Vitamin D and its receptor polymorphisms: New possible prognostic biomarkers in leukemias

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Abstract

Several factors such as chromosomal translocations, gene mutations, and polymorphisms are involved in the pathogenesis of leukemia/lymphoma. Recently, the role of vitamin D (VD) and vitamin D receptor (VDR) polymorphisms in hematologic malignancies has been considered. In this review, we examine the possible role of VD levels, as well as VDR polymorphisms as prognostic biomarkers in leukemia/lymphoma. Relevant English language literature was searched and retrieved from Google Scholar search engine (1985-2017). The following keywords were used: vitamin D, vitamin D receptor, leukemia, lymphoma, and polymorphism. Increased serum levels of VD in patients with leukemia are associated with a better prognosis. However, low VD levels are associated with a poor prognosis, and VDR polymorphisms in various leukemias can have prognostic value. VD biomarker can be regarded as a potential prognostic factor for a number of leukemias, including acute myeloblastic leukemia (AML), chronic lymphoblastic leukemia (CLL), and diffuse large B-cell lymphoma (DLBCL). There is a significant relationship between different polymorphisms of VDR (including Taq I and Fok I) with several leukemia types such as ALL and AML, which may have prognostic value.

Introduction

Vitamin D (VD) is a fat-soluble vitamin and an endocrine hormone that plays a role in bone formation and integrity via calcium and phosphate absorption from the intestine and their transfer to bones. VD is also involved in proliferation and differentiation of different malignancies including prostate, breast, bone and leukemias. Effect of VD as hormone on metabolism and immune cell regulation of skin is also discussed. Studies have been reported on gamma (IFNγ). VD is also capable of controlling the differentiation and that it has the ability to modulate the innate and adaptive immune system, affecting the proliferation of T helper type 1 (Th1) lymphocytes by repressing immune factors such as interferon gamma (IFNγ). VD is also capable of controlling the differentiation of immune cells such as Dendritic Cells (DCs), which indicates its immunosuppressive role along with calcium (Ca) homeostasis in immune processes.

VD is a polymorphic gene. rs1544410 (Bsm I), rs7975232 (Apa I), rs2228570 (Fok I), rs731236 (Taq I), and rs11568820 (Cdx2) are among the polymorphisms specifically addressed in this review. Essentially, these polymorphisms are enzymes that are distinguished due to the variances in their restriction enzyme cleavage sites.11 VDR is a transcriptional factor (TF) binding 1α 25(OH)2D3 in extremely low concentrations, and the effects of VD hormone are thus mediated by VDR.3 The relationship between VDR and the pathogenesis of prostate, breast, melanoma, and colorectal cancers has been reported.5-7,12,13 In recent years, due to further attention to VDR, the prominent role of this TF in
Vitamin D and gene regulation

In general, the involvement of VDR in nine signaling pathways has been reported. Among the cellular signaling pathways associated with VDR, three pathways have been studied more extensively than others: Lipid Signaling Pathway, PI3K Pathway, and MAPK pathway, in which VD plays a significant role. Studies have identified a group of hematopoietic regulator networks, including a network with presence of VDR that is involved in the differentiation of granulocytes and monocytes. On the other hand, the involvement of 1α 25(OH)2D3 in monocyte differentiation has been indicated.3 In a study using Iregulon plugin in Cytoscape software, 1045 target genes have been recognized for VDR. Following the classification of these genes based on their biological roles, it was found that 68 genes were present in cancer-related pathways, and that 40 genes were among the markers dysregulated in various cancers. In addition, 54 genes were among the factors that played a role in MAPK signaling pathway (Table 1). This classification was based on the Kyoto encyclopedia of genes and genome (KEGG) database. MAPK pathway has been recognized as one of the most important pathways involved in the development of cancers, especially leukemias.18

