Low Plasma Vitamin D (25-Hydroxycholecalciferol) in Children and Adolescents Diagnosed with Cancer: A Case-Control Study

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Abstract

Introduction: Children and young people with cancer are less likely to spend time outdoors and they may also have a limited dietary intake. In addition, some cancer treatments can increase vitamin D catabolism.

Objectives: This study aimed to investigate if there was an increased risk of poor vitamin D status in newly diagnosed childhood cancer patients compared to healthy controls in Scotland.

Methods: Plasma 25 (OH) D was measured in children and adolescents during initial cancer treatment and compared to 33 healthy controls. Vitamin D deficiency was classified as plasma 25 (OH) D <25 nmol/l, with a plasma 25 (OH) D of 25-49 nmol/l classified as insufficient.

Results: Forty-one patients (median age 3.8 years, IQR 1.9-8.0) were diagnosed with cancer, 63% were male. Twenty-three (56 %) had solid tumours, 18 (44%) had haematological cancers. Median (IQR) plasma 25 (OH) D at recruitment was 37.0 nmol/l (23.7-58.2). Ten patients (24%) had vitamin D deficiency and 17 (41%) patients were classified as insufficient. The median (IQR) plasma 25 (OH) D in the control group (n = 33) was 37.5 nmol/l (29.0-58.0). Six controls (18%) had vitamin D deficiency and 14 (42%) were classified as having insufficient results. Plasma 25 (OH) D did not differ (p > 0.05) between the patients and the controls.

Conclusions: Almost three in four Scottish children treated for cancer had vitamin D deficiency or insufficiency; there was no increased risk of poor vitamin D status compared to healthy controls. Assessment of vitamin D status at diagnosis and in response to the course of treatment appears necessary to optimise nutritional management.

Keywords: Children; Cancer; Vitamin D; Nutrition screening

Abbreviation: ICCC-3: The International Classification of Childhood Cancer, third edition; CNS: Central Nervous System; NHS: National Health Service; NS: Nutrition Support; PTH: Parathyroid hormone; RHSC: Royal Hospital for Sick Children

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Introduction

Vitamin D is currently attracting a great deal of scientific and media attention. Due to lack of sunlight exposure plus very few foods being fortified with vitamin D in the UK, children and adults are at high risk of being deficient or insufficient, especially in high latitude countries [1,2]. Vitamin D deficiency causes bone mass loss [3,4] with detrimental effects on bone growth and development, particularly important in children. Moreover, skeletal problem such as osteoporosis, reduced bone mass density and fractures, are a well-known issue in children with cancer [5-8] and vitamin D insufficiency has been suggested as a potential risk factor [5,9-12].

Children treated for cancer have an increased risk of poor vitamin D status because they may have reduced vitamin D_3 synthesis on the skin (limited time spent outdoors, need to protect the skin from UV rays due to the photosensitivity caused by some treatments), or reduced dietary intake or absorption as consequence of drug related side effects and liver and chemotherapy related kidney damage. Furthermore, patients treated for leukaemia may have a higher risk of deficiency [13] due to the increased vitamin D catabolism caused by steroids [14]. Therefore, given the increased risk for poor vitamin D status in childhood cancer patients and the pivotal role of vitamin D in growth and development it may be essential to maintain adequate vitamin D status from diagnosis throughout treatment. This case control study aimed to investigate (i) the vitamin D status of newly diagnosed childhood cancer patients; (ii) Whether there is an increased risk of poor vitamin D status in newly diagnosed childhood cancer patients compared to healthy childhood controls within the same geographical population.

Materials and Methods

Patient Selection and recruitment

In this study inclusion criteria included: (i) children under the age of 18 years,(ii) a cancer diagnosis according to The International Classification of Childhood Cancer, third edition (ICCC-3) [15] or Langerhans cell histiocytosis tumours, (iii) diagnosed between August 2010 and March 2013 (iv) attending the regional centre for Haematology and Oncology at the Royal Hospital for Sick Children (RHSC), Edinburgh (SE Scotland service - NHS Lothian, NHS Borders, NHS Fife, NHS Tayside) and of high northerly latitude at 55°N. Exclusion criteria were: (i) children on palliative care, (ii) and patients with unavailable plasma 25(OH)D result.

The study had ethical approval from NHS Scotland. The child and the parents or guardians were provided with full written information regarding the project to give them the opportunity for 'informed consent'. Patient's data remained confidential and all data was anonymised.

