International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Vitamin D and Pediatric Cancer Prevention: Dilemmas and Opportunities. A Systematic Review with A Critical Integrative Component

INPLASY2025110098
doi: 10.37766/inplasy2025.11.0098
Received: 29 November 2025
Published: 29 November 2025

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ADMINISTRATIVE INFORMATION

Support - Biotechlab Alberta Ltd.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025110098

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 November 2025 and was last updated on 29 November 2025.

INTRODUCTION

Review question / Objective Vitamin D deficiency associated to Pediatric Cancer and Vitamin D deficiency as Bony fractures in Pediatric Cancer Patients.

Rationale Vitamin D can be successful in treating numerous diseases, and an altered auto-immunity has been associated with vitamin D deficiency (VDD) [1-5]. It is crucial to emphasize the role of vitamin D in the pathogenesis of autoimmune hepatitis (AIH) [4]. After the turn of the last century, the interest in vitamin D increased enormously. Rickets has accompanied human civilization for centuries across both the Old and the New Worlds [3,6]. Still, despite supplementation of this vitamin in our diet, hypovita-minosis and child neglect cases continue to persist [6]. Population surveys indicate that essential sectors of the population, including pregnant women and children, will be affected by VDD or vitamin D inadequacy (VDI). Changes in habits with indoor living, inadequate sunlight exposure, vitamin-deficient diets, and high rates of nutritional al-lergies are likely playing a significant role in the growing inadequacy of vitamin sup-plementation for some people worldwide, probably more in children living in the Northern hemisphere [7,8]. Biochemically, vitamin D is a fat-soluble vitamin (Figure 1).

Figure 1. Vitamin D. [By NEUROtiker - Own work, Public Domain, https://commons.wikimedia.org/w/index.php?curid=2196572%5D. Creative Commons 4.0

Vitamin D plays a leading role in calcium homeostasis [9,10]. Vitamin D is tightly linked to immunity. It plays a remarkable role in inflammatory and cancer pathways [3,11,12]. The immune system's cellular components possess vitamin D receptors (VDRs). These receptors can metabolize the active form of vitamin D [calcitriol,

1,25-dihydroxy vitamin D, 1,25(OH)2D]. The storage form of vitamin D is 25-hydroxyvitamin D (25OHD). It can be converted to 1,25(OH)2D by activated T and B lymphocytes in vitro. In addition, 1,25(OH)2D acts on immune cells in an obvious au-tocrine or paracrine manner. This aspect has been considered crucial for several infec-tions, as suggested in the COVID-19 literature, being COVID-19 the coronavirus 2019 infection caused by the Severe Acute Respiratory Syndrome type II (SARS-CoV-2) [13-15]. In addition to its effects on immune cells, vitamin D increases calcium absorp-tion in the small intestine and participates in ciliary movement [5]. Nicolaysen et al. [16] and Haavaldsen et al. [17,18] also observed that animals on a low calcium diet had much greater calcium absorption efficiency than animals fed an adequate amount of calcium. Calmodulin, an intermediate calcium-binding messenger protein expressed in all eukaryotic cells, is localized in the hamster's ciliated cells. Thus, calcium is promi-nent for cilia's bioenergetic activity and the bile canaliculus of the liver [19-22]. In maintaining innate immunity, various studies have shown that it also plays an essential role in boosting the respiratory host defense [23-30]. Transforming growth factor-beta 1 (TGF-β1) reduces epithelial cell host defense by altering vitamin D-mediated expression of host defense peptides and proteins [31]. When primary CD4+ T cells from healthy donors were obtained and cultured under Th17-polarizing conditions, vitamin D re-duced the expression of Th17 markers. Subsequently, proinflammatory cytokine secre-tion also decreased. It predominantly involved interleukin-17A (IL-17A) and interferon gamma (IFN-γ) [32,33]. It induced an expansion of the CD4+ T cell subset expressing the highest levels of CD25 cells. It also upregulated CTLA-4 and Foxp3 expression [32-35]. It seems that vitamin D supplement plays a role in regulating the microbiome, increasing the abundance of beneficial bacterial strains [36].

