The Fergana Medical Institute Of Public Health, Uzbekistan

Shoxrux Ravshanjon Ogli Xabibullayev
Assistant Of The Department Of "Normal And Pathological Physiology" Of The Fergana Medical Institute Of Public Health, Uzbekistan

Sardorbek Solijon Ugli Bobojonov
Assistant Of The Department Of "Normal And Pathological Physiology" Of The Fergana Medical Institute Of Public Health, Uzbekistan

ABSTRACT

52 patients with rickets and 10 healthy children were examined. Among patients with rickets, 35 children were born in women with a complicated course of pregnancy (threat of termination, toxicosis of the first and second half). In 12 children, mothers had chronic liver and kidney diseases before giving birth.

The level of 25(OH) vitamin D (25-oxycalciferol) and 24.25 (OH)2 vitamin D (24.25-dioxycalciferol) was determined. The content of calcium-regulating hormones in the blood serum was determined by radioimmunological analysis. To assess the severity of the rickets process, the activity of alkaline phosphatase in the blood serum was determined using a standard kit.

The aim of our study was to determine the effect of specific prevention on the metabolism and course of the clinical form of rickets in young children.

KEYWORDS

Rickets, vitamin D, vitamin D metabolism, specific prevention of rickets, parathyroid hormone, calcitonin, young children.

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INTRODUCTION

In recent years, much attention has been paid to the role of vitamin D in the body. Vitamin D deficiency is proven through a number of mechanisms to cause inflammation, cancer, and cardiovascular disease. A 2014 meta-analysis from the University of California (USA) [21], as well as a 2017 study from the University of Athens (Greece) [22], showed that low vitamin D levels are associated with the risk of colon and breast cancer, metabolic syndrome, type 2 and type 1 diabetes, and other autoimmune diseases.

Clinical observations indicate that some children, despite specific prevention, develop symptoms of rickets [1, 2, 3]. In this regard, it is of practical interest to clarify the causes of the disease.

The objectives of these studies were to study the content of the three main active forms of vitamin D and calcium-regulating hormones in the blood of children who received vitamin D for preventive purposes. Taking into account seasonal fluctuations in the level of active vitamin D metabolites in the body [4, 5, 6], the examination of children was carried out in the winter-spring period.

In recent years, new scientific data on the metabolism of vitamin D has led to a change in views of it as a common vitamin. Currently, it is customary to talk about a complete vitamin-D-endocrine system that provides not only the regulation of phosphorus-calcium metabolism, but also supports the functioning of many organs and systems. Receptors for calcitriol, a hormone-active form of vitamin D, are found in at least 36 different tissues of the body. In striated and smooth muscle fibers, cardiomyocytes, keratinocytes, skin fibroblasts, chondrocytes, the action of the hormone, mediated by these receptors, is aimed at regulating the processes of cell growth and differentiation. By acting on the beta-cells of the pancreas, calcitriol stimulates synthesis and secretion: by binding to receptors on the medullary cells of the adrenal glands, it regulates the synthesis of catecholamines. The presence of specific vitamin D receptors in the organs of the male and female reproductive systems (vas deferens, endo and myometrial cells) provides antiproliferative action, regulation of follicular and spermatogenesis [7,9,21]. There is evidence of the neuroprotective effect of vitamin D [8,10,11], due to the ability of 1,25-dihydroxycholecalciferol to reduce the level of ionized calcium in the brain due to the formation of calcium-binding proteins, as well as by inhibiting the expression of calcium channels in the hippocampus. Much attention is currently being paid to the immunomodulatory and anti-inflammatory effects of calcitriol. The discovery of calcitriol receptors on many cells of the immune system, as well as the ability of mononuclear phagocytes to produce 1,25(OH)2D3, was evidence of the involvement of vitamin D in the functioning of the immune system [13,18,22].