Vitamin D level in leukemia/lymphoma

Most patients with newly diagnosed acute myeloblastic leukemia (AML) show VD deficiency, and low levels of VD are significantly associated with poor disease outcomes, but higher VD levels are related with a better outcome.19 VD level seems to be related to translocation type; for example, most patients with internal tandem duplications of fms-like tyrosine kinase 3 (FLT3-ITD) are associated with low VD levels, and the improvement of VD serum levels can entail better outcomes in patients.20 VD decreases proliferation and increases differentiation of hematopoietic stem cell (HSC) via modulation of main regulatory pathways for HSC proliferation and survival such as MAPK pathway and PI3K/AKT/mTOR.21 So hypothetically and based on this finding we can assume that VD and its analogues can inhibit excess proliferation of Leukemic stem cell (LSC) in leukemias. Also, it has been reported that co-treatment of leukemic cells with VD or its analogues modulate proliferation and differentiation of leukemic cells through changing the expression of hematopoietic growth factors, cytokines and their receptors.22 In addition, studies suggested that the effect of VD and its analogues as a differentiation therapy on leukemic cells relied on different cytogenetic abnormalities of leukemic blast cells.23 It is of note that combination of antioxidants and ceramide derivatives with VD or its analogues not only increased differentiation related cell cycle arrest of leukemic cells but also limited side effects of VD like hypercalcemia. Such differentiation agents in combination of VD can be an effective candidate for the treatment of leukemias.24,25 It is interesting that hematopoietic differentiation control of VD derivatives is attributed to inhibition and induction of erythroid and monocytic differentiation, respectively.26,27 It has been suggested that p27kip1, a cell cycle regulator of MAPK pathway, is a target gene of miR-181a and modulation of this miR can confer differentiation in cell lines such as HL60 and U937.28 So, hypothetically modulation of miR-181a could be of therapeutic importance in AML. Evaluation of low VD levels and their effects on Azacitidine, which is a chemotherapy drug used in patients with secondary oligoblastic AML and myelodysplastic syndrome (MDS), showed that elevating VD levels following treatment with this drug could lead to increased survival of patients. The in vitro synergistic anti-proliferative effect of Azacitidine in combination with VD has likely led to this improvement.29 In children with acute lymphoblastic leukemia (ALL), it has also been shown that low levels of VD and the consequent defect in Ca homeostasis are directly related to clinical outcomes of ALL patients, including skeletomuscular pain.12

Table 1. Evaluation of VDR targets by Iregulon plugin and cytoscape software.

