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Review Article

Vitamin D and hematologic malignancies: A comprehensive review of its role in therapeutic potential, pathogenesis, and prognosis

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Summary

Vitamin D has immunomodulatory, anti-proliferative, and pro-differentiative effects that are increasingly linked to hematologic malignancies, beyond its traditional function in maintaining calcium-phosphate balance. Patients with leukemia and lymphoma frequently have vitamin D deficiency, which has been linked to poor prognostic characteristics and a lower chance of survival. The active metabolite 1,25-dihydroxyvitamin D3 stimulates cellular differentiation, suppresses proliferation, and triggers apoptosis in acute leukemias (ALL and AML) by means of vitamin D receptor (VDR)-mediated transcriptional regulation. Based on empirical evidence, a higher tumor burden, a worse response to treatment, and an advanced disease stage are all associated with low vitamin D levels in chronic leukemias (CLL and CML). Similarly, hypovitaminosis D has been associated with worse treatment outcomes for both Hodgkin and non-Hodgkin lymphomas. By modifying cytokine production, immune cell function, angiogenesis, cell cycle regulation, and tumor–microenvironment interactions, vitamin D mechanistically affects leukemogenesis and lymphomagenesis. This review outlines the most recent molecular and clinical data that suggests vitamin D may be used as a prognostic biomarker and an adjuvant therapeutic target in hematologic malignancies. However, to elucidate its therapeutic impact and clinical utility, extensive prospective and randomized studies are needed.

Keywords: Vitamin D, Malignancy, Biomarker, Diagnosis, Prognosis

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Introduction

The unchecked growth of hematopoietic cells is the cause of Hematological malignancies (HM). About 67% of all HM diagnoses in Canada are leukemia and lymphoma, with comparable proportional numbers in the US and other countries.[1-3] Whereas lymphomas start in lymph nodes and other tissues, leukemias start in the bone marrow.[4] Myeloproliferative diseases and multiple myeloma (MM) are less prevalent. Leukemia classification is based on which cell lineage is involved: myeloid or lymphoid. This condition is further subcategorized based on the stage of cellular transformation and the growth rate of neoplastic cells. Leukemia originating from developing immune cells are generally fast growing and are referred to as acute, while leukemia originating in cells at more mature stages are slow growing when untreated and referred to as chronic.[5] The four primary leukemia subtypes—acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL)—are derived from these classifications. Initially, bone marrow malfunction is linked to leukemia's clinical manifestations, such as infections brought on by low neutrophil counts or bruising and bleeding brought on by thrombocytopenia. When the bone marrow is full, leukemia cells can enter the lymph nodes and cause lymphadenopathy, or they can enter the liver, spleen, and circulation.[5]

The two types of lymphomas are Hodgkin's (HL) and non-Hodgkin's (NHL), with NHL accounting for 90% of all lymphomas.[6] The presence of multinucleated Reed-Sternberg cells is a characteristic of HL [7]. Based on the location of the cell's genesis, NHL is a diverse collection of lymphomas. T or Natural Killer (NK) cells are responsible for the remaining instances, with B lymphocytes accounting for the bulk (85–90%)[6] (Figure 1). In two-thirds of instances, lymphoma manifests as a painless lymphadenopathy that typically affects a cervical lymph node and has the potential to grow rapidly. Additionally prevalent are constitutional symptoms, including fever, anorexia, and weight loss.[6,8]

Calcitriol (1α,25(OH)2D3), the physiologically active form of vitamin D, is produced by a carefully regulated multi-step process.[9] Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are the two primary forms of vitamin D that are created from ergosterol by UV-B light. Human skin's epidermis can also create

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7-dehydrocholesterol when exposed to UV-B rays.[10,11] When cholecalciferol is metabolized in the liver by 25-hydroxylase, 25-hydroxycholecalciferols [25(OH)D3, calcidiol, or circulating vitamin D] is created (Figure 2). This is the form of vitamin D that circulates in the blood. The kidney's 25-hydroxyvitamin D3-1α-hydroxylase produces the physiologically active 1α, 25-hydroxycholecalciferol [1,25(OH)2D3, calcitriol, or active form of vitamin D].[12,13] Once in the bloodstream, calcitriol attaches to the vitamin D-binding protein (VDBP) and moves to the kidney, bone, and gut, among other target organs, to regulate calcium and phosphate uptake, mobilization, and reabsorption.[10]

