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Underlying Hemato-oncologic, Gastrointestinal-nutritional Diseases, or Prematurity May Be Risk Factors for Hypovitaminosis D in Children

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Purpose: An adequate vitamin D level is important for normal growth, cancer prevention, controlling hormones, and immune regulation. However, no study has investigated vitamin D status in patients with serious illnesses, such as malignancies, malabsorption diseases, or prematurity in Korean children. Thus, we analyzed the results of 25-hydroxyvitamin D_3 (25-D) levels in children in a single tertiary medical center. **Methods**: Children who had their vitamin D level evaluated at Keimyung University Dongsan Medical Center from January 2004 to December 2014 were included. We reviewed the medical records and laboratory test results. **Results**: Ninety-three children (male:female = 48:45) who had their vitamin D levels measured were included. The most common reason for measuring vitamin D level was hypocalcemia with or without neurological signs. Among the subjects, 61 children had hypovitaminosis D (25-D < 30 ng/mL). A positive correlation was detected between 25-D and total calcium levels (p= 0.001). Negative correlations were found between 25-D and immunoreactive parathyroid hormone (iPTH) levels (p = 0.002) and between 25-D and alkaline phosphatase (ALP) levels (p = 0.021). Twenty-three subjects (37.7%) had a critical underlying condition, including a hemato-oncologic issue (18.0%), gastrointestinal or nutritional problem (11.5%), and prematurity or low birth weight (8.2%). **Conclusion**: The levels of total calcium, ALP, and iPTH were correlated with 25-D level. An underlying malignancy, malabsorption issues, or prematurity may be risk factors for hypovitaminosis D in children.

Key Words: Cancer, Children, Malabsorption, Prematurity, Vitamin D

Introduction

Low levels of vitamin D are associated with rickets and osteomalacia. More recently, vitamin D has been recently associated with normal growth and puberty, cancer prevention, control of hormones, and immune regulation [1,2]. Several studies have investigated vitamin D deficiency in breastfed infants and concomitant rickets or neurological symptoms [3-7]. Other studies have been conducted about vitamin D status in healthy Korean children and adolescents [8-11]. However, no study has evaluated vitamin D status in children who have a serious illness, including hemato-oncologic diseases, gastrointestinal-nutritional problems, or prematurity. Thus, in this study, we retrospectively reviewed the results of vitamin D status in children in a single tertiary medical center in Korea.

Materials and Methods

Subjects

Children who had their vitamin D level measured at Keimyung University Dongsan Medical Center from January 2004 to December 2014 were included in this study. We reviewed their medical records for laboratory test results, including total calcium, ionized calcium, phosphorus, 25-hydroxyvitamin D_3 (25-D), 1,25-hydroxyvitamin D_3 (1,25-D), immunoreactive parathyroid hormone (iPTH), alkaline phosphatase (ALP) and mean platelet volume (MPV). The presence of underlying disease and why the vitamin D test was performed were reviewed. Body mass index (BMI) was also calculated.

Statistical analysis

Statistical analyses were performed using SPSS ver. 22.0 software. Data are presented as means ± standard deviations. Analysis of variance (ANOVA) analysis with the Bonferroni method was used to compare variables between groups. Linear-by-linear association with the chi-square test was used to compare ratios between the groups. Pearson's correlation analysis was used to define the correlations between patient variables. Receiver-operator characteristic (ROC) curves were used to calculate the area under curve (AUC) and define cutoff values. An absolute correlation coefficient rho value > 0.3 and a p-value < 0.05 were considered significant. BMI was calculated as weight (kg)/height squared (m2).

Ethics statement

This study was approved by the institutional review board of Keimyung University Dongsan Medical Center (Approval No., 2015-06-061-001), which waived the requirement for informed consent.

Results

Subject characteristics and significant variables

A total of 93 children (male:female = 48:45) who had their vitamin D level determined were included. Among them, 61 children had hypovitaminosis D; 13 patients had a vitamin D deficiency (25-D $<$ 10 ng/mL) and 48 patients had a vitamin D insufficiency (10 ng/mL $\leq$ 25-D $<$ 30 ng/mL). Thirty-two children had an adequate vitamin D level (25-D $\geq$ 30 ng/mL). Significant differences in total calcium (p = 0.001), ALP (p = 0.015), and iPTH were observed ($p < 0.001$) between the three groups. No differences were found for the sex ratio, 1,25-D, ionized calcium, phosphorus, MPV, or BMI between the three

