Effect of Vitamin D Supplementation on Delayed Hyperphosphatemia in Pediatric Acute Lymphoblastic Leukemia Patients During Induction Chemotherapy

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OBJECTIVES Vitamin D plays a role in maintaining bone health and calcium metabolism, but recent studies cast doubt on vitamin D supplementation's benefits in survivors of acute lymphoblastic leukemia (ALL). Vitamin D supplementation could increase serum phosphate through increased intestinal absorption of phosphate and suppression of parathyroid hormone, which would lead to decreased renal phosphate excretion. Because of the potential for renal injury during induction chemotherapy for ALL, Vitamin D supplementation's potential for increasing hyperphosphatemia could outweigh its suggested but unproven benefits.

METHODS To measure the interaction between vitamin D supplementation and phosphate during chemotherapy induction, a retrospective study was done. Demographic data; clinical information about the diagnosis; laboratory data regarding calcium, phosphate, and vitamin D concentrations; and medication histories were reviewed.

RESULTS A retrospective study of 41 children with ALL showed no statistically significant difference in the final phosphate concentrations that were obtained (4.41 mg/dL vs. 4.53 mg/dL, $p = 0.635$) with regard to their vitamin D supplementation status. Longitudinal effects with vitamin D and phosphate showed a trend toward increasing phosphate concentrations in patients who received supplemental vitamin D (0.035 vs. 0.010 mg/dL per day; $p = 0.102$).

CONCLUSIONS Vitamin D potentially poses a risk of hyperphosphatemia in children undergoing induction chemotherapy for ALL.

ABBREVIATIONS ALL, acute lymphoblastic leukemia; CI, confidence interval; TLS, tumor lysis syndrome

KEYWORDS ALL; hyperphosphatemia; precursor cell lymphoblastic leukemia-lymphoma; vitamin D

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Introduction

In recent years, vitamin D supplementation has been increasingly prescribed to pediatric oncology patients.¹ It has an essential role in maintaining bone health and growth, has been postulated to protect against autoimmune disease, and plays a role in innate immunity.² Acute lymphoblastic leukemia (ALL) patients are thought to potentially benefit from vitamin D supplementation because chemotherapy agents such as corticosteroids and methotrexate are thought to cause decreased bone density through decreased bone formation and increased bone resorption.³ These patients may develop vitamin D deficiency from long inpatient stays and decreased outdoor activities—reducing exposure to sunlight, thus impairing endogenous vitamin D synthesis—and a lack of appetite, causing decreased dietary intake of vitamin D. Endocrinopathies further affecting bone health can be caused by alkylating agents and cranial irradiation. However, at least one recent large randomized controlled trial showed that vitamin

D and calcium supplementation provided no benefit in bone mineral density over nutritional counseling alone in survivors of childhood ALL.⁴

One of the common complications with ALL treatments is tumor lysis syndrome (TLS). Tumor lysis syndrome occurs in about 25% of patients with leukemia and has potential life-threatening sequelae.⁵ Treatment of hematologic malignancies with chemotherapy causes a rapid release of intracellular contents, including potassium, nucleic acids, and phosphorous from dying cancer cells. This results in metabolic disarray, including hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia. Untreated hyperphosphatemia may lead to cardiovascular calcium phosphate precipitation, acute renal failure, and an increased risk of morbidity and mortality.^{6,7} In the cardiology literature there have been concerns that vitamin D supplementation can contribute to hyperphosphatemia.⁸

More recently at our center, our pediatric oncology group has observed an increased incidence of hyper-

