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The Importance of Determining the Level of Bone Metabolism Markers and Vitamin D in the First Year of Life in the Kazakh Population

Akmaral Zhumalina, DMSc; Balash Tusupkaliev, DMSc; Anna Mania, MD; Irina Kim, Asst; and Mairamkul Zharlykasinova, PhD

OBJECTIVE The research aimed to determine the importance of vitamin D and markers of bone metabolism in the overall assessment of bone mineralization during a child's first year of life.

METHODS The 198 children were selected by screening all infants seen at our pediatric clinic over a 2-year period from 2020–2022 and including those who met the eligibility criteria of being aged 0 to 1 year, healthy with no chronic conditions, and not on vitamin D supplementation. Children were divided into 3 groups depending on the content of vitamin D in the blood serum: sufficient, insufficient, and deficient. The markers of bone tissue status included: markers of mineral metabolism (calcium, phosphorus, parathyroid hormone, calcitonin), a marker of bone formation (osteocalcin), resorption marker (deoxypyridinoline). Laboratory values were obtained at the time of study enrollment during the initial study visit. Labs were not repeated during the course of the study.

RESULTS A quarter of the infants exhibited vitamin D deficiency at enrollment with serum 25OHD concentrations below 20 ng/mL, which showed a positive correlation with serum calcium and phosphorus concentrations and a negative correlation with PTH, while osteocalcin and deoxypyridinoline concentrations remained consistent regardless of vitamin D status.

CONCLUSIONS The study's practical significance allows for the recommendation of using vitamin D concentrations as a marker to detect bone formation and mineral metabolism disorders in children during their first year of life. By identifying and addressing these issues early on, the health care system aims to ensure better musculoskeletal health for children.

KEYWORDS calcium; parathyroid hormone; phosphorus; osteocalcin

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Introduction

Describing the structure of vitamin D in 1922 and receiving the Nobel Prize for this work, Adolf Windaus gave an impulse to the medical world to study the effect of this vitamin on the development of all body systems.[1] It was determined that calciferol has the greatest impact on the musculoskeletal system, participating in the formation of bone tissue, and its deficiency poses a threat to the development of rickets and osteoporosis in children. The manifestation of these diseases is insufficient mineralization of bone tissue, which, without therapeutic intervention, can lead to irreversible consequences for skeletal formation and development. Therefore, it is important to find a method that will determine the violation of bone mineralization in young children to be able to prevent or minimize the manifestations of rickets or osteoporosis in the future.

The primary research challenge highlighted is the absence of consolidated methodologies for evaluating bone metabolism in young children, specifically those under one year of age. While densitometry, endorsed by the World Health Organization, stands as a pivotal diagnostic tool for osteoporosis, its application in infants presents technical hurdles.[2] Key studies from the International Society of Clinical Densitometry and more recent research have underscored these challenges, indicating a substantial gap in understanding densitometry's reliability for this particular age group.[3] Furthermore, a comprehensive review on osteoporosis diagnosis, encompassing global and Kazakhstani experiences, reiterates this limitation, emphasizing the method's aptness primarily for adults and children aged 5 and above.[4–6]

In light of these limitations, this research proposed examining bone metabolism markers and vitamin D concentrations as an alternative diagnostic approach for infants. Notably, studies from Kazakhstan have explored the relationship between bone metabolic rate, environmental factors, and vitamin D concentrations in older children, presenting a foundational

understanding.[7] However, the dearth of such insights for infants underscores a critical research void, emphasizing the need for further exploration tailored to this specific age bracket.

Our research aim was to determine the diagnostic value of markers of bone metabolism and vitamin D in determining the level of bone mineralization in children from birth to 1 year of the Kazakh population.

Material and Methods

During the research, the methods of clinical and laboratory examination and statistical processing of its results were applied.

The clinical and laboratory examination involved 198 children of 1 to 2 health groups of the Kazakh population aged from birth to 1 year, living in the Republic of Kazakhstan, Aktobe. To control for possible confounders, we did not include children with congenital or acquired diseases of the musculoskeletal system, chronic somatic diseases, and children who took vitamin D for therapeutic purposes.

Markers of bone mineral metabolism, markers of bone formation, and markers of bone resorption were selected for clinical and laboratory examinations. Clinical evaluations were performed at the time of enrollment into the study and included a full physical exam, dietary assessment, and developmental assessment. Physical exams specifically evaluated for signs of rickets such as craniotabes, rachitic rosary, bowed legs, or wrist swelling. Dietary intake of vitamin D, calcium, and phosphorus was estimated based on a 3-day food record completed by parents. Development was assessed using the Bayley Scales of Infant Development. Malnutrition and its severity were determined through a combination of clinical evaluations, dietary assessment, and developmental evaluation. These clinical evaluations were conducted by study physicians at the research center.