| ID category | Category name                           | Benjamini | P-value | Fold enrichment | N. Genes |
|-------------|----------------------------------------|-----------|---------|-----------------|----------|
| hsa05200    | Pathways in cancer                      | 2.53e-12  | 2.57e-15| 2.762           | 68       |
| hsa04020    | Calcium signaling pathway               | 2.22e-11  | 4.50e-14| 3.4             | 46       |
| hsa04360    | Axon guidance                          | 1.61e-8   | 5.14e-11| 3.484           | 34       |
| hsa04971    | Gastric acid secretion                 | 1.61e-8   | 6.55e-11| 4.45            | 25       |
| hsa04010    | MAPK signaling pathway                 | 2.76e-8   | 1.40e-10| 2.502           | 54       |
| hsa04725    | Cholinergic synapse                    | 5.79e-8   | 4.11e-10| 3.55            | 30       |
| hsa05202    | Transcriptional dysregulation in cancer| 5.79e-8   | 4.02e-10| 2.909           | 40       |
| hsa04960    | Aldosterone-regulated sodium reabsorption| 1.59e-7  | 1.29e-9 | 5.609           | 17       |
| hsa04510    | Focal adhesion                         | 2.66e-7   | 2.43e-9 | 2.667           | 42       |
| hsa05146    | Amoebiasis                             | 1.92e-6   | 1.85e-8 | 3.21            | 28       |
In Chronic Lymphoblastic Leukemia/Small Lymphoblastic Lymphoma (CLL/SLL), inadequate levels of VD have been associated with decreasing time to treatment and undesirable overall survival (OS) in patients. Assessment of the efficacy and safety of VD supplementation indicated that VD levels could be corrected without any risk for patients by administering different VD doses as required.\(^{30,31}\) The result of this study confirmed the prognostic role of VD levels in CLL/SLL since the VD levels have shown a significant correlation with OS. In Follicular Lymphoma (FL), there is a strong correlation between low VD levels and a poor outcome of FL.\(^{32}\) The study of cutaneous T-cell lymphoma (CTCL) patients with Mycosis Fungoides and Sézary’s Syndrome showed that the correction of VD deficiency and the type of supplement had no effect on overall clinical response, while vitamin deficiency affected the reduced synthesis of antimicrobial peptides mediated by VDR pathway, which was possibly associated with chronic infections in CTCL patients.\(^{33}\) Among Non-Hodgkin’s Lymphomas (NHL), Diffuse Large B-cell Lymphoma (DLBCL) patients having high interleukin 10 (IL-10) levels are associated with a poorer event-free survival (EFS) than those with lower IL-10 levels.\(^{34}\) IL-10 is a target of VDR,\(^{35}\) and perhaps the use of VD and its analogues repress this cytokine through VDR mediation. Investigation of the relationship between VD deficiency with DLBCL and T-cell lymphoma revealed that VD deficiency was associated with inferior OS and EFS in both diseases.\(^{36}\) In DLBCL patients treated with Rituximab, VD deficiency has been introduced as a risk factor, because VD deficiency inhibits the Rituximab-mediated toxicity; therefore, VD correction could increase the efficacy of Rituximab.\(^{37}\) There are also reports of the prognostic role of VD in other hematologic malignancies; for example, VD deficiency is an undesirable prognostic marker in multiple myeloma (MM).\(^{38,39}\) Thus, considering these findings, we can hypothesize that not only the prevalence of VD deficiency is high in hematologic malignancies, but it reduces the response of these patients to treatment. It is recommended to conduct clinical trials to evaluate the effect of VD supplementation on the therapeutic outcomes of these patients. Increasing Ca concentrations in CLL patients is associated with increased survival and proliferation of B-cells, as well as their resistance to apoptosis.\(^{40}\)

Role of vitamin D receptor polymorphisms in leukemias

Acute leukemias

Apa I, Fok I, Taq I, and Bsm I are important polymorphisms of VDR gene, which have been closely correlated with AML. For example, Taq I expression is associated with Complete Remission (CR) and prognosis, so that 70% of CR patients have the TC genotype and 30% have TT genotype of Taq I polymorphism.\(^{41}\) In the study of children with ALL, Apa I, Taq I, Bsm I, Cdx2, and GATA polymorphisms have been evaluated. In ALL patients, Bone Mineral Density (BMD) is damaged due to corticosteroid and methotrexate (MTX) consumption. Since the Tt genotype of Taq I and Bb genotype of Bsm I are related with a higher BMD in ALL patients, it is likely that the patients harboring these polymorphisms show a better response to treatment and be more resistant to drug-induced damage\(^{42}\) (Table 2).

### Chronic leukemias

The analysis of Fok I polymorphism in Chronic Myeloblastic Leukemia (CML) patients showed that ff was the dominant genotype among patients.\(^{43}\) This allele has already been shown to be associated with an increased risk of T-cell lymphoma.\(^{44}\) According to these findings, it may be assumed that the f allele has an uncertain role in the pathogenesis of CML, and further research is needed to understand its role and effect on prognosis of the disease, while this allele might also be used as a prognostic factor because its presence is related with a higher risk of T-cell lymphoma. The antagonistic effect of microRNA-214 (miR-214) on VDR signaling and inhibiting Hedgehog (Hh) signaling has been reported.\(^{45}\) Studies have shown that Hh antagonists may play a role in the treatment of CML and B-ALL.\(^{46,47}\) VDR antagonists inhibiting Hh signaling are likely to treat patients with CML and even patients with other leukemia types. There is a relationship between the mutated Ff genotype of Fok I polymorphism and the increased risk of CLL, but this relationship has little effect on the clinical outcome of the disease\(^{48}\) (Table 3).