Table 1. Baseline Characteristics of the Study Population

	Vitamin D Supplementation		Overall (n = 41)	p Value
	No, n = 19	Yes, n = 22		
Age, yr*	5.25 ± 3.04	7.32 ± 4.75	6.36 ± 4.14	0.101
Sex, female, No. (%)				
F	10 (52.6)	13 (59.1)	23 (56.1)	0.758
M	9 (47.4)	9 (40.9)	18 (43.9)	
Weight, kg*	21.88 ± 8.90	30.03 ± 20.20	26.25 ± 16.33	0.098
Height, cm*	115.89 ± 21.82	123.52 ± 27.07	119.99 ± 24.78	0.324
BSA, m ² *	0.83 ± 0.24	0.99 ± 0.43	0.92 ± 0.36	0.147
Diagnosis				
Pre-B ALL, No. (%)	17 (89.5)	20 (90.9)	37 (90.2)	1.000
T-cell ALL, No. (%)	2 (10.5)	2 (9.1)	4 (9.8)	
Baseline phosphate, mg/dL*	5.66 ± 1.19	5.25 ± 0.80	5.44 ± 1.01	0.219
Baseline Ca × Phos*	52.32 ± 12.49	47.91 ± 8.43	49.95 ± 10.61	0.202
Vitamin D concentration, mg/mL*	35.14 ± 6.64	21.89 ± 4.86	25.60 ± 8.04	0.001

ALL, acute lymphoblastic leukemia; BSA, body surface area; Ca, calcium (mg/dL); Phos, phosphate (mg/dL)

*Mean ± SD

phosphatemia in our ALL patients during induction chemotherapy, the first 4 weeks of treatment, sometimes requiring the use of phosphate binders. Elevated serum phosphate concentrations are expected within the first few days of induction therapy due to TLS, although they generally resolve quickly. In a number of our observed cases, patients were having hyperphosphatemia long after the TLS ended.

It was hypothesized that this hyperphosphatemia could be associated with vitamin D supplementation in induction, because vitamin D increases intestinal phosphate absorption.⁹ Furthermore, vitamin D supplementation and high serum concentrations of vitamin D have been shown to suppress the parathyroid hormone concentration, which would lead to decreased renal phosphate excretion.¹⁰ These two effects of high concentrations of vitamin D could synergistically contribute to increased serum phosphate. This association of vitamin D supplementation with hyperphosphatemia has not been studied in the pediatric oncology population. Here we share our observations about the potential unintended effect of hyperphosphatemia due to vitamin D supplementation.

Patients and Methods

This retrospective study was conducted in a large freestanding pediatric hospital, for patients admitted between September 2014 and September 2015. Eligible patients were older than 6 months and younger than 18 years, received a diagnosis of ALL, and were admitted to the inpatient service for induction chemotherapy. Patients without vitamin D (25-hydroxyvitamin D [25(OH)D]) measurements during the induction period were ex-

cluded. Local Institutional Review Board approved the protocol with the use of a waiver of informed consent for retrospective, deidentified data collection and analysis.

Data were collected for 29 days during induction therapy via retrospective chart review through an electronic medical record system. Information gathered included participant demographics, phosphate, calcium, calcium phosphate product, vitamin D supplementation, serum 25-hydroxyvitamin D concentrations, uric acid, alkaline phosphate, magnesium, blood urea nitrogen and serum creatinine, and dosage history of any phosphate binder or diuretics, because diuretics such as furosemide and acetazolamide can increase phosphate excretion. Because there was no standardized protocol for vitamin D supplementation, patients' records were queried for use of either ergocalciferol or cholecalciferol as supplements for vitamin D.

A *t*-test was used to compare differences for the mean of the phosphate concentrations and calcium phosphate products obtained between the vitamin D and non-vitamin D groups. The 95% confidence intervals (CIs) of the mean difference and 95% prediction intervals were calculated. Longitudinal effects and interactions for vitamin D and phosphate were determined with a linear mixed-effects model. Data were calculated from days 7 to 29 of therapy to exclude confounding from TLS. Statistical analysis was done using the R Statistical Programming Language.

