Vitamin D Status in Children With Hemato-Oncological Diseases in Northern Finland

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Brief Report

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Introduction

The most important vitamin D source is cutaneously formed vitamin D_3 (cholecalciferol) after exposure to ultraviolet B (UVB) radiation from sunlight.[1] At latitudes above 37° North, UVB radiation decreases markedly during the winter months of November through February.[2] Thus, other sources of vitamin D, including dietary vitamin D_2 (ergocalciferol), vitamin D_3, and vitamin D supplements, are particularly important in Northern latitudes.[2]

Hypovitaminosis D is prevalent in both healthy and chronically ill Finnish children and adolescents.[3] Vitamin D insufficiency (serum 25-hydroxyvitamin D [S-25-OHD] <50 nmol/L) is common in pediatric patients with malignancy due to poor diet, lack of sunlight exposure, and toxic effects of cancer therapy.[4] A high body mass index (BMI) and older age may be additional risk factors.[3,5]

The aim of this single-center study was to evaluate the prevalence of vitamin D deficiency in children with hemato-oncological diseases, living in Northern Finland, for whom vitamin D supplementation of 10 µg/day was recommended.

Methods

This prospective cross-sectional study was conducted between November 2014 and February 2015 in a tertiary university hospital in Northern Finland. All the patients lived between northern latitudes 64° and 70°. In total, 106 patients were eligible, and 101 (95%) consented to participate. The patients were recruited from pediatric hematology and oncology outpatient and inpatient clinics, and all the patients were counseled to take vitamin D supplements of at least 10 µg daily. Ethical approval was given by the Regional Ethics Committee of the Northern Ostrobothnia Hospital District (Ethical Approval Number 84/2014). Written informed consent was obtained from all the individual participants included in the study. Parental consent was obtained for participants under 16 years.

Clinical and demographic data were collected from the patients' files. A questionnaire was used to obtain information on the use of vitamin D supplements and other supplements, as well as dietary intakes. Vitamin D and calcium intakes were calculated from information on fish, egg, milk, cheese, and other dairy product consumption.[6] Information on physical activity, bone fractures, the use of sunblock, and holidays in sunny regions was obtained via the questionnaire.

Blood samples were obtained from all the patients in the Nordlab laboratory of Oulu.[7] S-25-OHD, parathyroid hormone, alkaline phosphatase, calcium, and phosphate were analyzed. Vitamin D deficiency was defined as S-25-OHD <50 nmol/L, and satisfactory, target, and excessive levels were defined as 50 to 75 nmol/L, 75 to 200 nmol/L, and >200 nmol/L, respectively, based on other studies[2-4,7] (Table 1).

Statistical Analysis

Differences in continuous variables between the 2 groups were tested by the Mann-Whitney *U* test. An exact χ^2 test was used to compare distributions between the 2 groups. A linear regression analysis was used to define independent variables associated with S-25-OHD levels. The statistical analyses were executed with IBM

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Table 1. Serum 25-OHD Levels and Definitions. Use of Vitamin D Supplementation With the Study Subjects.

		Vitamin D Supplement		
Serum 25-OHD (nmol/L)	Definition	Yes, n = 93, n (%)	No, n = 8, n (%)	All, n = 101, n (%)
<50	Deficiency	10 (11)	3 (37)	13 (13)
50-74.9	Satisfactory	36 (39)	4 (50)	40 (40)
75-200	Target range	47 (50)	1 (13)	48 (47)

Abbreviation: S-25-OHD, serum 25-hydroxyvitamin D.

SPSS Statistics for Windows, Version 22.0.0.2 (IBM Corp, Armonk, NY).

Results

Characteristics of the Cohort

There were 61 males and 40 females, and their mean age was 7.9 years (range = 0.5-18.6, standard deviation [SD] = 4.9). All but one patient of African origin were Caucasians. Sixty-two patients had malignant disease: acute leukemia (n = 37), lymphoma (n = 4), solid tumor (n = 18), and central nervous system tumor (n = 3); and 39 patients had benign disease. Sixty-four patients had received chemotherapy, and 28 patients had ongoing chemotherapy. Stem cell transplantation was performed for 11 patients.

The patients were classified into 4 categories based on weight (underweight, healthy weight, overweight, and obese) according to age- and sex-adjusted BMI (ISO-BMI: 2-18 year olds) and weight for height percent (<2 year olds).[8] Eight of the patients were underweight, 69 were of healthy weight, 19 were overweight, and 5 were obese.