The markers of bone mineral metabolism included: serum calcium, phosphorus, parathyroid hormone (PTH), calcitonin, and vitamin D. Laboratory analyses were conducted on blood samples collected at the time of enrollment. Serum 25-hydroxyvitamin D was measured using LC-MS/MS methodology by the hospital clinical laboratory to assess vitamin D status, as this is the circulating form that best reflects overall vitamin D concentrations from both sunlight exposure and dietary intake.

Osteocalcin was chosen as a marker of bone formation since the metabolic activity of osteoblasts is determined by its concentration in the serum. Deoxypyridinoline was chosen as a marker of bone tissue resorption since its pathway from entry into the bloodstream to excretion in the urine without metabolic transformations in unchanged form indicates bone tissue degradation.

Other specific lab tests performed were: serum calcium, phosphorus, parathyroid hormone, osteocalcin, and deoxypyridinoline. These were measured from the enrollment blood samples using standard automated clinical analyzer techniques in the hospital clinical lab.

Normative values for each marker and laboratory methods for their determination are shown in Table 1.

The recommendations of the US Endocrinological Society were used to categorize children into groups by the content of their serum vitamin D concentration.[8]

Statistical processing of the results of clinical and laboratory examinations was performed using Statistica 10 or SPSS 25 (StatSoft, USA). Comparative analysis of nonparametric data was performed using the Mann-Whitney *U* criterion, and analysis of dependencies—using Spearman rank correlation, in addition, descriptive and statistical methods were used. The criteria for correlation of the obtained results were determined by the Chaddock scale,[2] according to which the closeness of the relationship 0.1 to 0.3 corresponds to a weak character of the strength of the relationship, 0.3 to 0.5 (moderate), 0.5 to 0.7 (noticeable), 0.7 to 0.9 (high), 0.9 to 0.99 (very high), functional relationship is denoted as 1, and the absence of a relationship denoted as 0.

Results

Based on the serum concentration of 25(OH)D children were divided into 3 groups: the first group included 35 children with a serum vitamin D concentration between 30 and 75 ng/mL and were considered sufficient; a second group, with the serum vitamin D concentration between 20 and 30 ng/mL and were considered as insufficient; and the third group, with the serum vitamin D concentration < 20 ng/mL and were considered deficient (Table 2).

The results obtained using this categorization indicate that the number of children studied who have insufficient vitamin D concentrations were 5.6 times higher than the number of children whose vitamin D concentrations are within normal limits. Using the obtained results, the serum calcium, phosphorus calcitonin, PTH, values of markers of bone formation and resorption (osteocalcin and deoxypyridinoline) values were compared depending on the serum vitamin D concentration. (Table 3).

The rank correlation coefficient was used to identify the relationship between the values of bone metabolism parameter values and serum vitamin D concentrations. Using the Chaddock scale, the following types of relationships were identified between serum calcium and vitamin D—a weakly positive relationship ($0.01 < r < 0.29$, where r is the closeness of the relationship on the Chaddock scale); between serum phosphorus and vitamin D—no relationship ($r < 0.1$); between serum calcitonin and vitamin D—no relationship ($r < 0.1$); between serum PTH and vitamin D—moderately negative relationship ($-0.30 < r < -0.69$); between serum osteocalcin and vitamin D—moderately positive

Table 1. Normative Levels and Laboratory Methods for Determination of Bone Tissue Markers*

Types of Bone Tissue Markers	Markers	Normative Values and Their Dimensionality	Laboratory Methods of Determination
Markers of the bone mineral metabolism state	Calcium	1.9–2.6 mmol/L – for children under 10 days of age; 2.25–2.75 mmol/L – for children from 10 days to 2 yr of age	From blood serum by colorimetric, photometric method
	Phosphorus	1.45–2.16 mmol/L – for children under 2 yr old	From blood serum by colorimetric method with ammonium molybdate
	PTH	15.0-65.0 pg/mL	From blood serum by solid-phase chemiluminescent enzyme immunoassay
	Calcitonin	Less than 50 ng/L	From blood serum by solid-phase chemiluminescent enzyme immunoassay
	Vitamin D	30–80 ng/mL	From blood serum by electrochemiluminescent immunoassay
Markers of bone tissue formation	Osteocalcin	2.8–41 ng/mL	From blood serum by electrochemiluminescent immunoassay.
Markers of bone resorption	Deoxypyridinoline	13.7–41.0 nmol/mol	From urine by immunochemiluminescent analysis

PTH, parathyroid hormone

* All analysis used in this study was performed in our hospital clinical laboratory.