While vitamin D is crucial for overall health and may have protective effects against certain cancers, there is insufficient evidence to recommend it specifically for preventing cancer in children or increasing its supplementation in pediatric patients with cancer. Pediatric cancer guidelines focus on monitoring and correcting VDD in children who have already been diagnosed, as this can impact their prognosis and treatment outcomes.

Condition being studied VDD in pediatric patients with cancer for for bony fracture incidence and VDD in pediatric patients presenting with cancer.

METHODS

Search strategy This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [44].

2.1. Search Methodology and Criteria for Selection

We performed a comprehensive literature search of the PubMed, SCOPUS, and Cochrane databases through October 30, 2025. The search criteria encompassed vita-min D, pediatric cancer, childhood cancer, and prevention. Following the elimination of duplicates, the titles and abstracts of the retrieved records were evaluated to discover articles that may align with our established inclusion criteria: (1) The study population comprised children with cancer up to five years post-treatment cessation, with a minimum of 95% diagnosed at or below 18 years of age; (2) the study was observational; (3) the study was neither a case report nor a case series (n <10) and was published in English; and (5) the study constituted original research. We exclusively incorporated studies that assessed 25OHD levels (excluding 1,25[OH]2D), as serum 25OHD concen-trations are regarded as the most reliable clinical indication of vitamin D status in in-dividuals with normal renal function. We excluded studies involving childhood cancer survivors who commenced vitamin D supplementation more than 5 years after treat-ment discontinuation, as our objective was to evaluate the rationale and impact of vitamin D supplementation on bone health during cancer therapy. Before the elimina-tion of reviews, the reference list was examined for pertinent literature. Subsequently, all publications were acquired and evaluated according to the inclusion criteria. When multiple studies addressed the same cohort, we selected the article that provided the most pertinent data for our research inquiries. Ultimately, we conducted a cross-reference verification of all included publications via Web of Science. Article screening was undertaken separately by both authors.

Moreover, we adopted the SANRA methodology for research integrity (Scale for the Assessment of Narrative Review Articles) [45] and perused the grey literature. Grey literature includes information generated outside conventional commercial or aca-demic publishing channels, such as reports, conference proceedings, theses, and gov-ernment publications. A comprehensive analysis of gray literature components en-compasses the subsequent elements: 1) Reports (annual reports, research reports, tech-nical reports, project reports, and evaluations). 2) Working Papers (preliminary or draft iterations of studies not formally published). 3) Textbooks and Official

Documents (policy files, white papers, and technical documentation). 4) Conference Proceedings and Abstracts. 5) Theses and Dissertations. 6) Technical Reports and Grant Applica-tions/Dissemination Reports. 7) Patents. 8) Unpublished Clinical studies with data that may remain unreported in peer-reviewed journals. 9) Newsletters and websites. 10) Blogs and Social Media Publications. 11) Market and Industry Analysis. 12) Criteria and Protocols. The quality of the single papers was measured using a standard ad hoc method, as used in previous systematic reviews and meta-analyses conducted by the authors. We followed the Joanna Briggs Institute guidelines to conduct the review thoroughly and meticulously [46]. They were composed in English throughout the specified timeframe. For the targeted search, clearly defined Descriptors in Health Sciences and Medical Subject Headings (MeSH) were employed for each approach component and its associated terms. The Boolean operations AND, OR, and NOT were employed to amalgamate descriptions and scoping principles to ensure the robustness and verifiability of its claims and arguments [47,48].

Participant or population Pediatric patients with cancer.

Intervention 2.2. Data Extraction
We collected data regarding sample size, sex distribution, baseline age, country, study design, and pediatric cancer diagnosis. For observational studies, we also obtained data on the VDD threshold, the percentage of children receiving vitamin D supplementation, and the prescribed dosage. We focused on observational studies only, rather than mixing them with interventional studies, and a separate section of the discussion explains this choice.
2.3. Critical Evaluation
The two independent authors evaluated the validity of the included articles using the Newcastle-Ottawa Scale (NOS) for observational studies [49]. NOS has been used efficiently and effectively in our studies, exhibiting systematic reviews and meta-analyses [50-56]. Discrepancies in grading were resolved through consensus or by involving a third reviewer.
2.4. Integrative Review Component
We employed an integrative review process. An integrative review employs a non-experimental design, a systematic methodology, and a comprehensive search strategy to identify pertinent information that addresses a specific therapeutic inquiry. Researchers conduct an objective evaluation, summarize, and draw judgments regarding a subject area, using a theme analysis of chosen qualitative and quantitative research works related to the topic. Evidence may come from several studies, in which researchers objectively analyze, synthesize, and draw conclusions about a subject. They encompass systematic categorization and theme analysis of chosen qualitative and quantitative research projects. The approach of integrative review is complex and necessitates discernment and meticulous attention to detail. Typically employed when multiple types of evidence sources pertain to the inquiry, and the data is diverse. An integrative study of the facilitators and barriers affecting collaboration and teamwork between general practitioners and nurses in general practice [57,58].