Table 1. Subject characteristics and laboratory results for those who received vitamin D testing

	Hypovitaminosis D		Normal	*p*-value
	Deficiency	Insufficiency		
	25-D < 10 ng/mL	10 ng/mL ≤ 25-D < 30 ng/mL	25-D ≥ 30 ng/mL	
N	13	48	32	.
Age (yr)	1.9 ± 3.4	5.2 ± 6.7	3.1 ± 3.3	0.076
Sex (M : F)	8 : 5	26 : 22	14 : 18	0.278
25-D (ng/mL)	7.2 ± 2.1	18.3 ± 4.9	54.8 ± 21.9	.
1,25-D (pg/mL)	44.4 ± 26.8	70.0 ± 47.4	63.9 ± 42.6	0.224
Total calcium (mg/dL)	8.0 ± 1.8	9.1 ± 1.5	9.8 ± 1.2	0.001*
Ionized calcium (mEq/L)	2.0 ± 0.4	2.2 ± 0.4	2.3 ± 0.3	0.331
Phosphorus (mg/dL)	4.7 ± 2.3	5.1 ± 2.0	5.3 ± 0.9	0.626
ALP (IU/L)	1531 ± 1174	976.3 ± 846.4	718.4 ± 625.4	0.015*
MPV (fL)	8.4 ± 2.0	7.7 ± 1.0	7.5 ± 0.8	0.077
iPTH (pg/mL)	134.6 ± 103.0	64.9 ± 87.8	23.4 ± 16.9	< 0.001*
BMI (kg/m^2)	18.0 ± 3.6	18.7 ± 4.7	18.6 ± 4.4	0.900

25-D: 25-hydroxyvitamin D3, 1,25-D: 1,25- hydroxyvitamin D3, ALP: alkaline phosphatase, MPV: mean platelet volume, iPTH: immunoreactive parathyroid hormone, BMI: body mass index.

groups. The subject characteristics, laboratory test results, and respective *p*-values are described in Table 1.

Reasons for measuring vitamin D level

The most common reason that vitamin D level measured was hypocalcemia (n = 32). Eleven patients had symptomatic neurological signs related to hypocalcemia (seven convulsion, three tetany, and one spasms). The second reason was suspicion of rickets (n = 28), followed by bone problems, including a fracture or osteopenia detected on radiography (n = 11). The fourth reason was a hemato-oncologic work-up during chemotherapy or at the end of therapy (n = 10) (three had hypocalcemia or osteopaenia). The detailed reasons why the pediatrician measured vitamin D level are shown in Figure 1.

Correlations between vitamin D level and other variables

Negative correlations were detected between 25-D level and iPTH (rho = -0.315 and p = 0.002) and between 25-D level and ALP (rho = -0.240 and p = 0.021). A positive correlation was found between 25-D and total calcium levels (rho = 0.341 and p = 0.001). No associations were found between 25-D level and other variables, including phosphorus (rho = 0.086 and p = 0.415), 1,25-D (rho = -0.086 and p = 0.534), ionized calcium (rho = 0.185 and p = 0.208), MPV (rho = -0.094 and p = 0.368), or BMI (rho = -0.009 and p = 0.938). These results correspond to the ANOVA analysis shown in Table 1. The details of the correlations and statistical differences between the three groups detected by ANOVA with the Bonferroni method are shown in Figure 2.

