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Содержание витамина D и показатели метаболизма костной ткани у детей-казахов грудного возраста

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АННОТАЦИЯ

Обоснование. Недостаточность и дефицит витамина D регистрируют у значительной части населения. Витамин D наряду с формированием костной ткани включен во все виды обмена и определяет рост организма, развитие иммунитета и нервной системы. Последствия его дефицита могут быть отдаленными и в ряде случаев необратимыми. Проблема дефицита витамина D у детей грудного возраста изучена недостаточно.

Цель исследования — определить содержание витамина D и показатели костного метаболизма у детей-казахов в первый год жизни.

Материалы и методы. Обследованы 250 казахских детей грудного возраста. Определяли содержание витамина D в крови. Состояние костного метаболизма оценивали по концентрациям кальция, фосфора, паратгормона, остеокальцина и кальцитонина в сыворотке крови и дезоксипиридинолина — в моче.

Результаты. Недостаточность/дефицит витамина D отмечены у 77,8 % обследованных детей. Показатели костного метаболизма (концентрации общего кальция, фосфора, паратгормона, остеокальцина) зависели от степени снижения уровня витамина D. Наиболее чувствительным индикатором, реагирующим на изменение уровня витамина D, является остеокальцин. Уровень сывороточного витамина D можно использовать в качестве маркера в доклинической диагностике метаболических нарушений костного гомеостаза у детей.

Заключение. Подтверждено влияние витамина D на метаболические процессы в костной системе. Наиболее чувствительным индикатором, реагирующим на изменение уровня витамина D, является остеокальцин. Исследования в данном направлении могут быть основанием для обсуждения целесообразности субституции витамином D и уточнения схем дородового наблюдения.

Ключевые слова: дети грудного возраста; витамин D; костная ткань; метаболизм.

Как цитировать

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Vitamin D level and indicators of bone tissue metabolism in kazakh infants

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ABSTRACT

BACKGROUND: Insufficiency and deficiency of vitamin D are recorded in a significant part of the population. Vitamin D, along with the formation of bone tissue, is included in all types of metabolism, determining the growth and development of the body, immunity, and the normal development of the nervous system. The consequences of deficiency can be long-term and in some cases irreversible. The problem of deficiency in infants is not well understood.

AIM: To determine the content of vitamin D and indicators of bone metabolism in children of the first year of life of the Kazakh population.

MATERIALS AND METHODS: 250 infants of the Kazakh population were examined. The content of vitamin D in the blood was determined. The state of bone metabolism was assessed by the results of a blood test to determine the serum concentration of calcium, phosphorus, parathyroid hormone, osteocalcin, calcitonin, and in the urine — deoxypyridinoline.

RESULTS: There is a wide prevalence (77.8%) of vitamin D insufficiency/deficiency in children under one year old in the Kazakh population. The greatest decrease in vitamin D was found in newborns. Statistically significant differences were found in the levels of bone metabolism indicators, such as total calcium, phosphorus, calcitonin and osteocalcin in different age groups. Indicators of bone metabolism, such as total calcium, phosphorus, parathyroid hormone, osteocalcin, depend on the degree of decrease in vitamin D levels. The most sensitive indicator that responds to changes in vitamin D levels is osteocalcin. The level of serum vitamin D can be used as a marker for the preclinical diagnosis of metabolic disorders of bone homeostasis in children.

CONCLUSIONS: The study confirms the effect of vitamin D on metabolic processes in the skeletal system. The most sensitive indicator that responds to changes in vitamin D levels is osteocalcin. Research in this direction may be the basis for discussing the feasibility of vitamin D substitution and clarifying prenatal care schemes.

Keywords: infants; vitamin D; bone tissue; metabolism.

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BACKGROUND

Vitamin D insufficiency and deficiency are registered in a significant part of the global population. The high prevalence of vitamin D deficiency also increases the global burden of diseases [1]. Vitamin D, along with the bone tissue formation, is involved in all types of metabolism [2] and determines the body growth, as well as the immunity and the nervous system development [3, 4]. The consequences of vitamin D deficiency can be long-term and in some cases irreversible [5, 6]. The problem of such deficiency in infants is aggravated by the fact that the human nervous system develops in the first year of life. Vitamin D concentrations in newborns and their mothers were determined in few studies [7]. Based on the results of similar studies conducted in different regions, a decrease in vitamin D levels was revealed in pregnant women and their descendants [8]. In the Republic of Kazakhstan, such studies have not been found in the available literature; and they are extremely few in Russia [9]. The lack of extensive research hinders the development of organizational, treatment, and preventive measures.