Anonymised control data was obtained from a case-control study on Vitamin D in children with epilepsy compared to children without epilepsy. Controls were recruited from randomly invited healthy children who were attending the RHSC Emergency Department and who were having blood tests done as part of their assessment. At enrolment, control volunteers had 25(OH) D, parathyroid hormone (PTH), calcium, phosphate and magnesium checked; volunteers were invited for reassessment at six months post-baseline.

Data Collection

Patients were recruited as soon as diagnosis was confirmed (the duration of the study was 3 years). Clinical information including diagnosis, length of treatment and the need for nutrition support and demographic data, including age, gender and ethnicity were collected from medical and dietetic notes. Due to the limited numbers available in the study and the wide range of childhood cancer diagnosis, the cohort was grouped according to the wider definition of solid tumours (Lymphomas, CNS, Neuroblastoma, Renal, Bone, Soft tissue sarcomas, Germ cell tumour and Langerhans cell histiocytosis) and haematological cancers (Leukaemias). Measurements were taken at recruitment. Summer months were defined as the beginning of April to the end of September [16] Blood was taken by NHS staff for 25(OH) D, PTH, calcium, phosphate and magnesium when the patient had venepuncture for routine blood test or therapy.

Calcium, phosphate and magnesium were analysed using the Abbott Architect c8000 by the biochemistry department, Royal Hospital of Sick Children, PTH was analysed using the Immulite 2000 Intact PTH technique by the biochemistry department, Royal Infirmary

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of Edinburgh and plasma 25(OH) D was analysed using the liquid chromatography tandem mass spectrometry technique by the Clinical Chemistry Department, Royal Infirmary of Glasgow using standard techniques. Due to the limited sample size the data were combined to look at differences between the control and cancer cohort. For the controls, when both winter and summer samples were available, the average was used for statistical analysis. The results were compared with the reference values recommended in the British Paediatric and Adolescent bone group guidelines, which defines 25 (OH)D levels suboptimal (50-75 nmol/L), insufficient (25-50 nmol/L) and deficient (< 25 nmol/L).

Data analysis

The data was analysed using The Statistical Package for Social Studies (IBM-SPSS for Windows Statistics, version 19 UK).The data were tested for normal distribution by the Shapiro-Wilk Test. The results are presented as mean (± SD) for normally distributed data and median (IQR) when not normally distributed. Descriptive statistics were used to assess vitamin D status, plasma calcium, phosphate, magnesium status and parathyroid function (aim i). Comparison within the same group was carried out using the Wilcoxon signed-rank test. Comparison between control and childhood cancer groups was carried out using the Mann-Whitney test (aim ii). STROBE guidelines were followed for the presentation of the data (www.strobe-statement.org).

Results

A flow diagram of the cohort is shown in Figure 1; there was not a difference in gender distribuition, ethicity or age at diagnosis (p > 0.05) between the participants and non-participants. A total of 41 (59%) patients were included in the study with median (IQR) age at diagnosis 3.8 (1.9-8.0) years; 73% (n = 30) of the total cohort was male. Twenty-three patients (56%) had solid tumours and 18 (44%) had hematological cancers. All patients were white. Due to the time lapse between approaching the families and recruitment, all the participants were on cancer treatment at the time the blood was collected (mean time on treatment 14.6 days; IQR 7.3-21.9). Of note 13 patients (72%) in the hematological group were treated with steroids.
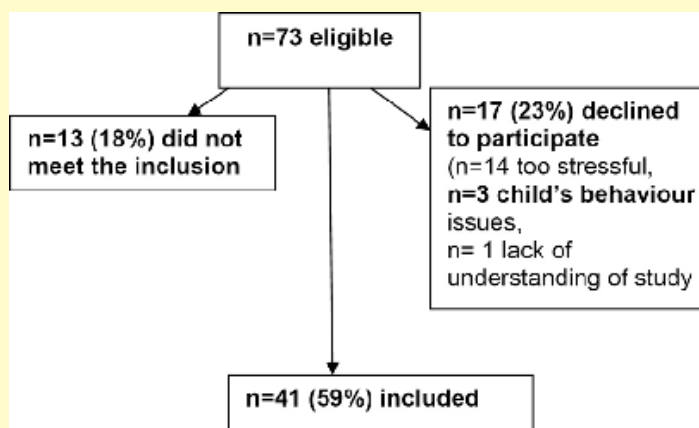

Figure 1: *Flow diagram showing all children and young people in cohort.*

There were 33 healthy volunteer control subjects (age median 7.1, IQR 4.7–9.08); 45% (n = 15) were male. Thirty-one (94%) were white and 2(6%) were non-white.

