

Evaluation of the relation between serum 25-OH vitamin D levels and clinical findings of febrile neutropenia in childhood cancer patients

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Abstract

Objective: This retrospective study aimed to evaluate the association between serum 25-OH vitamin D (25OHD) levels and the clinical course of febrile neutropenia in children with cancer.

Materials and Methods: Seventy-seven pediatric cancer patients with febrile neutropenia and 25OHD levels measured at diagnosis were included. Forty-four healthy children served as controls. Clinical data including febrile neutropenia duration and related parameters were retrospectively reviewed.

Results: The study included 77 patients (44 male, 33 female) and 44 controls (29 male, 15 female). Spearman correlation analysis revealed a significant negative correlation between 25OHD levels and neutropenia duration ($r=-0.249$, $p=0.029$) and number of febrile days ($r=-0.253$, $p=0.027$). However, multivariate regression analysis showed that 25OHD level was not an independent predictor of these outcomes; leukemia diagnosis was the only independent predictor ($p<0.001$).

Conclusion: Lower 25OHD levels were associated with longer neutropenia duration and more febrile days. However, this association was not independent of diagnosis. Vitamin D monitoring in pediatric cancer patients may be clinically relevant, but prospective studies are needed to confirm its role.

Keywords: children, cancer, febrile neutropenia, vitamin D, immunomodulation

Introduction

Vitamin D regulates cell differentiation and proliferation through its nuclear receptor. Beyond its role in bone metabolism, it has anti-inflammatory and immunomodulatory properties with effects on cancer, autoimmunity, infections, and cardiovascular health [1-3].

Deficiency is linked to increased risk of viral respiratory infections and sepsis [4]. Vitamin D receptors are

expressed on T cells, B cells, macrophages, and dendritic cells, suggesting a direct role in innate and adaptive immunity.

Febrile neutropenia causes 5% mortality in solid tumors and up to 10% in hematological malignancies. It is a critical, treatment-limiting complication in pediatric oncology [5]. Pediatric cancer patients are at high risk for vitamin D deficiency due to reduced sun exposure, chemotherapy-related malabsorption, and increased metabolic demands.

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Vitamin D deficiency is prevalent in pediatric oncology patients and may negatively affect clinical outcomes [6,7]. However, its specific impact on febrile neutropenia in children with cancer is not well established. This study aimed to investigate this association.

Materials and Methods

Study design and patients

This was a retrospective, observational, single-center study. The patient group consisted of children aged 0-18 years hospitalized in the pediatric oncology clinic of Dr. Sami Ulus Research and Education Hospital between January 2014 and January 2018, with 25OHD levels measured at cancer diagnosis.

The control group included 44 healthy children without chronic disease and was used to compare baseline 25OHD levels with those of cancer patients at diagnosis, providing a reference for the prevalence of vitamin D deficiency in this population.

The study focused on patients who did not receive vitamin D supplementation during the first two months after diagnosis but experienced febrile neutropenia. We analyzed the timing of febrile neutropenia onset, its severity, and its duration.

Definitions

Febrile conditions were defined as a body temperature $>38^{\circ}\text{C}$ measured via the tympanic route. Neutropenia was defined as an absolute neutrophil count (ANC) $<500/\text{mm}^3$, or an ANC $<1500/\text{mm}^3$ predicted to fall further. Neutropenia severity was classified as: severe (ANC $<500/\text{mm}^3$), moderate (ANC $500\text{-}1000/\text{mm}^3$), or mild (ANC $1000\text{-}1500/\text{mm}^3$).

25OHD levels were measured using liquid chromatography. Vitamin D status was classified as: deficient (≤ 15 ng/ml), insufficient (15-20 ng/ml), sufficient (20-100 ng/ml), and toxic (>150 ng/ml) [8]. The cut-off of ≤ 15 ng/ml for deficiency was chosen based on the classification recommended by the American Academy of Pediatrics and used in Turkish pediatric guidelines at the time of the study. Although a threshold of 20 ng/ml is more commonly used in recent literature, our cut-off reflects the standard applied in

clinical practice during the study period. None of the patients were receiving vitamin D supplements at the time of febrile neutropenia episode.