The highest AUC was detected for total calcium

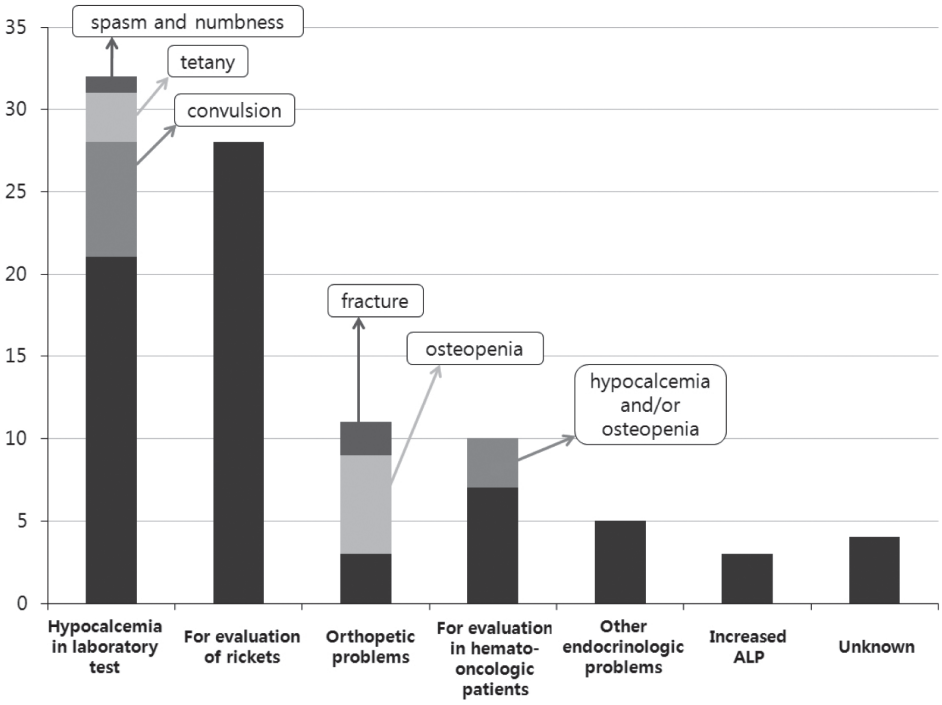

Fig. 1. Reasons for measuring vitamin D level in children in a single tertiary medical center.