Table 2. Demographic and Baseline Data of the Study Population*

Parameter	Serum Vitamin D Sufficient (30–75 ng/mL) in Group 1	Serum Vitamin D Insufficient (20–30 ng/mL) in Group 2	Serum Vitamin D Deficient (<20 ng/mL) in Group 3
Total number of patients	35	105 (5.6 times higher)	58
Mean age, mo	6.2 ± 2.4	6.8 ± 2.7	6.5 ± 2.5
Mean weight, kg	7.1 ± 1.2	6.8 ± 1.3	6.9 ± 1.3
Gender, % male	51%	48%	52%
Baseline diagnosis, % with rickets signs	5%	12%	20%
Serum calcium, mg/dL	9.4 ± 0.5	9.2 ± 0.6	9.0 ± 0.6
Serum phosphorus, mg/dL	5.0 ± 0.4	4.9 ± 0.4	4.8 ± 0.5
Nutritional status, % with malnutrition	12%	25%	30%
Drugs affecting vitamin D metabolism, % using anticonvulsants	4%	5%	7%

* Data presented as mean + SD or % as shown.

Table 3. Indicators of Markers of Bone Mineral Metabolism, Bone Formation and Resorption Depending on the Serum Vitamin D Concentration*

Group #	Total Calcium (Ca), mmol/L	Phosphorus (P), mmol/L	Calcitonin, pg/mL	Osteocalcin, ng/mL	Deoxypyridinoline, nmol/mol	PTH, pg/mL
Group 1	2.44	1.96	4.89	5.88	28.33	18.85
Group 2	2.39	1.79	5.49	3.51	27.43	21.07
Group 3	2.39	1.96	5.71	2.56	16.50	30.99

PTH, parathyroid hormone

* Group 1 has the highest serum vitamin D concentration between 30–75 ng/mL and was considered sufficient; Group 2 has an insufficient serum vitamin D concentration between 20–30 ng/mL; and Group 3 has a deficient serum vitamin D concentration < 20 ng/mL.

relationship ($0.30 < r < 0.69$); between serum deoxypyridinoline and vitamin D—moderately positive relationship ($0.30 < r < 0.69$).

The comparative analysis of bone metabolism indices relative to the serum vitamin D concentration for groups 1 and 2, 1 and 3, and 2 and 3 are shown in Table 4.

A difference in calcium serum, PTH, and osteocalcin ($p \leq 0.05$) was found between the group of children with sufficient serum vitamin D concentrations (group 1) and the group with insufficient levels (group 2). The statistical significance of other bone markers (phosphorus, calcitonin, deoxypyridinoline) was found to be insufficient, indicating the lack of sensitivity of their values to changes in vitamin D levels.

The result of the statistical analysis, shown in Table 4, was the confirmation of the influence of vitamin D levels on bone metabolism (calcium, PTH, osteocalcin), the most sensitive of which was osteocalcin.

Discussion

The first year of a child's life is an important stage in laying the foundation for good health in the future. Treatment of diseases detected at this age is more effective, and the chance of full recovery is much higher. An important role in the process of monitoring children's health is played by routine preventive examinations of children from birth to 1 year, which include monthly examinations by a pediatrician and routine preventive examinations with the collection of tests during the first year of life. In this case, an important role is played by preclinical diagnostic markers that can be obtained from blood and urine tests. Preclinical diagnostics is especially important for checking those body systems, and the presence of

Table 4. Comparison of Bone Metabolism Indicators Depending on the Serum Vitamin D Concentration Across Different Patient Groups

Variables (Units)	Group 1	Group 2	Group 3	Group 1 vs 2	Group 1 vs 3	Group 2 vs 3
Total serum calcium (90–110 mg/dL)	3768.5	11456.5[a]	1295.5[b]	1865.5	306.5	1715.0
Serum phosphorus (44.95–66.96 mg/dL)	3517.0	11,708.0	1077.0	2117.0	411.0	1361.5
Serum calcitonin (0.0–9.5 pg/mL)	3026.5	12,198.5	1052.5	2360.5	386.5	1628.0
Serum PTH (15.0–65.0 pg/mL)	2239.5[a]	12,985.5[a]	846.5[b]	1573.5	180.5	1393.0
Serum osteocalcin (2.8–41 ng/mL)	3834.5[a]	11,390.5[a]	1372.0[b]	1799.5	230.0	1351.5
Serum deoxypyridinoline (13.7–41.0 nmol/mol)	786.0	3870.0	168.0	549.0	12.0	86.0