The study aimed to determine the vitamin D level and bone metabolism indicators in Kazakh children of the first year of life.

MATERIALS AND METHODS

The cross-sectional study included 250 pediatric patients under 1 year of age, born in Aktobe. Sample size was calculated using Epi Info.

Belonging to the Kazakh nationality was established through a questionnaire and verification of data on birth certificates. The work is based on an analysis of the results obtained during a comprehensive clinical and laboratory examination of 250 children (94 (37.6%) boys and 156 (62.4%) girls). Parents or legal representatives of patients included in the study signed informed consent with permission to process personal data for scientific purposes. The pediatric patients were enrolled through random sampling. The work was performed at the clinical sites of West Kazakhstan Medical University.

Inclusion criteria were apparently healthy Kazakh pediatric patients, aged 0 to 12 months, without organic pathology and genetic syndromes, with satisfactory condition at the time of the study, with possibility of sampling blood for examination, availability of informed consent to participate in the study signed by parents or legal representatives.

Exclusion criteria were premature infants, age over 1 year, hereditary diseases of the musculoskeletal system, severe chronic somatic diseases, disability due to other diseases, the fact of taking vitamin D in a therapeutic

dose, refusal of parents or legal representatives to participate in the study.

For this purpose, the blood level of vitamin D was determined. The state of bone metabolism was assessed by the concentrations of calcium, phosphorus, parathyroid hormone (PTH), osteocalcin and calcitonin in the blood serum and deoxypyridinoline in the urine.

Serum calcifediol [25(OH)D] level was determined by immunochemiluminescent method using an Iflash analyzer 2022 (China). The supply of vitamin D was assessed in accordance with the criteria established in the national program "Vitamin D Deficiency in Pediatric Patients and Adolescents of the Russian Federation: Modern Approaches to Correction" of 2018; deficiency was defined as a 25(OH)D concentration of less than 21 ng/ml, insufficiency was established at 21–30 ng/mL, and adequate concentrations were higher than 30–75 ng/mL.

Serum calcium concentration was determined by the colorimetric photometric method on a biochemical automatic analyzer BA 400 (Spain). The concentration of total calcium in pediatric patients under 15 years of age was considered normal within the range of 2.2–2.7 mmol/l. Serum phosphorus concentration was assessed by a colorimetric method using ammonium molybdate on a BA 400 apparatus (Spain). The normal reference values for phosphorus levels in pediatric patients under 12 years of age are 1.45–2.16 mmol/l. The osteocalcin level was determined by immunochromatographic method on a Siemens Immulite 2000 Xpi analyzer (USA). Reference values for osteocalcin are 2.8–41 ng/ml. Serum calcitonin level was assessed by immunochromatographic method using an Immulite 2000 Xpi analyzer (USA). Its normal content is less than 50 ng/l. The concentrations of PTH and deoxypyridinoline were determined using the same analyzer. Reference values were 15–65 pg/ml and 13.7–41.0 nmol/μmol of creatinine, respectively.

Statistical analysis of the study results was performed using the Statistica 10 software package. Descriptive statistics methods were used. The Mann–Whitney *U* test was used for comparative analysis of nonparametric data. Analysis of dependence was performed using Spearman's rank correlation.

Correlation criteria were assessed using the Chaddock scale (Table 1).

Table 1. Chaddock scale [10]

Таблица 1. Шкала Чеддока [10]

Pairwise correlation coefficient	Bond strength
Less than 0.3	Weak
0.3 to 0.5	Moderate
0.5 to 0.7	Evident
0.7 to 0.9	High
More than 0.9	Very high

RESULTS

After a clinical examination, the level of 25(OH)D was determined in all pediatric patients. The children were distributed into three groups depending on the blood serum vitamin D level (Table 2).