The implementation of all the above effects of cholecalciferol is possible only in conditions of adequate functioning of the vitamin-D-endocrine system. The ability of this system to produce the hormone-active metabolite calcitriol depends on the content of 25(OH)D3 in the body. The activity of α1-hydroxylase, like any other enzyme, depends on the initial concentration of its substrate. In the study of Schwalfenberg G. K. [17], it was shown that in order to achieve half of the normal activity of α1–hydroxylase, the level of 25(OH)D3 in the blood serum should be about 100 nmol/l (40 ng/ml). The level of 25-hydroxycholecalcerol depends in turn on the amount of vitamin D entering the body. Thus, the study of the D-

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vitamin status of the body is fundamentally important in order to optimize the positive effect of cholecalciferol on the body as a whole [20, 21, 22]. Previously, a number of scientific studies have established the content of the main metabolites of vitamin D in the blood serum of healthy people [6, 12]. Most researchers recognize that the most informative indicator of the body's vitamin D supply is the level of 25 (OH)D3. This metabolite is synthesized in the liver, and its synthesis is not subject to such strict regulation as the formation of calcitriol. The level of 25-hydroxycholecalciferol is a total reflection of the endogenous formation of cholecalciferol in the skin and its intake as part of food or vitamin preparations [14,16,17,20].

In the course of numerous studies of the state of calcium homeostasis, concentrations of 25(OH)D3 were determined, corresponding to sufficient content, cholecalciferol deficiency and hypovitaminosis D [12, 16].

The question of the standards of 25 (OH)D3 in blood serum remains debatable to this day. At the same time, there is no doubt that the "normal" level can be considered 25(OH)D3, which provides the effect of cholecalciferol in all organs containing specific receptors for its hormone-active form 1,25(OH)2 D3 [19].

The main etiological factor in the development of infant rickets is considered to be a deficiency of vitamin D due to its inadequate intake in the body with food or insufficient synthesis in the skin under the influence of sunlight. In the classical variant, rickets is characterized by a decrease in 25 (OH)D3 up to its absence [3,5,7]. However, recently, there is evidence that the clinical manifestations of rickets in children of early age is not always correlate with the content of vitamin D in the body, and in some cases, the disease develops and the normal level of 25-hydroxycholecalciferol [15.21].

The aim of our study was to determine the impact of specific prevention for metabolism and for clinical forms of rickets in children of early age.

MATERIALS AND METHODS

The level of 25(OH) vitamin D (25-oxycalciferol) and 24.25 (OH)2 vitamin D (24.25-dioxycalciferol) was determined [7]. The content of calcium-regulating hormones in the blood serum was determined by radioimmunological analysis. To assess the severity of the rickets process, the activity of alkaline phosphatase in the blood serum was determined using a standard kit.

52 patients with rickets and 10 healthy children were examined. Among patients with rickets, 35 children were born in women with a complicated course of pregnancy (threat of termination, toxicosis of the first and second half). In 12 children, mothers had chronic liver and kidney diseases before giving birth. The course of pregnancy in the other women was physiological. In 32% of women with extragenital pathology and complicated pregnancy, non-specific symptoms of calcium deficiency were observed in the form of paresthesia, convulsive muscle movements, and exacerbation of dental caries. This could be a manifestation of developing vitamin D deficiency and calcium – phosphorus metabolism disorders in the last months of pregnancy.

All children were born full-term, were naturally or rationally displaced feeding with the use of complementary foods. The contingent of the examined children was taken under observation at the age of 6 to 12 months.

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18 of 52 patients with rickets from the 2nd month of life received vitamin D preparations (AquaDetrim) by fractional doses (500 IU per day). The rest of the children were given vitamin D for prophylactic purposes by a compacted method of 12,000 IU per day at the 2nd month of life for 3-4 weeks.