Numerous cellular processes linked to cancer, including differentiation, proliferation, angiogenesis, apoptosis, and the spread of cancer cells, are regulated by vitamin D.[14,15] Through the activation of cyclin-dependent kinase inhibitors, including p21 and p27, and the downregulation of cyclins, calcitriol inhibited the proliferation of cancer cells by triggering cell cycle arrest and impeding the advancement of the cell cycle.[16,17] Calcitriol triggers apoptosis by causing antiapoptotic and proapoptotic proteins, including caspases and members of the B-cell Leukemia/Lymphoma 2 protein (BCL-2) family.[18,19] Therefore, by blocking the synthesis of proangiogenic molecules, such as matrix metalloproteinases and vascular endothelial growth factors (VEGFs), vitamin D-induced apoptosis may aid in its anticancer effect and inhibit angiogenesis in growing tumors.[20] By inhibiting the synthesis of proinflammatory cytokines and chemokines, calcitriol's anti-inflammatory activities may contribute to its preventative benefits on cancer.[20] The purpose of this study was to examine the role and levels of vitamin D in major blood malignancies, such as AML, ALL, CML, CLL, HL, and important non-HL, because there is a lack of reliable information on the disease's relationship to vitamin D.

Vitamin D and Acute Lymphoblastic Leukemia (ALL)

Acute lymphoblastic leukemia (ALL) is the most prevalent kind of childhood malignancy, making up about 80% of pediatric leukemias.[21] According to several publications, most leukemia patients are VD3-deficient when they