Analysis of the Table 2 showed a decrease in vitamin D blood serum levels in 77.8% of pediatric patients. At the same time, insufficiency was detected in 23.8% of cases, and vitamin D deficiency was registered in more than half (54%) of children.

Indicators of mineral metabolism and its regulation depending on the vitamin D level are presented in Table 3.

The study of markers of mineral metabolism depending on the blood serum level of vitamin D (Table 3) showed that the concentrations of calcium, phosphorus, PTH, and calcitonin in all groups were within normal limits. This means that the levels of PTH and calcitonin are balanced. Consequently, calcium-phosphorus metabolism and the integrity of bone tissue are maintained at the proper level in the body.

Since the formation and resorption of bone tissue are independent processes, closely associated in the norm,

Table 2. Distribution of children into groups depending on the concentration of vitamin D in blood serum

Таблица 2. Распределение детей по группам в зависимости от концентрации витамина D в сыворотке крови

Group	Vitamin D concentration	Number of pediatric patients, n (%)
1	30–75 ng/ml (normal)	55 (22.2)
2	21–30 ng/ml (insufficiency)	59 (23.8)
3	Less than 21 ng/ml (deficiency)	134 (54)

Table 3. Indicators of mineral metabolism and its regulation depending on the vitamin D level

Таблица 3. Показатели минерального обмена и его регуляции в зависимости от содержания витамина D

Group	Total calcium, mmol/l				Phosphorus, mmol/l				Calcitonin, pg/ml				Parathyroid hormone, pg/ml			
	M	Me	Q ₁	Q ₃	M	Me	Q ₁	Q ₃	M	Me	Q ₁	Q ₃	M	Me	Q ₁	Q ₃
1	2.46	2.52	2.29	2.64	2.09	2.11	1.87	2.23	3.99	3.18	2.0	4.79	20.56	10.8	4.5	25.2
2	2.5	2.5	2.39	2.6	1.82	1.95	1.52	2.09	6.18	4.64	2.15	8.37	19.66	15.2	6.12	28.4
3	2.36	2.41	2.24	2.52	1.87	1.9	1.54	2.2	5.62	4.55	2.0	6.92	28.39	20.5	8.87	39.3

Note. M — arithmetic mean; Me — median; Q₁ — upper quartile; Q₃ — lower quartile.

Table 4. Average rates of bone remodeling depending on vitamin D content

Таблица 4. Усредненные показатели костного ремоделирования в зависимости от содержания витамина D

Группа	Дезоксипиридинолин, нмоль/ммоль креатинина				Остеокальцин, нг/мл			
	M	Me	Q ₁	Q ₃	M	Me	Q ₁	Q ₃
1	26.05	24.0	18.0	34.5	7.6	3.9	2.0	10.3
2	30.32	32.0	22.0	40.0	5.49	2.97	2.0	6.67
3	25.17	20.0	14.0	33.2	3.97	2.0	2.0	3.02

Note. M — arithmetic mean; Me — median; Q₁ — upper quartile; Q₃ — lower quartile.

and their relationship maintains the biochemical stability of the skeleton, indicators of the bone tissue remodeling were determined (Table 4).

All indicators were distributed within reference values. At the same time, the average values of osteocalcin, as a marker of bone tissue formation, with normal vitamin D levels were 7.6 ng/ml, 5.49 ng/ml with vitamin D insufficiency, and 3.97 ng/ml with vitamin D deficiency. As a result of the study, it was established that in group 3, in pediatric patients with the lowest vitamin D level in the blood serum, the concentration of osteocalcin shows a tendency to decrease, which may be due to the low metabolic rate in bone tissue and the dependence of osteocalcin on the blood level of vitamin D.

To establish relationships between bone metabolism parameters and vitamin D levels, a rank correlation coefficient was used. The noted correlations are significant at the $p < 0.05$ level. These coefficients were the following:

- 0.22 for total calcium level (normal range 2.25–2.75 mmol/l);
- –0.175 for calcitonin (normal range 0.0–9.5 pg/ml);
- 0.261 for osteocalcin (normal range 2.8–41 ng/ml);
- –0.185 for PTH (normal range 15.0–65.0 pg/ml);
- 0.088 for phosphorus (normal range 1.45–2.16 mmol/l);
- 0.107 for deoxyripyridinoline (normal range 13.7–41.0 nmol/mmol of creatinine).