Fourteen patients (34%) were on some type of nutrition support (providing 0.7 ug vitamin D/100 kcal to 1.9 vitamin D/100 kcal) at the time of data collection (n = 5 oral calorie supplements; n = 5 enteral tube feeding; n = 1 multivitamin; n = 2 food fortification; n = 1 enteral and parenteral nutrition). Median (IQR) time on nutrition support was 1.8 days (0.0-8.6). Table I shows the prevalence of deficient and insufficient vitamin D results in both control group and childhood cancer group according diagnostic group and nutrition support status.

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			Median (IQR)	Deficient n (% of total diagnostic group)	Insufficient n (% of total diagnostic group)
controls	Cases	n=31*	37.5 (29.0-58.0)	6 (18)	14 (24)
Childhood cancer	Cases	n=41*	37 (23.7-58.2)	10 (24)	17 (41)
	Diagnostic group	Solid n=23**	35.0 (16.0-60.0)	6 (29)	8 (38)
		Haematological n=18**	38.0 (27.7-52.2)	4 (22)	9 (50)
	NS	Not on NS n=27***	36.0 (23.0-58.0)	8 (44)	10 (55)
		On NS n=14***	39.0 (29.7-62.5)	2 (22)	7 (77)

*p>0.05

**p>0.05

***p>0.05

Table 1: *Plasma 25(OH) D results and prevalence of vitamin deficiency and insufficient at recruitment according to group, gender and nutrition support (NS).*

Twenty (49%) patients provided summer samples and 21 (52%) provided winter samples, and none provided both. The median (IQR) plasma 25 (OH) D in the childhood cancer cohort was 37.0 nmol/l (23.7-58.2) and 27 patients (66%) were either vitamin D deficient or insufficient; 10 (24%) had vitamin D deficiency and 17 (42%) were classified as having insufficient results. In the childhood cancer group, there were no statistical significant (p > 0.05) differences between plasma vitamin D levels and the following variables: diagnostic groups (p > 0.05) (Table I); summer (median 40.0, IQR 31.0-70.5) and winter plasma 25 (OH) D (nmol/l) (median 37.0, IQR 19.0-51.5). Finally there were no statistically significant differences between patients receiving nut support and those who were not (p > 0.05).

Thirty-three control samples were obtained. Seventeen (51%) controls provided winter samples 6 (18%) controls provided winter and summer samples and 10 (30%) provided summer only. The median (IQR) plasma 25(OH) D in the control group was 37.5 nmol/l (29.0-58.0). 20 participants (60%) were either vitamin D deficient or insufficient; 6 (18%) had vitamin D deficiency and 14 (42%) were classified as having insufficient plasma 25(OH) D. There was a significant difference (p < 0.05) between the plasma 25(OH) D (nmol/l) during summer months (median 56.5, IQR 45.5-78.0) and winter months (median 26.0, IQR 18.0-46.5.5). Plasma 25(OH) D was not significantly different between the healthy controls and the childhood cancer patients as a whole, according to season or when broken down into diagnostic groups (p > 0.05 for all).

Figure 2 and 3 shows the plasma PTH, calcium, phosphate and magnesium levels according to diagnostic group and the control. PTH was available for 38 patients (median 3.3 pg/ml; IQR 2.2-4.6)(Figure 2). Of all the patients with vitamin D deficiency at recruitment (n = 10), 30% (n = 3) had secondary hyperparathyroidism. There was no statistical significant correlation between PTH and 25(OH) D variables (p > 0.05; r = 0.18) in those patients with 25(OH) D < 50 nmol/l. Three patients with vitamin D insufficiency had low plasma PTH. In the control group one patient with vitamin D insufficiency had low plasma PTH.