RESULTS AND THEIR DISCUSSIONS

Clinical observations showed that in children with rickets of the second degree of severity and who received specific prevention by daily intake of physiological doses of vitamin D at 500 IU per day, the first symptoms of the disease developed at 4-5 months of life, were not pronounced and were mainly manifested by gradually developing minor bone deformities, which in some children were combined with muscle hypotension. All this did not focus the attention of parents and the doctor on the initial signs of the disease and delayed the timing of complex therapy. In children who received prevention of rickets by prescribing vitamin D by the compacted method, as a rule, the signs of the disease appeared at 6-7 months of life and were more distinct in contrast to children who were prescribed vitamin D continuously by the fractional method. Thus, bone deformities were manifested by hypertrophy of the osteoid tissue ("beads", "bracelets", parietal, frontal tubercles, etc.), muscle hypotension, weakness of the ligamentous apparatus were noted, in 11 children a moderate increase in parenchymal organs was revealed (the liver protruded from under the costal arch by 1.5-2.0 cm, the spleen was palpated in the left hypochondrium, protruding from under the costal arch by 1-1. 5 cm).

When determining the activity of alkaline phosphatase in the blood serum, we noted its moderate increase to 260-320 U/l (the norm is 180-200 U / l), which confirmed the severity of the rickets process and the height of the disease.

The results of the study of active metabolites of vitamin D in the blood of the observed children are shown in the table. According to our observations, the development of rickets in children, despite the specific prevention, in most cases can be explained by a different degree of severity of vitamin D deficiency in the body, as evidenced by a significant decrease in their serum content of 25-oxycalciferol – the main transport form of vitamin D – compared with the indicators in healthy people. At the same time, the lowest concentrations of this metabolite were observed in children who developed rickets 4 months after the end of the course of specific prevention.

When prescribing vitamin D for the prevention of rickets in fractional doses, the content of 25-oxycalciferol in children's blood was less different from that in healthy people. However, they had a pronounced decrease, about 3 times, in the content of dioxicalciferols -1.25 (OH) 2 and 24.25 (OH)2 of vitamin D. A slightly different pattern of changes in the level of these metabolites in the blood was revealed in rickets patients who received vitamin D prophylactically by the compacted method: along with a noticeable decrease in the content of 24,25-dioxicalciferol in the blood serum, fairly high levels of 1,25-dioxyvitamin D were observed, almost approaching those in healthy children. This may be due to the switching of the synthesis of metabolically active forms of vitamin D in the kidneys mainly to the formation of 1,25-dioxicalciferol as a metabolite of "emergency" action, aimed at maintaining the constancy of calcium metabolism in the conditions of the development of the disease and a decrease in the level of calcium in the blood serum.

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Our studies to determine the content of active forms of vitamin D in children with rickets indicate that low levels of 25-oxycalciferol do not limit the increased formation of the hormonal form of vitamin D [1,25 (OH)2 D].

It should be noted that the levels of 25-oxycalciferol detected by us in children with rickets, which developed despite specific prevention, are not as low as some authors note [8,9]. According to their data, vitamin D deficiency in rickets can be discussed in cases where the content of 25-oxycalciferol in the blood of patients is on average 10-15 ng / ml or less. However, this information can not be universally accepted as criteria for assessing the low vitamin D availability of the child's body, since the studies were conducted on a contingent of children living in a geographical region with a low level of ultraviolet radiation.

Table

The content of active metabolites of vitamin D, parathyroid hormone and calcitonin in rickets, taking into account specific prevention (M+m)

Group of children	25 OH-vitamin D, ng / ml	1,25 $(OH)_2$ vitamin D, ng / ml	24,25 $(OH)_2$ vitamin D, ng / ml	Parathyroid hormone, ng / ml	Calcitonin, ng / ml
Healthy	45,2±2,40	68,4±4,50	6,0±0,68	231,2±28,50	66,7±4,50
Rickets patients II degree of severity (subacute course) in the peak period: treated with fractional doses	34,8±1,40*	27,6±1,68*	1,69±0,08*	920, ±32,60*	42,4±4,40*
Treatment with the compacted method	24,2±1,20*,**	75,2±4,08**	1,38±0,03*,**	1246±46,0*,**	15,9±1,60*,**
Tested at 3 months after the end of vitamin D intake	21,5±1,11*,**	52,2±2,67*,**	1,5±0,05*	1385±48,3*,**	20,2±2,41*,**
Studied 5 months after the end of the course of specific prevention	11,2±0,88*,**,***	67,7±4,80**,***	0,8±0,05*,**,***	1208±32,4*,**	11,4±1,55*,**,***

Note. * - the differences are significant in relation to the indicators of healthy children, * * - in relation to the indicators of patients who received specific prophylaxis by the fractional dose method, * * * - in relation to the end dates of vitamin D intake by the compacted method.