Vitamin D Status

The median S-25-OHD level was 72.0 nmol/L (interquartile range [IQR] = 58.0-84.5). Among the patients, S-25-OHD levels were inadequate in 13%, satisfactory in 40%, and at target levels in 47%, and none had excessive levels (Table 1). The S-25-OHD levels of boys and girls were not significantly different (median = 74.0 vs 70.5 nmol/L, $P = .853$). The S-25-OHD levels of those with malignant and benign diagnoses were also not significantly different (median = 71.5 vs 75.0 nmol/L, $P = .727$). Furthermore, the S-25-OHD levels of patients with fractures were not significantly different from those without fractures (median = 71.0 vs 72.5 nmol/L, $P = .894$). There was no association between S-25-OHD levels and weight ($P = .543$), but there was a negative association between S-25-OHD levels and age ($P < .001$). When age increased by 1 year, the S-25-OHD level decreased by 1.6 nmol/L (95% confidence interval = 0.7-2.4). The mean serum parathyroid hormone level was 36.5 ng/L, and it was not associated with S-25-OHD levels ($P = .187$).

Vitamin D Intake From Supplements and Food

The median vitamin D supplement intake was 10.0 μg/day (IQR = 10.0-10.0). Among the patients, 92% used vitamin D supplements. Of those, 91% (85/93) used ⩾10 μg per day, and 16% (15/93) used 20 μg or more. Nine of 10 patients with S-25-OHD levels below 50 nmol/L used <10 μg/day, and 3 of 8 patients who did not take vitamin D supplements had S-25-OHD levels below 50 nmol/L. The S-25-OHD levels of the patients who took vitamin D supplements were higher (median = 75 nmol/L, IQR = 61.5-86.0 nmol/L) than those of the patients who did not take such supplements (median = 55.5 nmol/L, IQR = 42.0-61.8, $P = .005$). Most of the patients taking vitamin D supplements (n = 93) had satisfactory S-25-OHD levels (39%) or target levels (50%). In contrast, most of the patients who did not take vitamin D supplements (n = 8) were vitamin D deficient (37%) or had only satisfactory S-25-OHD levels (50%; $P = .028$).

According to the dietary questionnaire, the median total vitamin D intake, including both supplements and food, was 18.8 μg/day (IQR = 16.1-24.9; Table 2). There was no association between vitamin D intake and age ($P = .799$). The S-25-OHD level increased by 0.6 nmol/L when overall vitamin D intake increased by 1 μg ($P = .022$). Figure 1 shows the association between overall vitamin D intake and S-25-OHD levels in children with malignant ($\beta = 0.4$, $P = .254$) and benign ($\beta = 1.0$, $P = .009$) diseases. The mean level of dietary vitamin D resulting in the target level of S-25OHD (>75 nmol/L) was 22.5 μg (SD = 7.6 μg). The lowest level resulting in vitamin D sufficiency was 11.4 μg. The median total calcium intake per day was 1.084 mg (IQR = 825-1545).

Discussion

This cross-sectional study examined vitamin D intake and levels in a prospective cohort of children from Northern Finland who had hemato-oncological diseases

Table 2. Calculations of Nutritional Vitamin D and Calcium Intake. Overall Nutritional Intake Is the Sum of Daily Doses.

Nutrition and Portion Size	Vitamin D (μg)	Calcium (mg)	
Milk, 1 dL	1	120	
Yogurt and other dairy products, 1 dL	1	120	
Egg	1.3	—	
Fish, portion 60/120 g[a]	5	—	
Cheese slice 10 g	—	91	
Overall Nutritional Intake	**n (%)**	**Mean**	**SD**
Fish (times/month)[b]	96 (96)	3.8	2.9
None	4 (4)		
Milk (dL/day)		5.7	3.3
Dairy products (dL/day)		2.2	2.4
Cheese slices (pieces/day)		2.6	3.1
Eggs (pieces/week)		1.3	1.6

Abbreviation: SD, standard deviation.
[a]For children <12 years old, fish portions are 60 g; for children ⩾12 years old, fish portions are 120 g.
[b]Oily fish + white fish + oily and white fish.