Data collection

The duration of neutropenia, number of days with fever, presence of complications (e.g., mucositis, abscesses), use of glycopeptides and antifungals, and G-CSF (granulocyte colony-stimulating factor) use were recorded from patient files.

Statistical analysis

Data were analyzed using SPSS (Statistical Package for the Social Sciences). Normality was assessed using the Shapiro-Wilk test. As all continuous variables showed non-normal distribution ($p < 0.05$), non-parametric tests were used throughout. The Mann-Whitney U test was used for comparisons between two groups, and the Kruskal-Wallis test for comparisons among three or more groups. Spearman correlation analysis was performed to assess the relationship between 25OHD levels and continuous outcome variables. Multivariate linear regression analysis was conducted to identify independent predictors of neutropenia duration and number of febrile days, including 25OHD level, diagnosis (leukemia vs. other), sex, and G-CSF use as covariates. Results are reported with beta coefficients, standard errors, 95% confidence intervals, and p-values. Fisher's Exact test was used for categorical data. Statistical significance was set at $p < 0.05$.

Ethical approval

The study was approved by the Health Sciences University Ankara Pediatrics Hematology and Oncology Training and Research Hospital Ethics Committee (approval number: 2018-100, date: 09.07.2018) and was conducted in accordance with the Declaration of Helsinki. This study was conducted retrospectively through review of patient medical records.

Results

There were 77 children (44 male, 33 female) in the patient group and 44 children (29 male, 15 female) in the control group. The mean age of the patient group was 7.99 ± 5.1 years, while the control group had a mean

age of 8.36 ± 2.48 years ($p=0.197$). Among the patients, 42 had leukemia (54.5%), 13 had lymphoma (16.9%), and 22 had solid tumors (28.6%).

The mean 25OHD level in the patient group was 15.82 ± 8.63 ng/ml, while in the control group it was 18.08 ± 9.41 ng/ml ($p=0.060$). Vitamin D deficiency (25OHD <20 ng/ml) was found in 63.6% ($n=49$) of patients and 47.7% ($n=21$) of controls. Among the patients, 66.6% ($n=28/42$) with leukemia and 60% ($n=21/35$) with lymphoma or solid tumors had insufficient 25OHD levels ($p=0.120$).

The mean white blood cell count was $6182 \pm 1091 \times 10^3/\mu\text{L}$, the mean ANC at onset of febrile neutropenia was $938 \pm 468 \times 10^3/\mu\text{L}$, and the mean ANC at recovery was $2432 \pm 916 \times 10^3/\mu\text{L}$. The mean duration of neutropenia was 19.83 ± 16.65 days, and the mean number of days with fever was 4.66 ± 2.62 days.

In patients who received vitamin D prophylaxis during their first year of life (18.2%), the mean 25OHD level was 27.79 ± 7.39 ng/ml, compared to 13.16 ± 6.36 ng/ml in those who did not (81.8%) ($p<0.001$).

As 25OHD levels decreased, both the duration of neutropenia and the number of days with fever increased significantly ($p<0.05$) (Table 1). Patients with severe neutropenia (ANC $<500/\text{mm}^3$) had the lowest mean 25OHD levels (13.45 ± 7.76 ng/ml) compared to moderate (15.88 ± 10.88 ng/ml) and mild groups (16.69 ± 7.81 ng/ml), although this did not reach statistical significance ($p=0.164$).

In patients with leukemia, neutropenia duration was significantly longer (26.01 ± 19.65 vs 12.43 ± 7.15 days; $p=0.031$) and febrile days were more frequent (5.71 ± 2.91 vs 3.39 ± 2.25 days; $p=0.032$) compared to non-leukemic patients (Table 2).

Table 1. Clinical evaluation based on 25-OH vitamin D levels.