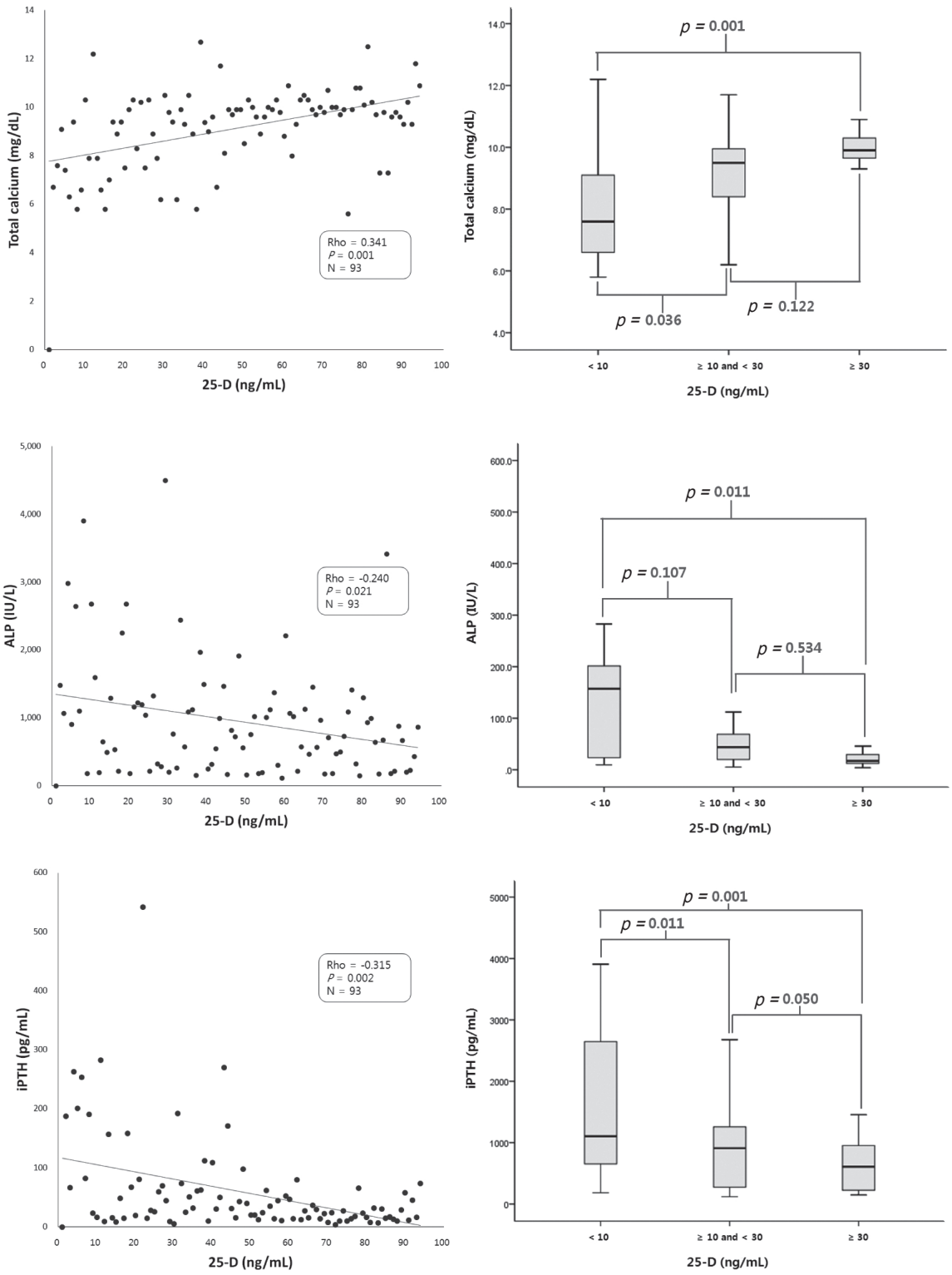

Fig. 2. Correlations between vitamin D level and other significant variables. 25-D: 25-hydroxyvitamin D_3, ALP: Alkaline phosphatase, iPTH: immunoreactive parathyroid hormone.

(AUC, 0.751) with sensitivity of 76.9% and specificity 72.5% when the cut-off value was 9.2 mg/dL in case of dividing the children into groups of 25-D < 10 ng/mL and 25-D ≥ 10 ng/mL. The AUC was highest for iPTH (AUC, 0.749) in those grouped by 25-D < 30 ng/mL and 25-D ≥ 30

Table 2. Cut-off values of variables in the patients with hypovitaminosis using a receiver-operator characteristic curve analysis

25-D (ng/mL)	Variables	AUC	Cut-off	Sensitivity (%)	Specificity (%)
10	Total calcium	0.751	9.2 mg/dL	76.9	72.5
	ALP	0.674	1068 IU/L	61.5	70.0
	iPTH	0.741	66.2 pg/mL	69.2	82.5
30	Total calcium	0.692	9.8 mg/dL	63.9	65.6
	ALP	0.623	717 IU/L	60.7	62.5
	iPTH	0.749	23.5 pg/mL	72.1	62.5

25-D: 25-hydroxyvitamin D_3, AUC: area under curve, ALP: alkaline phosphatase, iPTH: immunoreactive parathyroid hormone.

Table 3. Vitamin D status in children with underlying hemato-oncologic diseases

No.	Sex	Age (yr)	Diagnosis	25-D (ng/mL)	Time point of vitamin D test
1	F	2.3	BT	9.2	End therapy
2	M	12.7	WT	9.9	Several years after therapy
3	F	13.0	NHL	10.9	End therapy
4	M	15.4	BT	16.0	Several years after therapy
5	F	21.3	AA	17.7	During follow up
6	M	17.3	CML	18.9	During therapy
7	M	15.4	ALL	19.3	During therapy
8	F	11.8	LCH	20.7	During therapy
9	M	15.8	ALL	20.9	During therapy
10	F	13.0	ALL	25.7	During therapy
11	M	4.6	ALL	29.9	During therapy
12	F	8.5	ALL	44.7	During therapy
13	M	5.0	NBL	77.1	Several years after therapy
14	M	8.0	HLH	84.6	Several years after therapy

25-D: 25-hydroxyvitamin D_3, BT: brain tumor, WT: Wilms' tumor, NHL: non-Hodgkin's lymphoma, AA: aplastic anemia, CML: chronic myeloid leukemia, ALL: acute lymphoblastic leukemia, LCH: Langerhans cell histiocytosis, NBL: neuroblastoma, HLH: hemophagocytic lymphohistiocytosis.

ng/mL, with sensitivity of 72.1% and specificity of 62.5% when the cut-off value was 23.5 pg/mL. The respective AUC, cut-off values, sensitivities, and specificities are shown in Table 2.

Underlying diseases in children with hypovitaminosis D

Fourteen patients who had a hemato-oncologic disease had their vitamin D levels checked. Among them, two were vitamin D deficient and nine were insufficient. The 25-D levels of the subjects and the time points of the test are shown in Table 3. Patients 1 and 7 were also treated with the bisphosphonate derivatives, pamidronate and alendronate for osteopenia. Seven children had gastrointestinal or nutritional problems and were tested for vitamin D. All had hypovitaminosis D. The vitamin D levels and disease profiles are shown in Table 4. Nine subjects were premature or low birth weight and had their vitamin D levels

Table 4. Vitamin D status in children with underlying gastrointestinal and nutritional problems

No.	Sex	Age (yr)	Diagnosis	25-D (ng/mL)
1	M	0.9	Microvillous inclusion disease	4.6
2	M	1.8	Food allergy	11.5
3	M	0.0	Eosinophilic gastroenterocolitis	11.8
4	F	1.1	History of necrotizing enterocolitis	11.9
5	F	0.0	History of duodenal atresia, after operation	15.1
6	F	1.6	Diet restriction due to atopic dermatitis and food allergy	15.3
7	M	5.4	Non erosive reflux disease, quadriparesis	22.8

25-D: 25-hydroxyvitamin D_3.