### Lymphomas

Fok I polymorphism in Plasmablastic Lymphoma (PBL) potentiates tumor growth inhibition.\(^{49}\) A relationship has been reported between Taq I, Fok I, and Bsm I variants with some types of NHL; for example, the B allele of Bsm I polymorphism and t allele of Taq I polymorphism are associated with DLBCL, and the f allele of Fok I polymorphism is related with T-cell lymphoma.\(^{44}\) The study of Hodgkin’s lymphoma (HL) and NHL cases showed that VDR was strongly expressed on HL tumor cells, and it was concluded that VDR was a diagnostic factor for HL. However, as there was not a high expression of VDR in NHL cases, the same function of VDR in NHL was not addressed by this study.\(^{50}\) In another study, no correlation was found between Fok I, Bsm I, Taq I, Apa I, and Cdx2 variants with disease progression in HL patients.\(^{51}\) Increased interleukin-6 (IL-6) is a major cause of ane-

Table 2. Different genotypes of Taq I polymorphism in acute leukemias.

| Effect of genotype | Chromosome | Leukemia | Ref. |
|--------------------|------------|----------|------|
| Tt genotype is associated with higher BMD | 12q13.11 | ALL | 42 |
| TC and TT genotypes are associated with CR | 12q13.11 | AML | 41 |

ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; BMD: Bone mineral density; CR: Complete remission.

Table 3. Different genotypes of Fok I polymorphism in chronic leukemias.

| Effect of genotype | Chromosome | Leukemia | Ref. |
|--------------------|------------|----------|------|
| Ff genotype is associated with higher risk for CLL | 12q13.11 | CLL | 48 |
| Ff genotype has a significant correlation with CML | 12q13.11 | CML | 43 |

CLL: chronic lymphoblastic leukemia; CML: chronic myeloblastic leukemia.
emia in HL, and because IL-6 gene is a target of VDR, it is possible to manipulate VDR and affect the expression of IL-6 gene to reduce anemia complications in HL patients. Figure 1 shows vitamin D metabolism and targets of vitamin D receptor.

### Other blood disorder

In MM, the TT genotype of Taq I and the mutated C allele of Taq I have a significant relationship with increased risk of disease. Another study reported that Fok I polymorphism inhibited tumor growth in MM patients. A study has indicated that DCs in MM patients have an abnormal function and that their defects are related to tumorigenicity in cancer. This study showed that enhanced IL-6 production by tumor, which was correlated with DC deficiency, led to the inhibition of precursor DC colonies and switched commitment of these CD34+ cells to monocytes. On the other hand, studies have shown that IL-6 is among VDR targets repressing this cytokine. Therefore, manipulation of VDR may reduce tumorigenesis of cancer by affecting IL-6.

In Aplastic Anemia (AA), GG genotype and G allele of Bsm I polymorphism are correlated with the increased risk of AA. Moreover, the supportive role of GA genotype and G allele of Bsm I has been raised in this disease. Carriers of TT genotype from Taq I polymorphism show a poor response to treatment and even have a higher risk of MDS/AML transformation, and Taq I polymorphism could be considered as a prognostic biomarker for AA. Decreased expression of VDR may be related with hyperimmunity of AA patients, and VD supplementation may be able to partially correct the abnormal immune function of patients through the effects of VDR signaling pathway (Table 4).