In accordance with the weakly expressed positive or negative correlations revealed between routine indicators of bone metabolism and vitamin D levels, a null hypothesis was formulated, suggesting the possibility of an influence of vitamin D level on bone metabolism indicators. A comparative assessment of bone metabolism indicators depending on the level of vitamin D by groups is presented

Table 5. Comparison of bone metabolism parameters depending on the level of vitamin D in groups 1 and 2**Таблица 5.** Сравнение показателей костного метаболизма в зависимости от уровня витамина D в 1 и 2 группах

Bone metabolism parameters	Rank sum in group 1	Rank sum in group 2	Mann-Whitney U test	Fisher's Z test	p level
Total calcium (normal range 2.25–2.75 mmol/l)	3256.5	3413.5	1583.5	0.369	0.711
Calcitonin (normal range 0.0–9.5 pg/ml)	2760.5	3909.5	1220.5	-2.401	0.018
Osteocalcin (normal range 2.8–41 ng/ml)	3834.5	11390.5	1799.5	2.541	0.011
Intact parathyroid hormone (normal range 15.0–65.0 pg/ml)	3023.5	3646.5	1483.5	-0.929	0.352
Phosphorus (normal range 1.45–2.16 mmol/l)	3742.0	2928.0	1098.0	3.087	0.002
Deoxypyridinoline (normal range 13.7–41.0 nmol/μmol creatinine)	1227.5	2012.5	632.5	-1.45	0.147

Table 6. Comparison of bone metabolism parameters depending on the level of vitamin D in groups 1 and 3**Таблица 6.** Сравнение показателей костного метаболизма в зависимости от уровня витамина D в группах 1 и 3

Bone metabolism parameters	Rank sum in group 1	Rank sum in group 3	Mann-Whitney U test	Fisher's Z test	p level
Total calcium (normal range 2.25–2.75 mmol/l)	6243.0	11902.0	2722.0	2.87	0.003
Calcitonin (normal range 0.0–9.5 pg/ml)	4496.0	13649.0	2956.0	-2.19	0.027
Osteocalcin (normal range 2.8–41 ng/ml)	6701.0	11444.0	2264.0	4.21	0.00002
Intact parathyroid hormone (normal range 15.0–65.0 pg/ml)	4364.0	13781.0	2824.0	-2.58	0.009
Phosphorus (normal range 1.45–2.16 mmol/l)	6205.0	11940.0	2760.0	2.76	0.005
Deoxypyridinoline (normal range 13.7–41.0 nmol/μmol creatinine)	1947.5	3617.5	1061.5	0.99	0.32

Table 7. Comparison of bone metabolism parameters depending on the level of vitamin D in groups 2 and 3**Таблица 7.** Сравнение показателей костного метаболизма в зависимости от уровня витамина D в группах 2 и 3

Bone metabolism parameters	Rank sum in group 2	Rank sum in group 3	Mann-Whitney U test	Fisher's Z test	p level
Total calcium (normal range 2.25–2.75 mmol/l)	6984.0	12126.0	2946.0	3.033	0.002
Calcitonin (normal range 0.0–9.5 pg/ml)	6166.5	12943.5	3763.5	0.786	0.431
Osteocalcin (normal range 2.8–41 ng/ml)	6918.0	12192.0	3012.0	2.852	0.004
Intact parathyroid hormone (normal range 15.0–65.0 pg/ml)	5189.0	13921.0	3359.0	-1.898	0.057
Phosphorus (normal range 1.45–2.16 mmol/l)	5682.0	13428.0	3852.0	-0.542	0.587
Deoxypyridinoline (normal range 13.7–41.0 nmol/μmol creatinine)	3122.0	3781.0	1225.0	2.273	0.022

in Tables 5–7. The criteria are significant at the p level lower than 0.017.

Analysis of the Table 5 results showed statistically significant differences between the groups of pediatric patients with normal levels and insufficiency of vitamin D in terms of osteocalcin ($p \leq 0.01$) and phosphorus ($p \leq 0.01$).