	<15 ng/ml mean$\pm$SD	15-20 ng/ml mean$\pm$SD	>20 ng/ml mean$\pm$SD	p-value
Duration of neutropenia (days)	22.40 $\pm$ 16.44	18.00 $\pm$ 15.49	16.43 $\pm$ 17.15	0.044*
Fever ($^{\circ}\text{C}$)	38.4 $\pm$ 0.43	38.6 $\pm$ 0.48	38.6 $\pm$ 0.41	0.059
Number of febrile days	5.14 $\pm$ 2.27	5.12 $\pm$ 3.13	3.86 $\pm$ 2.89	0.015*
WBC ($10^3/\mu\text{L}$)	5859.52 $\pm$ 9747.02	3402.86 $\pm$ 1625.92	7363.21 $\pm$ 13679.91	0.744
ANC at onset ($10^3/\mu\text{L}$)	903.10 $\pm$ 468.27	1227.14 $\pm$ 234.36	919.64 $\pm$ 415.09	0.205
ANC at recovery ($10^3/\mu\text{L}$)	2289.52 $\pm$ 643.39	2742.86 $\pm$ 945.60	2570.71 $\pm$ 1208.70	0.392

ANC: Absolute neutrophil count, WBC: White blood cell. *Statistically significant ($p<0.05$). p-values were calculated using the Kruskal-Wallis test.

Table 2. Clinical evaluation according to diagnosis.

	Leukemia (n=42 mean$\pm$SD	Others (n=35) mean$\pm$SD	p-value
25OHD level (ng/ml)	15.18 $\pm$ 9.00	16.59 $\pm$ 8.24	0.481
Duration of neutropenia (days)	26.00 $\pm$ 19.65	12.43 $\pm$ 7.15	0.031*
Fever ($^{\circ}\text{C}$)	38.57 $\pm$ 0.44	38.49 $\pm$ 0.44	0.473
Number of febrile days	5.71 $\pm$ 2.91	3.39 $\pm$ 2.25	0.032*
WBC ($10^3/\mu\text{L}$)	7833.57 $\pm$ 14420.57	4202.29 $\pm$ 2887.73	0.118
ANC at onset ($10^3/\mu\text{L}$)	985.95 $\pm$ 452.33	881.71 $\pm$ 420.84	0.302
ANC at recovery ($10^3/\mu\text{L}$)	2406.90 $\pm$ 761.93	2464.29 $\pm$ 1084.46	0.786

ANC: Absolute neutrophil count, WBC: White blood cell, 25OHD: 25-hydroxy vitamin D. *Statistically significant ($p<0.05$). p-values were calculated using the Mann-Whitney U test.

Table 3. Multivariate linear regression analysis for predictors of neutropenia duration and number of febrile days.

Variable	Beta	SE	p-value	95% CI
Neutropenia duration (days)				
25OHD level	-0.289	0.209	0.171	-0.706 to 0.127
Leukemia diagnosis	14.538	3.479	<0.001*	7.603 to 21.474
Sex (male)	2.442	3.615	0.502	-4.765 to 9.650
G-CSF use	-3.803	3.719	0.310	-11.217 to 3.612
Number of febrile days				
25OHD level	-0.047	0.033	0.160	-0.112 to 0.019
Leukemia diagnosis	2.341	0.546	<0.001*	1.251 to 3.430
Sex (male)	0.234	0.568	0.681	-0.898 to 1.366
G-CSF use	-0.419	0.584	0.475	-1.584 to 0.745

Spearman correlation analysis demonstrated a significant negative correlation between 25OHD levels and neutropenia duration ($r=-0.249$, $p=0.029$) and number of febrile days ($r=-0.253$, $p=0.027$), indicating that lower vitamin D levels were associated with longer and more febrile courses.

Multivariate linear regression analysis, adjusting for sex, diagnosis, and G-CSF use, showed that 25OHD level was not an independent predictor of neutropenia duration (Beta=-0.289, 95% CI: -0.706 to 0.127, $p=0.171$) or number of febrile days (Beta=-0.047, 95% CI: -0.112 to 0.019, $p=0.160$). Leukemia diagnosis was the only significant independent predictor for both outcomes (neutropenia duration: Beta=14.538, 95% CI: 7.603 to 21.474, $p<0.001$; febrile days: Beta=2.341, 95% CI: 1.251 to 3.430, $p<0.001$) (Table 3).