Comparator None.

Study designs to be included Observational studies.

Eligibility criteria Observational studies of pediatric patients with cancer.

Information sources A comprehensive analysis of gray literature components encompasses the subsequent elements: 1) Reports (annual reports, research reports, technical reports, project reports, and evaluations). 2) Working Papers (preliminary or draft iterations of studies not formally published). 3) Textbooks and Official Documents (policy files, white papers, and technical documentation). 4) Conference Proceedings and Abstracts. 5) Theses and Dissertations. 6) Technical Reports and Grant Applications/Dissemination Reports. 7) Patents. 8) Unpublished Clinical studies with data that may remain unreported in peer-reviewed journals. 9) Newsletters and websites. 10) Blogs and Social Media Pub-lications. 11) Market and Industry Analysis. 12) Criteria and Protocols. The quality of the single papers was measured using a standard ad hoc method, as used in previous systematic reviews and meta-analyses conducted by the authors. We followed the Jo-anna Briggs Institute guidelines to conduct the review thoroughly and meticulously [46]. They were composed in English throughout the specified timeframe. For the targeted search, clearly defined Descriptors in Health Sciences and Medical Subject Headings (MeSH) were employed for each approach component and its associated terms. The Boolean operations AND, OR, and NOT were employed to amalgamate descriptions and scoping principles to ensure the robustness and verifiability of its claims and arguments [47,48].

Main outcome(s) The search in PubMed, SCOPUS, and Cochrane produced 635, 324, and one record, respectively. After eliminating duplicates, 443 titles and abstracts were evaluated, and 18 full-text articles were subsequently examined (Figure 2). This review encompasses 12 papers dealing with hematologic malignancies [59-70], two papers with children harboring a solid tumor [71,72], and four papers with any childhood cancer diagnosis [73-76] (Table 1). The study samples ranged from 20 to 171 participants. The median or mean base-line age of the study cohort ranged from 3.9 to 15.0 years. The serum 25OHD threshold for VDD varied across studies; levels below 20 ng/mL were the most used threshold, employed in 55% of the studies that established a criterion. Four studies (36%) em-ployed a threshold of 12 ng/ml or less.

Quality assessment / Risk of bias analysis Substantial concerns regarding potential bias in the incorporated studies were noted. The primary limitations of the observational studies included low participation rates, insufficient measurement of prognostic factors (25OHD not assessed via liquid chromatography-tandem mass spectrometry, the gold standard, and/or evaluated at varying timepoints), absence of adjustment for significant confounders (no multivaria-ble analysis), and inadequate statistical analysis or reporting.

The most recent Iranian study targeted VDD or insufficiency [70]. In this study, vitamin D levels are compared between participants with and without relapse and as-sessed as a predictive factor for relapse-free survival [70]. Children with newly diag-nosed acute lymphoblastic leukemia were recruited as the case group. Demographic data and food habits were obtained through interviews. Furthermore, serum 25-hydroxyvitamin D3 was quantified. The case group was monitored for 36 months to evaluate recurrence-free survival (RFS). A total of 358 participants were incorporated in the study (n = 169 cases vs n = 189 controls). The average concentrations of 25(OH)D3 were 28.05 ± 18.87 in cases and 28.76 ± 12.99 in controls, respectively ($p = 0.68$). VDD was identified in 15.4% (n = 26) of the case group and 4.2% (n = 8) of the control group, respectively ($p < 0.001$). Relapse occurred in 18.34% of patients, and vitamin D levels of 20 ng/mL or higher were associated with prolonged recurrence-free survival ($p = 0.044$ by log-rank test). This study found that VDD and VDI in children with ALL were con-siderably elevated compared to controls. Furthermore, diminished levels of Vitamin D were correlated with an elevated risk of relapse.