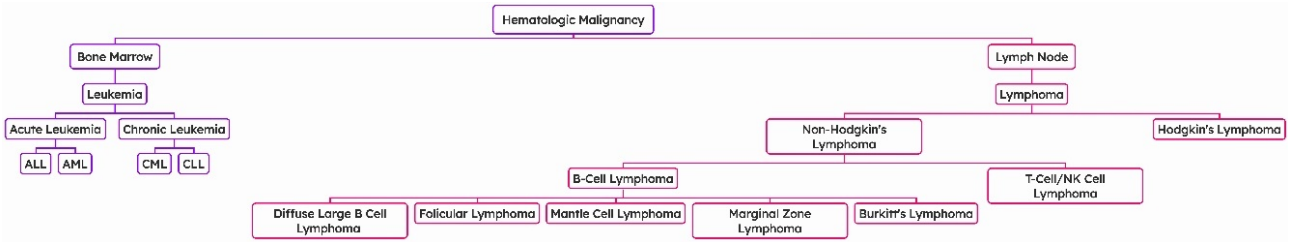

Figure 1. Classification of blood malignancies

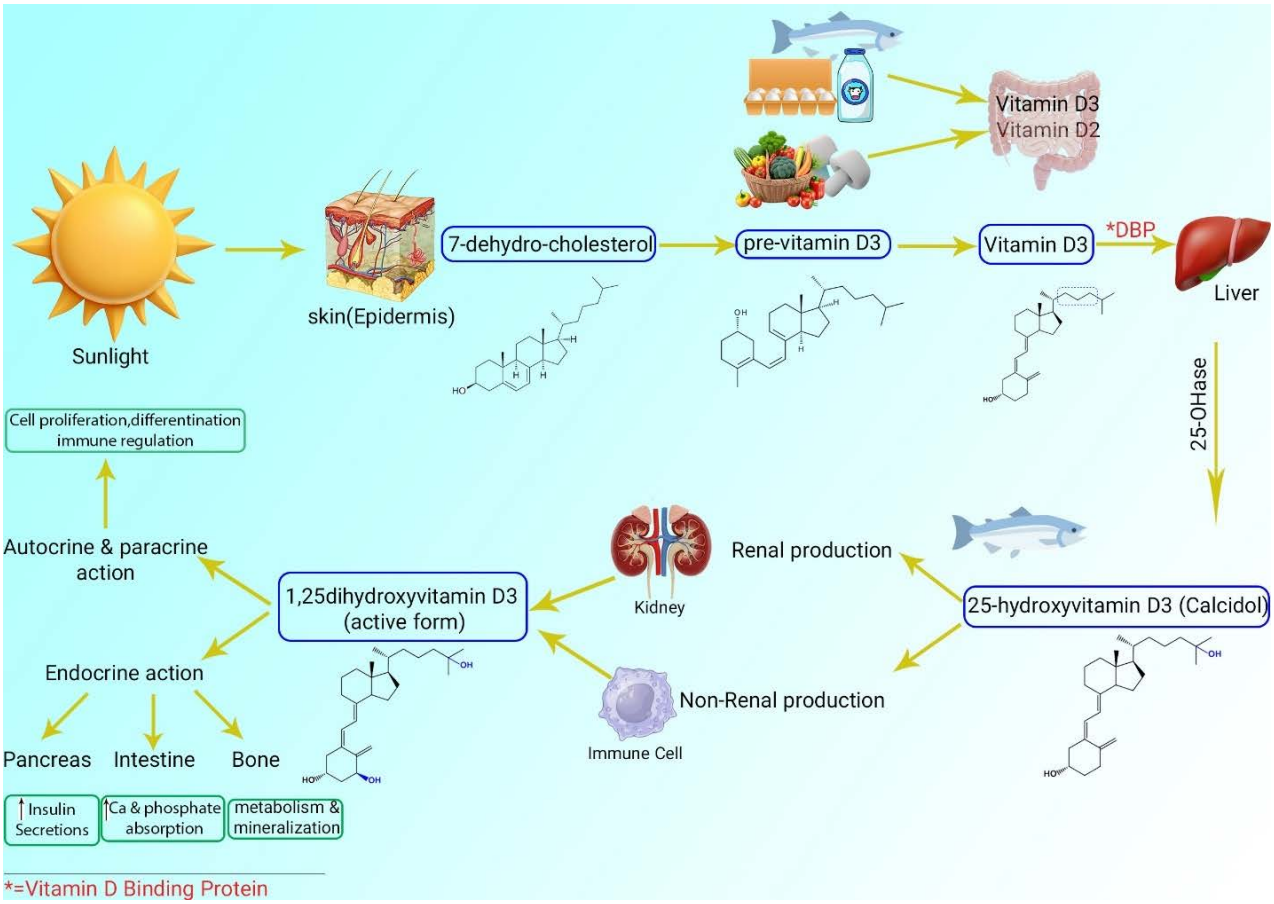

Figure 2. Vitamin D3 synthesis from sun exposure and food

are diagnosed.[22,23] Given the known role of vitamin D in immune regulation and cancer biology, its impact on ALL progression has been investigated in both in vivo and in vitro studies.

A 2020 study examining BCR-ABL Arf–/– ALL demonstrated that vitamin D status influences disease progression and survival, with vitamin D deficiency affecting immune cell dynamics, including increased frequencies of regulatory T cells (Tregs).[24] Consistent with these findings, previous studies have reported a positive correlation between $CD4^+$, forkhead box P3 (FOXP3)-positive regulatory T cells (Tregs), and ALL progression.[25] In vitro experiments further showed that vitamin D may enhance the proliferation of BCR-ABL ALL cells in the presence of bone marrow stroma, suggesting a role in modulating the leukemic microenvironment. Clinically, vitamin D deficiency is common among newly diagnosed ALL patients and has been associated with adverse outcomes, including a higher risk of febrile neutropenia and infections.[26]

These findings highlight the importance of vitamin D status in ALL progression and patient prognosis, warranting further investigation into its potential as a therapeutic target.

Vitamin D and Acute Myeloid Leukemia (AML)

Acute myeloid leukemia (AML) is an aggressive hematopoietic malignancy with a very high mortality rate. Despite initial responses to standard chemotherapy, the prognosis is poor for most patients. Furthermore, older individuals, who comprise the majority of patients with AML, are mostly unfit for intensive cytotoxic therapy.[27] The active form of vitamin D, 1α,25-dihydroxyvitamin D3 (1,25D3), is a well-known inducer of monocyte/macrophage differentiation and growth arrest in various subtypes of AML cells in culture.[28,29]

In AML cases, frequent observation showed vitamin D deficiency in these patients, suggesting an intriguing potential role in disease pathogenesis.[30] Also, higher serum vitamin D levels have been associated with improved prognosis in AML patients.[31]

For the first time, a study showed that vitamin D promotes autophagy in AML cells by inhibiting miR-17-5p-induced Beclin-1 overexpression. MiR-17-5p may thus be useful as a novel biomarker for predicting AML therapeutic outcomes.[32] Following previous studies, Xu et al demonstrated strong in vitro and ex vivo evidence to support the combination therapy of 1,25(OH)2D3 and 5-Azacytidine (AZA) for AML treatment.[33] The "Warburg Effect," a phenomenon involving enhanced glycolysis, has been linked to a worse prognosis in leukemic blasts of acute myeloid leukemia (AML). Fructose-1,6-bisphosphatase (FBP1), an enzyme involved in gluconeogenesis, can also act as a tumor suppressor by inhibiting glycolysis and cancer cell growth. Overexpression of 1,25 VD3-induced FBP1 could be a potential therapeutic target to block this effect and reduce energy production in AML blasts.[34] These results imply that both the prognosis of AML and its treatment outcomes may be significantly influenced by the patient's vitamin D levels.