Given the role of vitamin D in calcium absorption and metabolism, calcium was also measured. Median (IQR) plasma calcium was 2.3 mmol/l (2.1-2.3). Of the patients with solid and haematological cancers, 17% (n = 4) and 27% (n = 5) respectively, had hypocalcaemia upon recruitment. Comparison between groups was not possible because of the difference in age ranges and the small sample size. Six patients with either insufficient or deficient plasma 25(OH) D had hypocalcaemia below the normal ranges (Figure 3). Hypophosphataemia can be caused by vitamin D deficiency therefore plasma phosphate was assessed. Median (IQR) plasma phosphate was 1.3 mmol/l (1.1-1.5). Plasma phosphate (mmol/l) was below normal ranges in 22% (n = 5) patients in the solid group and 10% (n = 17) in the haematological group (Figure 3). Although there was no significant correlation between plasma phosphate and 25(OH) D (p

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> 0.05) at any point in time, 2 patients with low plasma 25(OH) D had also hypophosphatemia. Median (IQR) plasma magnesium was 0.86 (0.79-0.93). Plasma magnesium was below normal ranges for only 1 (6%) patient in the haematological group. Plasma calcium, phosphate and magnesium were within normal ranges for the control group (Figure 3).
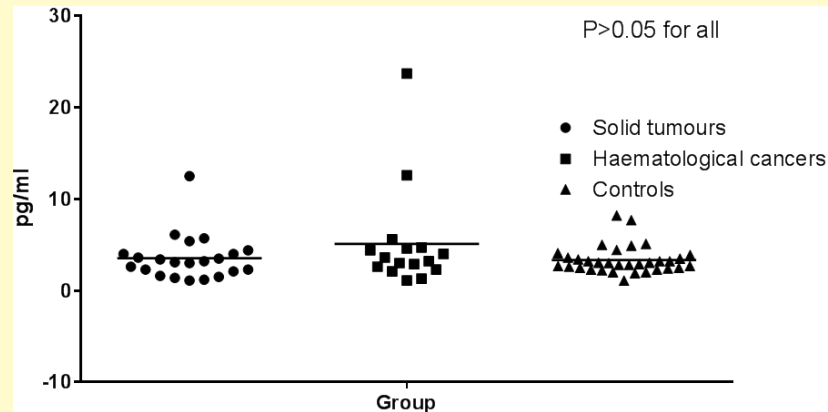

Figure 2: *PTH levels at recruitment according to diagnostic group (p > 0.05 for all).*
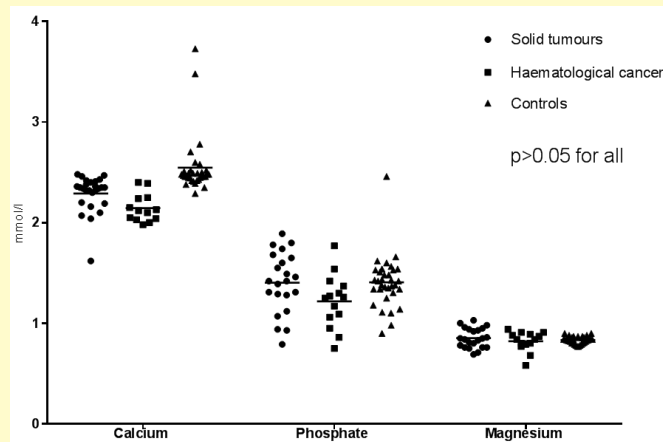
Figure 3: *Plasma calcium, phosphate and magnesium levels at recruitment according to diagnostic group (p > 0.05 for all).*

Discussion

This case-control study has shown a high prevalence of deficiency and insufficiency serum 25 (OH) D in newly diagnosed childhood cancer patients. However, the vitamin D status of the childhood cancer patients was comparable to that of the healthy controls from the same population. These findings suggest that newly diagnosed cancer patients in high latitudes in the Northern hemisphere such as Scotland are at no higher risk of poor vitamin D status than healthy children from the same geographical area.

Remarkably, this study did not indicate any seasonal differences in plasma vitamin D in the childhood cancer cohort, unlike that observed in the healthy controls, and as has been reported elsewhere [17]. In healthy populations, plasma 25(OH) D concentrations show a marked seasonal variation, being lowest during winter and highest during summer [16]. In the UK, the population relies on

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body stores and dietary vitamin D to maintain vitamin D status during winter months. These findings support the idea that children in the period prior to diagnosis and during cancer treatment do not have enough sun exposure to allow vitamin D synthesis. Therefore, it highlights the inability of the child to replenish their vitamin D stores during the summer months and the resulting importance of dietary sources to meet vitamin D requirements in this cohort.

It is important to note that the proportion of winter samples in the controls was higher compared to the childhood cancer group (30% vs 51%) which may have affected the results causing an increased risk of poor vitamin D status in the control group.

Although plasma level between patients receiving nutrition support and those who were not were comparable, the prevalence of vitamin D deficiency was higher in the non-nutrition support group. However, considering the limited sample size and the small length of nutrition support treatment, it is not possible to draw any conclusion on the role of nutrition support supplementing vitamin D and vitamin D status.

