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REVIEW ARTICLE

Vitamin D deficiency and graft-versus-host disease in hematopoietic stem cell transplant population

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Abstract
Vitamins are the organic compounds that have long been known to play a significant role in our body by functioning as hormones and antioxidants. Vitamin D, a fat-soluble vitamin, is the main regulator of calcium hemostasis in our body. At the same time, it is also known to show its potential effects on the immune system by modulating the differentiation, activation, and proliferation of T and B lymphocytes. The immunomodulatory properties of vitamin D are also known to have a crucial role in the prevention and treatment of graft-versus-host disease. Patients undergoing hematopoietic stem cell transplantation are particularly at risk of vitamin D deficiency. This review article expands our understanding of vitamin D, its immunomodulatory effects, and its role in prevention and treatment of graft-versus-host disease.
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Introduction

Vitamins are the organic compounds in our body that are essential for fulfilling a large number of physiological processes by functioning as hormones and antioxidants, and as regulators of tissue growth and differentiation [1,2]. Vitamin D, in its active form as vitamin D_3, is the main regulator of calcium hemostasis in our body and is important for the mineralization of bones [3,4]. It is a fat-soluble vitamin synthesized in the skin as 7-dehydrocholesterol. This process requires ultraviolet radiation from the sunlight [5,6]. 7-Dehydrocholesterol is then converted in the liver to 25-dihydroxycholesterol, the main circulating form of vitamin D [5]. Finally, 25-dihydroxycholesterol is metabolized in the kidney as 1,25-dihydroxycholesterol or calcitriol, the physiologically active form of vitamin D (see Table 1).

Apart from its traditional actions of regulating calcium and phosphate reabsorption and maintaining the adequate amount of these minerals in our body [4,7,8], calcitriol also play additional roles including cell regulation, apoptosis, antiproliferative, anti-inflammatory, and immunoregulatory functions [4,7,8]. It can also be metabolized by immune cells such as activated T cells and B cells [6,9]. Interestingly, vitamin D also performs immunomodulatory actions including the inhibitory effects on T lymphocytes, decreasing the proliferation of B cells, plasma cells, and immunoglobulin G (IgG) secretion [10,11]. This immunomodulatory action is attributable to its interaction with vitamin D receptors (VDRs) expressed on the immune cells including dendritic cells, macrophages, and B and T lymphocytes [12,13]. The upregulation of vitamin D receptors on immune cells is also thought to play a critical role in the development of graft-versus-host disease (GVHD) in patients with bone marrow transplant (BMT) [12,13]. A study by Robien et al. [14] suggests that maintaining adequate levels of vitamin D in BMT recipients reduces the risk of GVHD, infections, graft rejection, and disease relapse. It has also been shown that the incidence of GVHD in post-transplant patients is lower among those with adequate vitamin D when compared to the vitamin D-deficient population of patients. This review article expands our understanding of vitamin D, its immunomodulatory effects, and important role in prevention and treatment of GVHD.

Immunomodulatory effects of vitamin D-effects of B and T lymphocytes

The active form of vitamin D, $1,25(OH)_2$ vitamin D (or calcitriol), influences the immune system in highly specific ways, which extends to both innate and adaptive immune responses [15,16]. Calcitriol shows an inhibitory effect on adaptive immunity by T cell proliferation and reducing the expression of interleukin-2 (IL-2), interferon (IFN)-gamma, and mRNA in T lymphocytes [15—17]. These inhibitory effects are highly pronounced in the compartment of memory T lymphocytes [15]. The overall action is to block the induction of helper T lymphocyte cytokines such as IFN-gamma, and to promote TH-2 cell responses, by enhancing IL-4 production [15].

In addition to the inhibitory effects on T lymphocytes, calcitriol also reduces proliferation of B lymphocytes, IgG secretion, and differentiation of plasma cells [18—20]. Vitamin D also inhibits cells of the innate immune system by inhibiting the differentiation and maturation of dendritic cells-via reduction of major histocompatibility complex class II (MHC-II) expression molecules and of CD40, CD80, and CD86 [9,21—23]. Some of the effects of vitamin D on the innate immune system are stimulatory, for example, stimulation of *in vitro* monocyte proliferation, and increase in the production of IL-1 by monocytes and macrophages [17,24,25]. The role of vitamin D in limiting the pathologic immune responses also predicts its crucial role in autoimmune processes [9,25]. It is interesting to know that calcitriol levels are found to be low in patients with systemic lupus erythematosus (SLE) and type 1 diabetes [26,27]. The level of vitamin D, however, is inversely related to the disease activity in rheumatoid arthritis [28,29]. Vitamin D deficiency may also predispose to autoimmune disease, such as type 1 diabetes [30,31]. A study by van Etten et al. [9] outlines that children with rickets, which is caused by vitamin D deficiency, are more prone to get diabetes and infections [30,32]. The infectious complications in them are attributable to calcitriol's capacity to upregulate bactericidal power of the macrophages [6,17,33,34].