Moreover, in the same direction, an American study emphasizes VDD in patients with cancer [76]. Children with cancer face an elevated risk of vitamin D deficiencies due to pre-diagnosis health issues, the disease itself, and cancer treatments. This IRB-approved retrospective matched case-control study of children with and without cancer encompassed three races. This study is the inaugural investigation to directly compare serum 25(OH)D levels and status in newly diagnosed pediatric cancer patients with age-, sex-, and race-matched cancer-free children from the same geographic re-gion in the United States, all of whom are devoid of other conditions that adversely affect 25(OH)D levels. Ordinal logistic regressions, both univariable and multivariable, were conducted. Among the 544 youngsters (average age of 8.5 years, 53% female), there were 136 newly diagnosed cancer patients and 408 matched non-cancer controls. At the time of cancer diagnosis, serum 25(OH)D levels were significantly.

Strategy of data synthesis Previous consensus recommendations fail to emphasize the importance of vitamin D in preventing cancer, but both an Iranian study [70] and an American study [76] highlighted the critical role of VDD in potentially triggering or co-triggering a micro-environment that initiates or promotes neoplastic onset or progression [77-79]. These considerations are not trivial, given the strong connection between vitamin D and our immune system [80-84].

In the Iranian study, 358 participants were assessed (n = 169 cases and n = 189 controls); 15.4% of children with ALL had VDD, compared with 4.2% in the control group. Despite the bold statement, this study is limited by a restricted sample size. On the other side, another study indicated that most adults with AML exhibit VDD and concluded that elevated vitamin D levels correlated with improved outcomes [85]. Moreover, UVB radiation appears to reduce the prevalence of leukemia, and vitamin D levels can be elevated through dietary intake or enhanced UVB exposure. A study analyzing the Global Cancer (GLOBOCAN) 2012 database demonstrated an inverse correlation between leukemia incidence rates and solar UVB radiation [86,87]. It seems that the risk of non-Hodgkin lymphoma considerably decreased with increased sun exposure [88]. Notwithstanding the study's location in a sun-drenched area, a significant prevalence of VDD/VDI is observed, driven by factors such as air pollution and limited outdoor activity. Previous research by Kelishadi et al. indicates that over 40% of children aged 4 to 10 in Isfahan experience Vitamin D deficiency or insufficiency, potentially attributable to air pollution [89]. Furthermore, research indicates that in children, the incidence of VDD is

greater in biological girls than in boys, which is hypothesized to result from reduced outdoor activity [90]. Although a higher prevalence of underweight was observed in children with leukemia, no statistically significant connection with relapse was identified. Still, a co-risk for fatty liver, favoring a hematogenous neoplasm, needs to be further clarified [91].

VDD and VDI are linked to a heightened risk of developing colon, prostate, and breast cancer [92-100]. Therefore, the significance of vitamin D in malignancies, including juvenile leukemia, warrants deeper consideration, and we are concerned that general pediatricians and family doctors overwhelmingly accept consensus statements. Vitamin D controls around 200 genes, including those responsible for cellular proliferation, differentiation, death, and angiogenesis [101-105]. An animal study indicated that AML-harboring mice receiving CYP27B1 gene therapy (which encodes 1-alpha-hydroxylase) had prolonged overall life compared to those receiving no treatment [106]. A notable disparity in RFS was observed between persons with adequate vitamin D levels and those with VDD/VDI regarding the association between VDD and disease recurrence. Numerous studies indicate that sufficient vitamin D levels can improve outcomes in adult patients with leukemia. Still, some studies highlight that improved outcomes are challenging to fully observe in school-age children with leukemia [107,108]. Nevertheless, Nematollahi et al. demonstrate ineluctably the significantly higher rate of serum VDD/VDI among children with ALL in comparison with the control group [70]. In addition, a lower level of vitamin D is associated with a higher risk.

Subgroup analysis Hematological malignancies; solid tumor; any tumor diagnosis.

Sensitivity analysis Not available.

Language restriction English.

Country(ies) involved Canada.

Keywords vitamin D; cancer; children; prevention.

Contributions of each author

Author 1 - Joseph Feulefack.
Author 2 - Consolato Sergi.