Vitamin D and Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is a prevalent, incurable leukemia in the US, affecting B, T, and natural killer cells. It results from uncontrolled B lymphocyte growth, crowding out healthy cells, and can cause bone marrow and peripheral blood pathology.[35-37]

An in vitro investigation revealed that vitamin D analogs induced p53-independent selective apoptosis in primary CLL cells.[38] High vitamin D levels are indicative of a longer time to initial therapy in CLL, while vitamin D deficiency is proposed as a risk factor for the disease.[38,39] Studies demonstrated Vitamin D insufficiency was linked to lower TTFT (time to first treatment) and OS (overall survival) in CLL patients, which is consistent with the findings of a prior study.[38,39] Also, according to a long-term retrospective study, vitamin D treatment for CLL patients in a watch-and-wait active surveillance is substantially linked to a longer TFS (at any age) and a longer TTFT for young patients (those aged ≤65).[40]

Vitamin D and Chronic Myeloid Leukemia (CML)

Chronic myeloid leukemia (CML) is a blood cancer caused by abnormal cell growth. It results from a genetic mutation in early cell development that causes a translocation between chromosomes 9 and 22, forming the Philadelphia chromosome. This causes the BCR gene to fuse with the ABL1 gene, creating a BCR-ABL1 fusion gene that leads to uncontrolled cell growth. Also, a protein with consistent tyrosine kinase activity is produced by this fused gene.[41] CML, a rare form of leukemia, affects 15% of newly diagnosed cases in adults, affecting 1-2 individuals per 100,000. Both men and women are affected, and despite improved treatments, achieving a complete cure remains challenging, and relapses are common.[42]

Tyrosine kinase inhibitors (TKIs), such as imatinib and dasatinib, significantly enhance the survival and outlook of CML patients, demonstrating the efficacy of targeted therapies, although not all patients respond positively.[43] Due to the anticancer properties of vitamin D, it has been demonstrated that inecalcitol, an analog of calcitriol and a vitamin D3 receptor (VDR) agonist, and imatinib or dasatinib work in concert to kill some CML cell lines.[44] In line with these findings, significant vitamin D shortage was seen in long-term CML patients on imatinib mesylate treatment, suggesting that vitamin D levels and how they interact with imatinib mesylate may be crucial in the management of CML. However, randomized controlled clinical research by Arkapal Bandyopadhyay et al. revealed no appreciable advantage of vitamin D3 supplementation in CML patients' early treatment responses.[45] Following these results, Xu et al. demonstrated that BCR-ABL1–driven CML progression requires VDR. They further showed that targeting VDR may help eradicate leukemia stem cells (LSCs) and inhibit CML cell proliferation, even in the absence of BCR-ABL mutations. Additionally, they

reported that DDIT4-mediated DNA damage induces senescence in chronic myeloid leukemia when the vitamin D receptor is lost.[46]

Vitamin D and Hodgkin's Lymphoma (HL)

One of the most common lymphomas in the Western world is Hodgkin lymphoma (HL). Some HL patients have recurrent cancers that are challenging to cure, even though their overall prognosis is favorable. Vitamin D has long been thought to be a possible cancer therapy. The vitamin D receptor is the mechanism by which vitamin D works. In 2012, a study found that whereas normal, non-neoplastic B cells and all B-NHLs examined had minimal or no expression of VDR, the great majority of HL patients had significant expression of the protein. VDR's nuclear localization points to an active form of the protein in HL.[47] But, Gharbaran et al. demonstrated that the HL cell lines used in their study showed low but varying levels of VDR expression, while VD3 and vitamin D3 analogs reduced growth and increased VDR accumulation.[48] The relationship between vitamin D and Hodgkin lymphoma has not been extensively studied. A study found that 50% of patients were vitamin D-deficient before chemotherapy, with deficiency being more common in relapsed patients. Vitamin D status is an independent predictor of outcomes and may influence HL chemosensitivity. Supplementing vitamin D with cholecalciferol showed increased antiproliferative effects and improved tumor chemosensitivity compared to chemotherapy alone. Also, HL patients with vitamin D insufficiency have worse PFS (progression-free survival).