### Table 4. VDR Polymorphisms related with leukemias.

| VDR gene polymorphism | Allele-genotypes | Chr. | Effection mechanism in prognosis | Leukemia | Ref. |
|-----------------------|------------------|------|---------------------------------|----------|-----|
| Taq I                 | TT and TC        | 12q13.11 | CR and GP                      | AML      | 41  |
| Taq I                 | Tt               | 12q13.11 | Higher BMD                     | ALL      | 42  |
| Bsm I                 | Bb               | 12q13.11 | Higher BMD                     | AML      | 41  |
| Fok I                 | F                | 12q13.11 | Probable role in CML pathogenesis | CML | 43  |
| Fok I                 | Ff               | 12q13.11 | Higher risk for CLL            | CLL      | 48  |
| -                     | -                | 12q13.11 | Strong expression of VDR may be a marker for HL tumor cells | HL | 50  |
| Taq I                 | T                | 12q13.11 | Correlated with DLBCL          | DLBCL    | 44  |
| Fok I                 | F                | 12q13.11 | Correlated with T cell lymphoma | T cell lymphoma | 44  |
| Taq I                 | TT and C         | 12q13.11 | Correlated with MM             | MM       | 53  |
| Bsm I                 | GG               | 12q13.11 | Higher risk for AA             | AA       | 55  |
| Taq I                 | TT               | 12q13.11 | Poor response to treatment     |          |     |

### Table 5. VDR targets in leukemias.

| Target gene | Chromosome | Type of effect | Leukemia | Ref. |
|-------------|------------|----------------|----------|-----|
| CAMP        | 3p21.31    | Unknown        | AML      | 65  |
| CDKN1B      | 12p13.1    | Activation     | AML      | 62  |
| CYP1A1      | 15q24.1    | Unknown        | AML      | 64  |
| EGFR        | 7p11.2     | Repression     | AML      | 64  |
| HOXA10      | 7p15.2     | Activation     | AML      | 67  |
| IL-6        | 7p15.3     | Repression     | AML      | 15  |
| SKP2        | 5p13.2     | Repression     | AML      | 68  |
| CDKN1B      | 12p13.1    | Unknown        | ALL      | 63  |
| IL-10       | 1q32.1     | Repression     | ALL      | 35  |
| CDKN1B      | 12p13.1    | Unknown        | CML      | 63  |
| CYP1A1      | 15q24.1    | Unknown        | CML      | 64  |
| HOXA10      | 7p15.2     | Activation     | CML      | 67  |
| IL-2        | 4q27       | Repression     | CLL      | 14  |
| IL-6        | 7p15.3     | Repression     | CLL      | 15  |
| BGLAP       | 1q22       | Unknown        | MM       | 69  |
| CKRN1B      | 12p13.1    | Activation     | MM       | 62  |
| IL-6        | 7p15.3     | Repression     | MM       | 15  |
| SKP2        | 5p13.2     | Repression     | MM       | 68  |
| CDKN1B      | 12p13.1    | Activation     | HL       | 63  |
| ERBB2       | 17q12      | Unknown        | HL       | 70  |
| IL-10       | 1q32.1     | Repression     | HL       | 35  |

CAMP: cathelicidin antimicrobial peptide; CDKN1B: cyclin dependent kinase inhibitor 1B; CYP1A1: cytochrome P450 family 1 subfamily A member 1; EGFR: Epidermal growth factor receptor; HOXA10: homeobox A10; IL-6: interleukin 6; SKP2: S-phase kinase associated protein 2; IL-1R: interleukin-10; IL-2: interleukin-2; BGLAP: bone gamma-carboxylase protein; ERBB2: erb-b2 receptor tyrosine kinase 2.
Discussion

Several genes are affected by VD and its receptor (VDR), through which VD regulates gene expression in vital biological processes and metastasis; on the other hand, VDR plays a role in cell differentiation via signaling pathways such as MAPK and PI3K (Table 5). In this regard, anticancer activity of VDR is attributed to its inhibitory and promotion effect on proliferation and differentiation of malignant cells, respectively. Increased expression of p21 and p27 and consequently G0/G1 cell-cycle arrest is involved in differentiation process which is induced by VDR. So, VD, VDR and its analogues as differentiative inducer agents can be a therapeutical approach for leukemias in future. The above findings justify the role and effect of VD and VDR in leukemia/lymphoma. A higher level of VD in serum of AML patients is associated with a good response to treatment, longer survival, and better prognosis; therefore, low VD levels can be considered as a risk factor that can be readily and economically improved. Overall, low VD levels can be regarded as a biomarker of poor prognosis in patients with AML and ALL, which is associated with an unfavorable OS in patients with SLL/CLL and T-cell lymphoma. Low VD is also indicative of a poor