Significant statistical differences were revealed between the groups of pediatric patients with normal vitamin D levels (group 1) and vitamin D deficiency (group 3) in terms

of total osteocalcin ($p \leq 0.01$), phosphorus ($p \leq 0.01$), calcium ($p \leq 0.01$), and PTH ($p \leq 0.01$). A tendency towards a decrease in the levels of calcitonin and deoxypyridinoline was established.

According to the Table 7, significant statistical differences were revealed between the group of subjects with vitamin D insufficiency and the group with this vitamin deficiency in terms of osteocalcin ($p \leq 0.01$) and total calcium ($p \leq 0.01$). It can be concluded that the most sensitive indicator of changes in vitamin D levels is the concentration of osteocalcin.

DISCUSSION

Vitamin D (a fat-soluble vitamin and prohormone) is essential in bone metabolism through the regulation of calcium phosphate homeostasis and in many extraosseous processes. Vitamin D deficiency represents a global public health problem [1]. According to the study, vitamin D insufficiency is registered in 77.8% of infants, reaching a degree of severe deficiency in 54% of cases, despite the fact that the population of the Republic of Kazakhstan lives in a zone of high insolation. In newborns, such a deficiency occurs even in countries with higher insolation and is determined by a deficiency of this vitamin in their mothers [11]. Vitamin D insufficiency in pregnant women causes decreased bone density and reduced body size in their descendants [12].

Assessment of bone metabolism is impossible without studying the balance of various inorganic substances. Calcium and phosphorus are the main essential inorganic substances that make up bone tissue. They are essential in functioning of human organs and systems; therefore maintaining an optimal level of these substances in the blood serum is an important compensatory mechanism. Calcitonin, PTH and vitamin D are the main regulators of calcium and phosphorus metabolism.

The study results revealed weak positive correlations between vitamin D and calcium concentrations, as well as between osteocalcin and vitamin D levels. Weak negative correlations were registered between PTH and vitamin D levels, as well as between serum calcitonin and vitamin D concentrations.

In accordance with the associations registered between routine parameters of bone metabolism and vitamin D levels, a null hypothesis was formulated, suggesting the possibility of an influence of vitamin D levels on parameters of bone metabolism. Significant statistical differences were demonstrated between groups of pediatric patients with normal vitamin D levels and vitamin D insufficiency in the levels of osteocalcin ($p \leq 0.01$) and phosphorus ($p \leq 0.01$).

When comparing the parameters of bone metabolism depending on the level of vitamin D in groups with its normal level and deficiency, significant statistical differences were revealed in the concentrations of osteocalcin ($p \leq 0.01$), phosphorus ($p \leq 0.01$), calcium ($p \leq 0.01$), and PTH ($p \leq 0.01$). The fact of an insignificant decrease in calcitonin, as well as deoxy pyridinoline, was established. Significant statistical differences were also revealed between the group of pediatric patients with vitamin D insufficiency and the group of pediatric patients with vitamin D deficiency in terms of osteocalcin ($p \leq 0.01$) and total calcium ($p \leq 0.01$).

CONCLUSIONS

The study confirms the effect of vitamin D on metabolic processes in the skeletal system. The most sensitive indicator that responds to changes in vitamin D levels is osteocalcin. Research in this field may be the basis for discussing the feasibility of vitamin D substitution and clarifying prenatal care regimens.

ADDITIONAL INFORMATION

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Author contributions. All authors confirm the concordance of their authorship, according to the international ICMJE criteria (all authors made a significant contribution to the preparation of the article, read and approved the final version before its publication).

The author contributions are distributed as follows. *A.K. Zhumalina* created the concept and design of the study; *I.S. Kim* collected the material, performed the statistical data processing, wrote the text of the article, and processed the literature; *V.M. Delyagin* performed the material processing, literature analysis, and the article editing.

Ethics approval. The work follows the principles of the 1964 Declaration of Helsinki, updated in October 2013 at the 64th General Assembly of the World Medical Association in Fortaleza (Brazil). The study was approved by the local ethics committee of the West Kazakhstan Medical University named after Marat Ospanov on 12.04.2020 (protocol No. 10, registered on ClinicalTrials.gov under identification number NCT05375331).

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