Table 5. Vitamin D status in children who were premature or low birth weight

No.	Sex	Age (yr)	Diagnosis	25-D (ng/mL)
1	M	0.4	Prematurity (IUP 35 + 5 wks, 2,520 gm)	5.3
2	M	0.1	LBW, Twin (IUP 37 + 4 wks, 2,200 gm)	6.9
3	F	0.6	Prematurity, LBW (IUP 35 + 2 wks, 2,000 gm)	12.1
4	M	1.0	Prematurity, LBW (IUP 34 + 5 wks, 2,140 gm)	22.0
5	M	0.3	LBW (IUP 38 wks, 2,360 gm)	26.0
6	F	0.2	Prematurity, LBW (IUP 30 + 3 wks, 1,380 gm)	30.2
7	F	0.3	Prematurity, LBW, Twin (IUP 34 + 3 wks, 1,960 gm)	35.6
8	M	0.0	Prematurity, VLBW (IUP 31 wks, 1,410 gm)	36.8
9	M	1.0	Prematurity (IUP 36 wks, 2,760 gm)	99.9

25-D: 25-hydroxyvitamin D_3, IUP: intrauterine period, LBW: low birth weight, VLBW: very low birth weight.

evaluated. Among them, five had hypovitaminosis D. The vitamin D levels, gestational ages, and birth weights are shown in Table 5.

Among the 61 patients with hypovitaminosis, 23 subjects (37.7%) had an underlying serious illness, including hemato-oncologic issues (11cases, 18.0%), gastrointestinal or nutritional problems (7cases, 11.5%), and prematurity or low birth weight (5cases, 8.2%).

Discussion

This is the first vitamin D status survey in children including underlying serious illnesses in Korea. The negative correlation we found between iPTH and vitamin D was also reported previously [9]. We analyzed the AUC of the ROC curves for total calcium, ALP, and iPTH. Our results will help pediatricians determine when to evaluate about vitamin D in a practical clinical setting because hypovitaminosis D has no specific symptoms or signs. For example, if total calcium is < 9.2 mg/dL and ALP is > 1068 IU/L, the pediatrician can check 25-D suspecting deficiency.

Negative correlations have been consistently reported between 25-D level and obesity [9,12-14]. Although mechanisms are not fully understood, sedentary life sytle can affect low expose of sun. and increased adipocyte uptake of Vitamin D can make low circulating vitamin D. However, we found not difference in BMI between the three groups (Table 1). Patients undergoing chemotherapy for a hemato-oncologic disease under or those with gastrointestinal/nutritional problems often lose weight. Thus, we cannot generalize the negative correlation between vitamin D level and BMI in children with an underlying disease.

Low vitamin D level is strongly associated with high MPV [15]. Low vitamin D level increased the level of proinflammatory cytokines. This may lead to high MPV level. And high MPV increases risk of cardiac disease. However, we found no correlation. This may have occurred because of the smaller number of subjects and the different vitamin D deficiency cut-offs used in the two studies (25-D level 20 ng/dL in previous study vs. 30 ng/mL in this study).

Some limitations of this study should be discussed. First, not all hemato-oncologic patients in our center from 2004 to 2014 were included in the vitamin D evaluation. We suggest that vitamin D status should be checked at a cancer diagnosis and then regularly until the end of chemotherapy considering the relationship between carcinogenesis and vitamin D [1,16,17]. Second, we could not investigate the correlation between iron and vitamin D. Iron status was not routinely checked with vitamin D. Iron status is generally correlated with vitamin D level in breastfed infants [5,6]. However, the opposite result in hemato-oncologic patients may have occurred because of repeated transfusions.

In conclusion, vitamin D status and other correlated variables were somewhat different between children with an underlying disease and healthy individuals. Total calcium was positively correlated with 25-D level. ALP and iPTH were negatively correlated with 25-D level. Underlying hemato-oncologic, gastrointestinal-nutritional diseases, or prematurity can be risk factors for hypovitaminosis D in children.

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