Figure 1. Vitamin D metabolism and targets of vitamin D receptor are shown in this figure. Vitamin D receptor targets different genes and thus affects biological functions. VD: vitamin D; CYP: cytochrome P; DHCR-7: 7-Dehydrocholesterol reductase; VDR: vitamin D receptor; TSPAN7: Tetraspanin-7; BCL6: B-cell lymphoma 6 protein; LDB1: LIM domain-binding protein 1; MAX: myc-associated factor; CEBPB: CCAAT/enhancer-binding protein beta; NR4A3: nuclear receptor subfamily 4, group A, member 3; RXRB: Retinoid X receptor beta; TCF3: Transcription factor 3; CDKN1B: Cyclin-dependent kinase inhibitor 1B; MMP9: Matrix metallopeptidase 9; ERG: ETS-related gene; WTT: Wilms’s tumor; IGF1: Insulin-like growth factor 1; MLL: myeloid/lymphoid or mixed-lineage leukemia; RARA: Retinoic acid receptor alpha; FLI1: Friend leukemia integration 1; MDM2: Mouse double minute 2 homolog; IL2RB: Interleukin-2 receptor subunit beta; TRAF2: TNF receptor-associated factor 2; RAC2: Ras-related C3 botulinum toxin substrate 2; PDGFRA: platelet-derived growth factor receptor; AT2: Activating transcription factor 2; TGFB: Transforming growth factor beta; PTPN7: Protein tyrosine phosphatase non-receptor type 7; AKT1: RAC-alpha serine/threonine-protein kinase; FGFR1: Fibroblast growth factor receptor 1; FGFR10: Fibroblast growth factor receptor 10; MAPK10: Mitogen-activated protein kinase 10; PRKCG: Protein kinase C gamma type.
prognosis in MM. Taq I seems to be a biomarker of good prognosis in ALL and AML, and mutated Fok I phenotypes due to the presence of f allele could be used as a prognostic marker in CML and CLL patients. This is while Fok I in MM and PBL may be associated with a good prognosis. Taq I polymorphism in MM is associated with an increased risk of associated disease and has prognostic value. In AA, Bsm I and Taq I are associated with a poor prognosis.

The association between different miRs and VD and VDR should be studied more because of possible therapeutic role of miRs. It has been suggested that the active form of VD exerts its anti-tumor effects by regulation of gene transcription and miR regulation. MiR-214 is an antagonist of VDR. Studies indicate that miR-214 negatively regulates phosphatase and tensin homolog (PTEN) at protein level and activates the Akt signaling pathway, and that the reduced PTEN gene expression is related with a poor prognosis in AML. In patients with relapse, PTEN gene expression is lower than that of normal people. The role of miR-214 in the down regulation of PTEN gene has also been indicated in CLL. Thus, considering the fact that miR-214 is an antagonist of VDR, miR-214 manipulation could resolve the negative effect of this miR on VDR, improving the prognosis of AML and CLL patients by increasing the expression of PTEN gene. Furthermore, VDR can play an important role in future therapeutic strategies of cancer via targeting a number of targets, particularly IL-2, IL-6, IL-10 cytokines as well as CDKN1B gene. For instance, the aberrant IL-6 signaling contributes to cancer through signal transducer and activator of transcription 3 (STAT3). IL-2 and IL-6, which are among VDR targets, play a role in B-cell development. Therefore, the repression of these two cytokines by VDR following the consumption of VD and its analogues could have beneficial effects on CLL patients.

Conclusion and future perspectives

In summary, it was shown in this review that VD and VDR polymorphisms could be used as prognostic biomarkers for various types of leukemia/lymphoma, including AML, CLL/SLL, DLBCL, T-cell lymphoma, MM and AA. There is a significant relationship between polymorphisms of Taq I, Fok I, and Bsm I with leukemia/lymphoma.

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