Vitamin D and Non-Hodgkin Lymphoma (NHL)

Vitamin D and Diffuse Large B-Cell Lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent clinical subtype of aggressive non-Hodgkin lymphoma, causing over 40% of aggressive lymphomas. With over 150,000 new cases annually, 40% of DLBCL patients may experience relapse or refractory disease.[49-51] Han et al. demonstrated that, in the Pfeiffer cell line derived from diffuse large B-cell lymphoma (DLBCL), calcitriol in combination with rapamycin (RAPA) inhibited cell proliferation, increased the proportion of cells in the G1 phase, and enhanced cell-cycle arrest. They further showed that this combination suppressed the expression of VDR and 25-hydroxyvitamin D-24-hydroxylase (CYP24A1), the enzyme responsible for $1,25(OH)_2D_3$ degradation.[52] Numerous studies have demonstrated that DLBCL patients with vitamin D deficiency have worse EFS (event-free survival), PFS (progression-free survival), and OS (overall survival). Furthermore, greater OS and EFS were associated with higher Vitamin D levels in DLBCL patients.[53-56]

Vitamin D and Follicular Lymphoma (FL)

Another type of B-cell lymphoma is follicular lymphoma (FL), an indolent lymphoid malignancy derived from germinal center B cells. Recent advances in FL treatment have significantly improved patient survival. However, FL remains an incurable disease, with some patient groups exhibiting early disease progression, histologic transformation, or an increased risk of treatment-related toxicity. Furthermore, as a relapsing disease, response rates and durations of disease control decline with each successive line of therapy.[57] Several studies have shown that patients with vitamin D deficiency have worse progression-free survival (PFS), overall survival (OS), and event-free survival (EFS).[58,59]

Vitamin D and Mantle Cell Lymphoma (MCL)

Another subtype of B-cell NHL, mantle cell lymphoma (MCL), is an uncommon form of B-cell neoplasm that is typified by the proliferation of mature B-cells, usually expressing CD5. With a typical age of about 65, it primarily affects older men. Even though it is typically categorized as aggressive, it displays a variety of clinical behaviors.[60] The predictive significance of VDD in patients with MCL was investigated by Xu et al. Following the studies of Xu and colleagues, for the first time, Brosseau et al. showed that combined lenalidomide/VD3 therapy causes cell death in MCL cells by inducing BH3-only BCL2-interacting killer (Bik) expression due to its promoter demethylation, a process akin to 5-azacytidine.[61,62]

Vitamin D and Marginal Zone Lymphoma (MZL)

Marginal zone lymphomas (MZL) account for 7% of all non-Hodgkin lymphomas, with 7,460 cases diagnosed in the USA in 2016.[63-65] Their epidemiology and natural history are not well understood, though a family history of lymphoma is a notable risk factor. Infectious agents and autoimmune diseases such as Sjögren syndrome, systemic lupus erythematosus, and Hashimoto thyroiditis are among the genetic and environmental risk factors for extranodal MZL.[65,66]

The primary circulation form of vitamin D (VitD), 25(OH)2D3, has been implicated in the pathogenesis, progression, and treatment of hematological cancers, according to recent preclinical and epidemiological data. It has also been demonstrated that patients with hematological diseases have lower serum levels of Vitamin D3.[67] In contrast to the findings of earlier research, Jonathan et al demonstrated that routine vitamin D supplementation has no function in improving the outcomes of rituximab therapy for indolent lymphoma, such as MZL.[68]

Vitamin D and Burkitt's Lymphoma (BL)

Burkitt's lymphoma is a highly aggressive B-cell lymphoma and the most rapidly proliferating human cancer. It is common in children and adolescents but accounts for only 1 to 2% of non-Hodgkin lymphomas in adults. Persons with Burkitt's lymphoma typically have a dramatic clinical presentation, which warrants immediate evaluation, given the characteristically rapid growth of the lymphoma and spread to extranodal anatomical sites, including intra-abdominal organs and the central nervous system (CNS).[69]

The findings of a study suggest a mechanism in which vitamin D is required for innate immunity to overcome the ability of Burkett's lymphoma cells to evade macrophage-mediated antitumoral responses. Also, this study underscores the importance of vitamin D for sustaining innate immunity and implies that the therapeutic activation of the vitamin D pathway may even result in triggering tumoricidal effector mechanisms of LAM (lymphoma-associated macrophages).[70] Vitamin D3 serum levels were linked to the highest NK = cell-mediated antibody-dependent cellular cytotoxicity (ADCC), according to Neumann et al.[71] Actually, rituximab and obinutuzumab work primarily through NK-cell-mediated ADCC, and their effectiveness greatly increased in patients with vitamin D3 deficiency and insufficiency following vitamin D3 therapy. Specifically, rituximab had weaker ADCC activity than obinutuzumab.