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All the children we observed with rickets had a marked decrease in the concentration of 24,25-dioxycholecalciferol in the blood; its indicators were especially low when the disease developed 4 months after the end of the course of specific prevention. It is characteristic that low levels of 25-oxyvitamin D in the blood correspond to a reduced amount of 24,25-dioxicalciferol. Since the main physiological effect of the latter metabolite is associated with a direct effect on the processes of bone formation, the increase in the content of 1,25-dioxyvitamin D and a decrease in the level of 24,25-dioxy vitamins D in the blood serum observed in rickets cause the presence of complex pathological processes in the bone tissue – osteomalacia, osteoporosis, hyperproduction of osteoid tissue.

Analyzing, along with the content of active metabolites in the blood, the indicators of calcium-regulating hormones, it can be noted that in children with rickets, there is a regular increase in the functional activity of the parathyroid glands and inhibition of the formation of calcitonin by thyroid C-cells. Less pronounced changes in the content of parathyroid hormone and calcitonin in the blood were observed in children with rickets and receiving specific prevention by fractional doses, when there is no significant lack of vitamin D in the body.

The development of rickets against the background of specific prevention by the method of fractional doses may be associated with a number of risk factors. Mainly such factors were the burdened antenatal period (chronic extragenital diseases and complicated course of pregnancy in the mother). These conditions are usually accompanied by certain disorders of the metabolism of vitamin D, calcium and phosphorus in the mother-fetus-newborn system, as well as tension in the function of the endocrine glands that produce calcium-regulating hormones. Therefore, it is possible that some of the children in this group had manifestations of early and late hypocalcemia with subsequent activation of the parathyroid glands, which led to the appearance of rickets, despite the preventive administration of vitamin D. The development of rickets in children at risk could also be promoted by non-compliance with the measures of non-specific prevention of the disease, early transition to mixed or artificial feeding, frequent intercurrent diseases.

According to our observations, among children who received specific prevention of rickets by the compacted method, the disease developed under the influence of certain risk factors at the 3rd month or 4 months after the end of vitamin D intake. At the same time, there were quite low concentrations of 25-hydroxy -, 24,25-dioxicalciferols in the blood, which progressively decreased as the time from the end of preventive vitamin D intake increased. In the same children, a more significant increase in the activity of the parathyroid glands and suppression of thyroid C-cells were noted, which may be due not only to an increasing deficiency of vitamin D in the body, but also to the development of hypomagnesemia, often noted in rickets. It is known that magnesium and calcium play an

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important role in the regulation of parathyroid hormone synthesis.

Studies conducted in children with rickets by the end of the 2nd month after the end of preventive vitamin D intake showed that the levels of all vitamin D metabolites and calcium-regulating hormones in them did not statistically differ from those in children who received vitamin D by fractional doses.

CONCLUSIONS

1. The degree of reduction in the level of the main active metobolites of vitamin D in the body of children with rickets depends on the method of specific prevention. The least pronounced clinical manifestations of the disease and vitamin D deficiency in children who received vitamin D for prophylactic purposes by fractional doses. However, this method of prevention is not effective enough in children at risk.
2. The most pronounced deficiency of vitamin D in the body in rickets is noted in cases where children have not received vitamin D for prophylactic purposes for more than 4 months. In this regard, it can be recommended that the duration of the break between courses of specific prevention of rickets by the compacted method does not exceed 3 months.

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