Some other actions of vitamin D at the cellular level include anti-inflammatory effects, inhibition of angiogenesis, and anticancer effects via calcitriol [35—40].

Deficiency of vitamin D in hematopoietic stem cell transplant patients

One of the potential long-term complications of solid transplant, as well as BMT, is osteoporosis and osteoporotic bone fractures [41]. In a prospective study on 44 patients who underwent bone marrow transplantation, 6%—9% showed decreased bone mineral density (BMD) in the first 6 months after BMT. The rate of bone turnover was also found to be increased during the first year of transplantation. From 12 months after BMT, the BMD of the lumbar spine area increased by 2.4% ($p = .002$). Other BMD changes included the femoral neck ($p = .087$), trochanter area, and total hip ($p = .095$) [41]. The excretion of bone resorption marker type I carboxyterminal telopeptide was found to be increased by 41% ($p = .0001$), thus highlighting the importance of vitamin D deficiency in the first 2 months after transplant [41].

It has been reported that most of the bone loss after BMT happens in the first 6 months [42]. There are a number of factors that could explain low vitamin D levels after BMT.

Table 1 Some common signs and symptoms of chronic graft-versus-host disease (GVHD).

Organ or site	Diagnostic (sufficient for diagnosis)	Distinctive (insufficient alone for diagnosis)	Common (seen in both acute and chronic GVHD)
Skin	Poikiloderma, lichen planus-like, sclerosis or morphea	Depigmentation	Erythema, maculopapular rash
Nails		Dystrophy, onycholysis/nail loss	
Scalp and body hair		Alopecia, scaling	
Mouth	Lichen planus-like, vaginal scarring or stenosis	Xerostomia, mucocoele, ulcers, pseudomembrane	Gingivitis, erythema
Eyes		Keratoconjunctivitis, sicca syndrome	
Genitalia	Lichen plus-like, vaginal scarring, or stenosis	Erosions, fissures, ulcers	
Liver			Mixed hepatitis
Lung	BO by lung biopsy	BO diagnosed by pulmonary function tests and radiology	
Muscle and Fascia	Fasciitis, joint contractures	Myositis and polymyositis	
Hematopoietic			Thrombocytopenia, eosinophilia, hypo or hypergammaglobinemia, autoantibodies
Other			Effusions

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BO.

Drugs such as corticosteroids and cyclosporine A are the probable cause of this rapid bone turnover, along with poor diet and avoiding sun exposure [42]. This low BMD and deficiency of vitamin D is not just limited to the adult patients, but also occurs in the pediatric cancer population. Children are also found to have high prevalence of asymptomatic fractures after hematopoietic stem cell transplantation (HSCT) [41]. Bechard et al. [43] found significant bone loss and vitamin D deficiency, and low BMD during the first 30 days after transplant. This bone loss persisted until 100 days after the transplant (adjusted mean 25OHD dropped from 29.2 to 17.7 ng/mL at 100 days after transplant). Vitamin D deficiency was found in 50% of the children who underwent HSCT [43]. A case-control study from the United Kingdom was conducted on 61 children with a history of malignancy. It found low vitamin D levels in 62% of the cases (25OHD < 20 ng/mL; $p < .01$). A similar study from Brazil supports these finding by reporting a high prevalence of 25-hydroxyvitamin D deficiency (25.7 ng/mL, s = 31.9 ng/mL) after HSCT (32% vs. 8%, $p = .01$). One hundred eighty days after transplantation, vitamin D levels were further decreased (20.9 ng/mL) among the study participants ($p = .01$) [43]. All the above studies recommend the assessment of vitamin D levels and regular supplementation after HSCT in children and adults [43,44].