Thus, vitamin D3's impact on NK-cell-mediated ADCC is significant and can enhance the therapeutic results of immunotherapies that use these antibodies. Bold et al[72] demonstrated the immune-modulatory effects of calcitriol on activated NK-cells in vitro, which is consistent with these findings. More specifically, NK-cells derived from healthy volunteers that were co-cultivated with B-cell lymphoma DAUDI and U2932, activated with Interleukin-2, and treated with calcitriol by prolonged stimulation demonstrated a higher ADCC against these tumor cells.

Discussion

In economically developed parts of the world, hematological malignancies, or blood cancers, rank as the fifth most prevalent type of cancer. Traditionally, they are categorized by site based on whether the malignancy was initially found in the bone (myelomas), lymph nodes (Hodgkin and non-Hodgkin lymphomas), or blood (leukemias).

According to recent preclinical and epidemiological data, patients with hematological diseases have lower serum levels of vitamin D3 (VitD3), and the primary circulation form of VitD, 25(OH)2D3, may be important in the etiology, progression, and treatment of hematological cancers.[67] We conclude that, across a variety of cancer types, including lymphomas, higher circulating levels of vitamin D are associated with improved overall survival (OS), reduced cancer-specific mortality, and better disease-free survival. In addition, in vitro studies have demonstrated the beneficial effects of vitamin D and its analogs. However, further research is required to better understand the clinical benefits of vitamin D supplementation in patients with lymphoma. Moreover, animal models and clinical trials investigating the effects of vitamin D analogs (VDAs) in these diseases are needed. Calcitriol has been shown to protect against various types of cancer.[73] However, it does not impair ALL cell proliferation or survival; actually, calcitriol protected ALL cells from dexamethasone in a minor but reliable way. This raises concerns about potential adverse effects on leukemia treatment, especially in children with low vitamin D levels and osteopenia. Clinicians should exercise caution before administering high doses of vitamin D to leukemia patients.[74] In accordance with the results of this study, Malecka et al. showed that patients who had greater levels of 25(OH)D in their serum had more severe thrombocytopenia and required transfusions more frequently. These patients also had greater incidences of hyperdiploid karyotype and B-cell leukemia.[75] As a result, the role of vitamin D in ALL patients is controversial and requires further study.

Regarding the function of vitamin D in AML, there are two main obstacles: 1. vitamin D's hypercalcemic effects in these patients, and 2. Certain subtypes of AML are sensitive to vitamin D. Therefore, to overcome these obstacles, vitamin D administration should be considered after molecular identification of the disease type. Additionally, vitamin D analogs should be used to mitigate potential adverse effects.

Conclusion

The active metabolite 1,25-dihydroxyvitamin D3 stimulates cellular differentiation, suppresses proliferation, and triggers apoptosis in acute leukemias (ALL and AML) by means of vitamin D receptor (VDR)-mediated transcriptional regulation. A higher tumor burden, a worse response to treatment, and an advanced disease stage are all associated with low vitamin D levels in chronic leukemias (CLL and CML). Based on these findings, we demonstrate that a broad strategy that incorporates a plant-based diet, sufficient physical activity,[76] and/or eventually vitamin D supplementation may be useful to combat blood malignancies, such as leukemia and lymphoma, and, more broadly, non-communicable diseases and their comorbidities.

Authors' Contribution

Conceptualization: Abolfazl Jalilvand, Nesa Rashidi.
Supervision: Nesa Rashidi.
Writing–original draft: Abolfazl Jalilvand, Mohammadhossein Kouhpaeenejad, Leila Faeli, Nesa Rashidi.
Writing–review & editing: Abolfazl Jalilvand, Mohammadhossein Kouhpaeenejad, Leila Faeli, Nesa Rashidi.

Competing Interests

The authors declare no conflict of interest.

Ethical Approval

Not Applicable.

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