This study showed that vitamin D deficiency was associated with secondary hyperparathyroidism in some patients in the childhood cancer. If left untreated, secondary hyperparathyroidism can lead to severe clinical problems such as osteomalacia and rickets, so longitudinal monitoring during cancer treatment and eventual supplementation vitamin D is essential to minimise bone mass loss and optimise children's and adolescents' growth.

A limitation of this study is that some children were already on treatment at the time of blood sampling. However the very short course of treatment at the time of sampling is unlikely to have affected vitamin D status.

Although the results have not shown a specific increased risk in the childhood cancer patients at diagnosis, plasma vitamin D has been reported to be insufficient in acute lymphoblastic leukaemia (ALL) patients [5,6,18,19] and solid tumours patients at both diagnosis [5,6,18,19] and in remission phase [6,11,17].

Halton and co-workers [5] in a study conducted in Ontario, Canada (43.2°N), observed vitamin D plasma levels below normal range in 70% of children (n = 40) treated for ALL at both diagnosis, and after one year of treatment. A lower prevalence of plasma vitamin D deficiency has been reported in another study conducted in Rotterdam, Netherland (51.9°N) [20], where only 20% and 4.5% of ALL patients (n=61) had decreased plasma vitamin D at diagnosis and during therapy respectively. Moreover, some literature suggests an increased risk for poor vitamin D status in haematological patients after treatment [19] which highlights the possible detrimental effect of steroid therapy on vitamin D status [14] This would put this group of patients at even higher risk of vitamin D deficiency than their solid tumour counterparts.

The difference in the findings compared to the literature may be explained by the latitude of the countries where the studies were conducted. The study centre being more southerly than the others [5,20] may have led to an increased poor vitamin D status for both patients and controls.

As discussed, it is plausible that childhood cancer patients are not exposed to sun light, even before diagnosis, due to the debilitating effects of undiagnosed disease and then side effects of treatments. Moreover, it is unlikely that the diet adequately compensates for the luck of sun exposure, considering the limited sources of dietary vitamin D and the poor nutritional status during cancer therapy. Therefore, considering the increased risk of poor vitamin D status in the high latitude countries, the well-known increased risk of vitamin D deficiency during cancer therapy and the need to sustain growth and development during childhood cancer therapy, monitoring of vitamin D status from diagnosis and eventual supplementation may be essential, particularly in those countries at high latitudes.

Although these findings and the literature suggest the need for screening and potential supplementation of vitamin D, the efficacy and the safety of vitamin D supplementation to improve vitamin D status in children treated for cancer has not yet been proven. In a study [19] carried out in 40 patients affected by ALL and solid tumours, vitamin D supplementation was reported to improve vitamin

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D status in all patients apart from the haematological group. This differential response to vitamin D supplementation observed among the diagnostic groups may be explained by the increased vitamin D catabolism in ALL patients consequent to steroid therapy [13].

However, pharmacological doses given for a prolonged period of time may lead to increased plasma 25 (OH) D accompanied by hypercalcaemia. It has been shown that patients with granuloma forming diseases might develop vitamin D toxicity witnessed by hypercalcaemia at relatively low plasma 25(OH) D as a consequence of unregulated 1,25(OH) 2D production [21,22]. Therefore, it has been suggested [23] that pharmacological doses should be not prescribed to this patients group. It is now pivotal to establish if the current guidelines for vitamin D supplementation for healthy children applies to the cancer patients with other types of malignancies. Future research should aim to assess nutritional status from diagnosis throughout the treatments and monitor the changes in vitamin D status in response to supplementation according to specific treatments protocols and childhood cancer diagnosis.

Conclusions

This study demonstrated that newly diagnosed high latitude (Scottish) childhood cancer patients have a poor vitamin D status. However, the prevalence of low plasma vitamin D was comparable to the healthy controls. Extended longitudinal monitoring of vitamin D status in children with cancer should be considered, and supplementation likely needed. Furthermore, research is needed to clarify the role of nutrition supplementation and support in maintaining normal vitamin D status.

Statement of Authorship

DCW designed the study; IP created the database; IP and RRI collected the data from the cancer patients; CB collected the control data; JM, MB and DCW supervised the study. IP and DCW prepared the manuscript with additions, comments and corrections by all the authors. All authors have read and approved the final draft. DCW is the guarantor of the article.

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