Results

A total of 41 children were available for the study. The mean age was 6.36 years and ranged from 1.67 to 16 years. The study population comprised 23 fe-

Figure. Linear mixed-effects model curves demonstrating longitudinal effects and interactions between vitamin D and phosphate. Plot of individual patients' phosphate concentrations from days 7 to 29 of induction period with best-fit curves of the phosphate concentrations for the vitamin D supplementation and no vitamin D supplementation groups.

male and 18 male patients; 22 who received vitamin D supplementation and 19 who did not receive vitamin D supplementation; and 37 pre-B ALL and 4 T-cell ALL. There was no statistically significant difference between the vitamin D and non-vitamin D groups with respect to age, sex, weight, height, body surface area, diagnosis, and baseline phosphate and calcium phosphate product. However, baseline vitamin D concentrations were significantly different between the 2 groups (Table 1).

Calculated mean phosphate concentrations from the last concentrations recorded were 4.41 and 4.53 mg/dL for the vitamin D and non-vitamin D groups, respectively. The *t*-test revealed no statistically significant difference between the 2 groups (CI [-0.38, 0.61]; *p* = 0.635). The mean calcium phosphate products were 37.36 and 38.89 for the vitamin D and non-vitamin D groups, respectively (CI [-3.4, 6.4]; *p* = 0.538). However, analysis of longitudinal effects and interactions between vitamin D supplementation and phosphate exhibited an increasing trend in phosphate concentrations with prolonged vitamin D supplementation

in induction. The linear mixed-effects model showed that initial phosphate concentrations from day 7 of therapy were 3.58 and 4.12 mg/dL for the vitamin D and non-vitamin D groups, respectively. Phosphate concentrations increased by 0.035 mg/dL per day in the vitamin D supplementation group compared with an increase of 0.010 mg/dL per day in the non-vitamin D group (Figure and Table 2). Although a trend toward higher phosphate concentrations was observed, the rates were not statistically different (*p* = 0.102).

Discussion

This was the first study of which we are aware that explored whether there is a relationship between vitamin D supplementation and high serum phosphate concentrations in pediatric oncology. This study evaluated the risk for hyperphosphatemia because of its potential for serious consequences, such as calcium phosphate precipitation, cardiovascular calcifications, and increased morbidity and mortality in the acute

Table 2. Phosphate Trends Over Time From Days 7 to 29 of Induction of Vitamin D Supplementation and Non-Vitamin D Supplementation Groups

Day 7 Phosphate Value, mg/dL, Mean ± SEM	
Non-vitamin D group	4.12 ± 0.172
Vitamin D group	3.58 ± 0.230
Change in Phosphate mg/dL/day, Mean ± SEM	
Non-vitamin D group	0.010 ± 0.014
Vitamin D group	0.035 ± 0.016

setting of induction chemotherapy for leukemia, when hyperphosphatemia can also be a complication from TLS and renal insufficiency.

Vitamin D supplementation was used primarily in patients with low vitamin D concentrations (25-hydroxyvitamin D <30 ng/mL). Overall, phosphate concentrations increased between days 7 and 29 of induction therapy, with a greater increase in the vitamin D supplementation group. However, although there was a trend toward a difference in the rates of rise in the phosphate concentration, there was no statistically significant difference in the final phosphate concentrations between the vitamin D and non-vitamin D groups. Of note, none of the patients experienced significant effects from hyperphosphatemia or had a calcium phosphate product greater than 60 on vitamin D supplementation.

Some limitations to this study include small sample size and a lack of standardized protocols for laboratory evaluations and vitamin D supplementation. A lack of a standard protocol for obtaining serum phosphate evaluations and variable laboratory data points after patient discharge may have led to variability in the availability of data in the later weeks of induction. Furthermore, there was no standard protocol for when vitamin D supplementation was initiated, and the dosage and the type of vitamin D prescribed varied because of provider preference.

Our data suggest that although vitamin D supplementation is generally a safe treatment for children and adolescents with ALL in the induction phase of chemotherapy, it may increase the risk for hyperphosphatemia. In situations when hyperphosphatemia is a greater risk, such as with underlying renal insufficiency or TLS, it may be advantageous to delay vitamin D supplementation until after induction, when the risk for hyperphosphatemia is less. Larger randomized controlled trials with standard protocols for vitamin D supplementation and phosphate concentration monitoring would provide more information about the dosage, efficacy, and long-term safety of this treatment.

ARTICLE INFORMATION

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