PTH, parathyroid hormone

* Calculations were made using Statistica software.
[a] Statistically significant difference between Group 1 and Group 2 ($p < 0.05$).
[b] Statistically significant difference between Group 1 and Group 3 ($p < 0.05$).
See Methods for age group definitions.

disorders which can be irreversible in case of delayed detection or cause general developmental delay.[9,10] Such systems include the musculoskeletal system, since at the stage of bone formation and growth, an insufficient amount of minerals, which are the "building material" of bone tissue, can lead to the development of rickets or osteoporosis, and they, in turn, can cause irreversible changes that affect the functional properties of the musculoskeletal system and the physical condition of the body as a whole. In this study, it was statistically proven that the level of vitamin D obtained from blood serum can serve as a marker for detecting bone metabolism disorders in children from birth to one year, which may be signs of rickets or osteoporosis.

The only measurement method recognized by the World Health Organization for the diagnosis of osteoporosis is densitometry. And although this method is fast, painless, and achieves high diagnostic accuracy (bone loss of 2%–5% is recorded),[2] its use in young children causes technical problems. This issue was raised by Kalkwarf et al[3] from the International Society of Clinical Densitometry. They studied the literature on this topic, which concerned the measurement of bone mineral density for children from birth to 5 years, the data obtained were insufficient for the interpretation of densitometry measurements. Although this study was conducted in 2013, a more recent work by Guss et al,[4] published in 2021, which concerned the use of densitometry for children and adolescents, also did not confirm the possibility of using the method and interpreting its results for children under 1 year. In the work of Sakhova et al,[5] a literature review was conducted to collect and analyze information on the diagnosis and treatment of osteoporosis, considering the world experience in general and the experience of the Republic of Kazakhstan in particular.

The work of Zhumalina et al[6] compared markers of bone metabolism in children and adolescents with short height due to their residence in an ecologically polluted region and children living in an ecologically favorable region. This study established the dependence of bone metabolic rate on the purity of the environment in which the formation and growth of bone tissue of children and adolescents take place. Amanzholkyzy et al[7] conducted a study that recognized the association of the vitamin D receptor gene (VDR) with bone mineral density in children of the Western region of the Republic of Kazakhstan. The study traced the dependence of bone mineral density on the level of vitamin D, which was determined in the laboratory in each child studied. These studies are of practical use, providing a comprehensive assessment of the dependence of changes in bone metabolism markers on environmental conditions and vitamin D levels in children over 5 years of age. However, none of the studies included children under the age of 1 year, so it is not correct to make similar conclusions about this age group.

Levin[11] considered the genetic aspect of vitamin D-dependent rickets, the cause of which is a congenital inability to maintain sufficient concentrations of active forms of vitamin D, reviewed updated information on the 3 forms of vitamin D-dependent rickets, and treatment protocols for patients. Chanchlani et al[12] noted that regardless of the type of rickets, its early detection significantly increases the effectiveness of treatment until complete recovery. In this case, the method of early detection can be used to determine bone metabolism disorders using a marker of vitamin D level, the diagnostic reliability of which has been proven by this research, and further clinical and laboratory examinations will help to determine the type of disease and offer an effective treatment process.

Along with the identification and treatment of diseases associated with insufficient levels of vitamin D, an equally important issue is to find out the causes of its decline in children. There are 3 main causes of deficiency of any organic or inorganic element in the body: insufficient intake, insufficient absorption, and excessive excretion.

Benedik[13] described 2 ways of vitamin D intake into the body—endogenous synthesis under the influence of solar radiation of the ultraviolet spectrum and dietary intake through the consumption of food of animal and vegetable origin, and also made recommendations on foods and dietary supplements that will help prevent vitamin D deficiency and deficiency. However, this study did not include recommendations to prevent vitamin D deficiency in the most at-risk group, which includes breastfed infants. This issue was researched in the research of Jullien,[14] who's proved the effectiveness and safety of vitamin D supplements for infants (in a dosage of 400 international units) to prevent rickets and improve bone health. Akhmetzhanova and Ivanova[15] monitored bone mineral density and vitamin D supply in healthy children of Semey, Republic of Kazakhstan. The study aimed to identify the relationship between solar energy exposure and the level of vitamin D in the body, for which the autumn-winter season was chosen, characterized by a limited amount of solar energy. The result showed that 93% of children participating in the study had hypovitaminosis D. From this study it can be concluded that children living in climatic regions with a long period of limited exposure to solar energy may be at risk of bone metabolism disorders caused by a decrease in vitamin D levels.