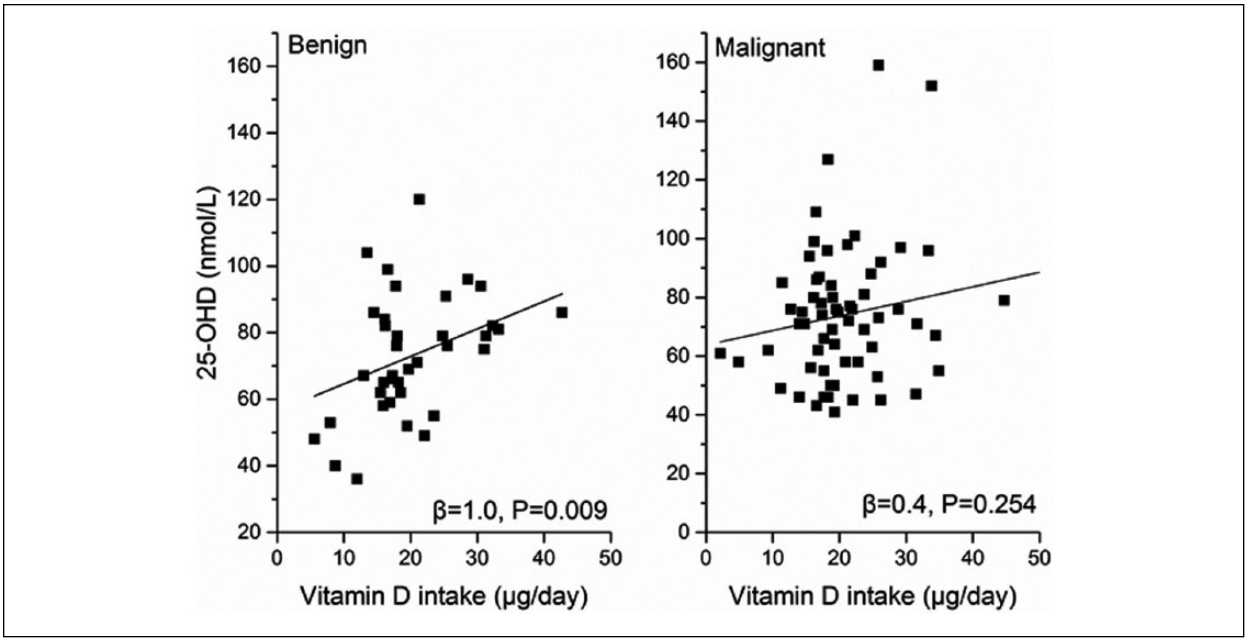

Figure 1. Association between overall vitamin D intake and S-25-OHD levels in children with malignant (A; β = 0.4, *P* = .254) and benign (B; β = 1.0, *P* = .009) diseases. S-25-OHD rose to 0.6 nmol/L when reported overall vitamin D intake increased by 1 μg (*P* = .022).
Abbreviation: S-25-OHD, serum 25-hydroxyvitamin D.

and were instructed to take a vitamin D supplement (10 μg/day). Vitamin D levels were satisfactory in 87% of the patients, and almost half of the patients had S-25-OHD within the target range. As expected, S-25-OHD levels were higher when vitamin D supplements were taken. Vitamin D deficiency was observed in only 13% of the patients. Vitamin D supplementation has been recommended in Finland since the 1940s.[9] The Current Finnish Nutritional Council guidelines recommend vitamin D supplementation for all children and adolescents, with 10 μg/day recommended for infants between 2 weeks and 2 years and 7.5 μg/day for children between 2 and 18 years.[10] Vitamin D supplementation of 10 μg/day is recommended by our center for children receiving treatment for hemato-oncological diseases. This recommendation is based on earlier findings, which showed

that such patients had a high risk of vitamin D insufficiency.[4] Some of the patients received higher doses of vitamin D because the benefits of adequate vitamin D levels have received a great deal of public attention in Finland. Thus, the doses that some parents gave their children were higher than those officially recommended. In the present study, the median total vitamin D intake, including vitamin D from supplements and food, was surprisingly high (18.8 μg/day). This can be explained by the high level of consumption of fish and the high concentration of vitamin D in dairy products (1 μg/dL). Among the vitamin-D-deficient patients, 90% reported vitamin D supplementation of ⩽10 μg/day.

S-25-OHD levels decreased with increasing age, suggesting that older children have an increased risk of having inadequate vitamin D levels. Therefore, a higher dose of vitamin D supplementation, up to 20 μg/day, should be considered for these children. Previous studies demonstrated that both healthy and chronically ill adolescents had a high risk of vitamin D deficiency.[3,11] Vitamin D insufficiency has been reported to be common with high BMIs and among allogeneic stem cell transplantation patients.[12] In the present study cohort, we did not observe similar findings.

Conclusion

Vitamin D supplementation of at least 10 μg/day resulted in a satisfactory vitamin D status in most of the patients (87%). None of the patients had excessive levels, even with supplemental doses that exceeded 10 μg/day. Vitamin D supplementation can be recommended for chronically ill pediatric hemato-oncological patients, especially at latitudes where UVB exposure is insufficient. A higher dose than 10 μg/day may be beneficial, especially in older children who have lower vitamin D levels than younger children.

Author Contributions

JL, MM, TP, OM, AHS and RN designed the study. JL, MM and RN were responsible for enrolling the patients in this study and collecting the data. JL and RN prepared the manuscript. TP was responsible for the data analysis. All authors edited and approved the final manuscript. All authors are accountable for the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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