Discussion

This retrospective study examined the association between 25OHD levels and febrile neutropenia in pediatric cancer patients. Lower vitamin D levels were associated with longer neutropenia duration and more febrile days in univariate analysis. However, multivariate regression revealed that leukemia diagnosis, rather than vitamin D status, was the independent predictor of these outcomes. From a clinical perspective, patients with 25OHD levels below 15 ng/ml had a mean neutropenia duration of 22.4 days and 5.1 febrile days, compared to 16.4 days and 3.9 days in those with sufficient levels. This difference of approximately 6 days

of neutropenia and 1.2 febrile days may translate into prolonged hospitalization, increased antibiotic use, and higher treatment costs, even if the association was not independent in multivariate analysis.

Our univariate findings are consistent with those of Gupta et al.[9], who reported that low vitamin D levels were associated with prolonged febrile neutropenia in pediatric patients. A large retrospective study by Penkert et al.[10] involving 378 children with newly diagnosed ALL showed that vitamin D deficiency at diagnosis was associated with a 1.7-fold increased risk of febrile neutropenia and a 1.73-fold increased risk of clinically documented infection during induction therapy.

Vitamin D exerts immunological effects through its nuclear receptor (VDR), expressed on T cells, B cells, macrophages, and dendritic cells. VDR activation induces antimicrobial peptides such as cathelicidin, enhances phagocytosis, and modulates cytokine responses. These mechanisms may be particularly relevant in neutropenic cancer patients [1,2]. García-García et al.[11] reported that cathelicidin—an antimicrobial peptide induced by vitamin D—was independently linked to sepsis progression in pediatric cancer patients with febrile neutropenia, supporting a potential mechanistic link.

The fact that 25OHD level lost its significance after adjusting for leukemia diagnosis suggests that the association between vitamin D and febrile neutropenia outcomes may be confounded by disease type. Leukemia patients receive more intensive and prolonged myelosuppressive chemotherapy, which independently

prolongs neutropenia and increases febrile episodes. This finding highlights the importance of controlling for diagnosis when interpreting vitamin D-outcome associations in pediatric oncology.

Vitamin D deficiency was found in 63.6% of our patients, consistent with the literature. Risk factors included reduced sun exposure during hospitalization, chemotherapy-related malabsorption, and corticosteroid use [6]. Patients who received vitamin D prophylaxis in infancy had significantly higher 25OHD levels (27.79 ± 7.39 vs 13.16 ± 6.36 ng/ml; $p < 0.001$), underscoring the long-lasting benefit of early supplementation.

This study has several limitations. The retrospective, single-center design carries risk of bias and limits generalizability. The patient cohort was heterogeneous regarding malignancy type and chemotherapy protocols. Vitamin D levels were measured only at diagnosis, not during febrile episodes, which may not reflect levels at the time of neutropenia. Important confounders such as chemotherapy intensity, nutritional status, and corticosteroid use were not included in the regression model. The sample size was relatively small. Future prospective studies with larger, homogeneous cohorts and serial vitamin D measurements are needed.

Conclusion

Lower 25OHD levels were associated with longer neutropenia duration and more febrile days in pediatric cancer patients. However, this association was not independent after adjusting for leukemia diagnosis. Regular monitoring of 25OHD levels and supplementation in cases of deficiency may be clinically relevant. Further prospective studies are needed to clarify the independent role of vitamin D in this population.

Author contributions

Conception and design: B.O., G.Ş.; Data acquisition: B.O., G.Ş.; Data analysis: B.O., G.Ş.; Data interpretation: B.O., G.Ş.; Drafting of the manuscript: B.O.; Critical revision of the manuscript: B.O., G.Ş. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Health Sciences University Ankara Dr. Sami Ulus Research and Education Hospital Ethics Committee (Date: 09.07.2018, Decision/Protocol No: 2018-100). Written informed consent was not required due to the retrospective design of the study, as approved by the ethics committee.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that during the preparation of this study, the following AI-assisted technology was used: Claude (Anthropic) in May 2026. Extent of Use: Claude was used for language editing, formatting the manuscript and title page according to the journal's requirements, and drafting routine correspondence with the editorial office. All AI-assisted content was reviewed and edited by the authors, who take full responsibility for the accuracy and integrity of the manuscript. The authors confirm that they have critically reviewed and edited any AI-generated content and take full responsibility for the integrity, accuracy, and originality of the publication. The authors certify that the original human contribution is maintained and that AI-assisted tools are not listed or cited as authors.

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