One of the main factors affecting the insufficient absorption of vitamin D is obesity. This is caused by the fact that fat-soluble vitamin is distributed in fat mass, liver, muscles, and blood serum. Consequently, an increase in the volume of adipose or muscle tissue reduces the concentration of the distributed vitamin in it.[16] Recently, the problem of obesity in children has become widespread, as evidenced by the number of studies related to this issue in recent years.[17,18] Thus,

in the electronic database of medical and biological publications PubMed for the query "obesity in children," the number of related articles from 2002 to 2022 was 55,207,[19] of which 42,962 were published in the last 10 years from 2012 to 2022.[20] Pietrobelli et al[21] conducted an analysis of published scientific studies conducted to minimize obesity in children in the first 1000 days, including the timing of conception, pregnancy, and life after birth. One of the probable reasons' scientists called obesity of parents during conception and gestation. Fiamenghi and de Mello[22] conducted a systematic review and meta-analysis of studies of patients diagnosed with obesity and vitamin D deficiency aged from birth to 18 years and concluded that children and adolescents diagnosed with obesity are at greater risk of vitamin D deficiency. The results obtained from the new pediatric reference ranges were described by Geserick et al.[23] Based on the findings of the reviewed studies,[21–23] obesity in children can be considered a risk factor for disorders of bone formation and metabolism. In this case, the method of detecting bone metabolism disorders using a marker of vitamin D level, substantiated in the study, is recommended for mandatory use in children of this risk group.

Excessive excretion of vitamins and other mineral elements from the body is most often associated with pathological changes in the kidneys or liver since the metabolism of vitamin D begins in the liver, where its first hydroxylation takes place, and continues in the proximal tubules of the kidneys, where it is converted to the hormonally active form of vitamin D.[24–26]

When studying the main function of vitamin D associated with bone mineralization, it is worth paying attention to other aspects of the effect of this vitamin on various body systems. Lopez et al[27] conducted a study in which they described the non-classical effects of vitamin D. After reviewing the available information on the topic, the authors found a new purpose of 25–hydroxyvitamin D as a steroid hormone by establishing its relationship with cardiovascular diseases, chronic metabolic disorders, and neoplasms, and proposed its use as a prevention and treatment of these diseases.

Bilezikian et al[28] concerned that the use of an individual approach depending on the factors underlying vitamin D deficiency in various diseases; determining the role of vitamin D supplements for the prevention and treatment of COVID-19; the use of active vitamin D analogs for patients with severe renal and hepatic insufficiency.

Analyzing the results of the research conducted and the studies of other authors cited above, a tendency to a steady level of interest of scientists around the world in the preventive and therapeutic functions of vitamin D can be noticed.[29–31] This is determined by its influence on the mineral metabolism of the most important substances in the body, which in turn affect the functioning of all organ systems.[31–33] Thus, a comprehensive study of aspects related to this vitamin will open up new areas of its application, the most relevant of which is the mechanism of slowing down aging.

Limitations of this study include the retrospective design and inclusion of patients from a single center. The control group was not matched to deficient groups for age or nutritional status. Additionally, patients were categorized based on a single lab value which may not reflect long-term magnesium or phosphorus status.

Conclusions

In the study, a significant correlation between bone metabolism indicators and vitamin D levels was observed, underscoring the diagnostic potential of serum vitamin D levels in assessing bone metabolism disorders in infants. Identifying at-risk groups, such as children with malnutrition, obesity, or residing in low sunlight regions, further refines diagnostic precision. These findings have profound implications for early diagnosis and potential interventions, offering insights for health care practitioners to prioritize vitamin D monitoring in high-risk pediatric populations. Additionally, exploring the role of vitamin D in the elderly, considering factors like estrogen levels, may pave the way for broader applications in combating age-related bone degeneration.

Article Information

Affiliations. Department of Children's Diseases No. 1 with Neonatology (AZ, BT, IK, MZ), West Kazakhstan Marat Ospanov Medical University, Aktobe, Republic of Kazakhstan; Department of Infectious Diseases and Child Neurology (AM), Poznan University of Medical Sciences, Poznan, Poland.

Correspondence. Akmaral Zhumalina, DMSc; akmaralzhumalina2@gmail.com

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