Vitamin D and chemotherapy-induced toxicity

Low levels of vitamin D have been linked with increased occurrence of infections, tuberculosis, breast cancer, and colon cancer [6]. However, the correlation between vitamin D deficiency and increased incidence of chemotherapy-induced toxicity has not been widely studied [45]. A case report by Fink et al. [46] mentioned the case of a 59-year-old female with history of breast cancer, receiving chemotherapy (docetaxel, carboplatin) developed severe stomatitis and dysgeusia during the course of her chemotherapy. The serum vitamin D levels were found to be severely reduced, 6.3 ng/mL (reference range, 20—60 ng/mL). The patient was started on vitamin D supplementation, and her stomatitis, dermatitis, and altered taste symptoms showed marked improvement in the span of 2 weeks. Another patient, who was receiving chemotherapy for pancreatic cancer mentioned in the same case report, showed significant improvement in his symptoms of dysgeusia after his serum vitamin D levels were improved via supplementation [46]. A study by Kitchen et al. [47] demonstrates contrary results in relating vitamin D deficiency with chemotherapy-induced toxicity. Their study included 165 cancer patients; 29 out of 41 (71%) patients suffered from grade II chemo-induced toxicity, versus 136 out of 200 (68%) patients with low vitamin D levels [46]. The study found increased occurrence of fatigue, hand—foot reactions, and dry skin among patients with normal vitamin D levels compared with the deficient group. Overall, the study did not find any statistically significant results or positive correlation between low vitamin D levels and chemotherapy-induced toxicity ($p = .78$) [46]. A larger multicenter prospective study including a larger sample size is required to study this association [46].

Graft versus host disease

GVHD is the result of immunological attack by the donor T lymphocytes after allogeneic HSCT. The immunological attack is on the recipient organs such as liver, gut, and skin tissue. The severity of the condition depends on the recipient's age, source of the transplant, toxicity profile of the

drugs used during the process of transplantation, and the use of GVHD prophylaxis [47].

According to the consensus by the National Institutes of Health (NIH), GVHD is divided into two main types: acute and chronic, along with their subcategories. Acute GVHD has strong inflammatory components and includes the disease of gastrointestinal symptoms (severe diarrhea and abdominal pain), cholestatic hepatitis, and maculopapular erythematous rash. Acute GVHD also includes the persistent and recurrent cases of GVHD and the late-onset acute case occurring after 100 days of transplantation. Chronic GVHD disease shows more autoimmune and fibrotic features, and includes conditions such as bronchiolitis obliterans syndrome, cutaneous sclerosis, and an overlap syndrome that has the distinctive characteristics of both chronic GVHD along with acute GVHD features [47—49].

GVHD is fatal in almost 15% of hematopoietic transplant recipients [47]. Chronic GVHD alone occurs in about 30%—65% of the transplant recipients and has a 5-year mortality rate of 30%—50% [47].

Acute GVHD includes the donor T lymphocytes' allogeneic reaction against the recipient tissues medicated by cell-surface factors [50]. The tissue damage by T lymphocytes calls other immune cells, such as neutrophils and natural killer cells (NK cells), which amplifies tissue damage and thus initiating the GVHD in its full form [47].

Current literature supports the involvement of innate immune system in initiation and augmentation of acute GVHD [51]. Bacterial lipopolysaccharides are released from the injured tissue activating the Toll-like receptors (TLRs) causing cytokine activation, thus favoring the development of acute GVHD [51]. Also, the polymorphism of the genes that code TLR4 and NOD-like receptors (NLRs) are associated with higher unpredictable incidence of GVHD [52,53]. The role of antigen presenting cells (APCs) is also important in GVHD. The introduction of minor histocompatibility antigens by MHC-I on recipient APCs can lead to CD8 T cell-dependent acute GVHD, and the donor APCs can amplify this response [54,55]. In the studies performed on mouse, the depletion of B lymphocytes results in decreased incidence of GVHD. However, B cells can also have a protective role in GVHD by controlling the differentiation of T lymphocytes and by inhibiting the proliferation of alloantigen specific T lymphocytes. These functions of B lymphocytes are mediated via secretion of IL-10 and by the induction of alloantigen-specific regular T lymphocytes by B cells [56—58].

For chronic GVHD, recent data show that its complex immune pathology involves both B and T lymphocytes [48]. B cells are involved in chronic GVHD via circulating antibodies reacting with recipient cells [59,60]. There are two classes of antibodies that come under this umbrella. First, the antibodies directed against antigens are not present in the recipient. The example includes antibodies against the HY proteins (Y-chromosome-encoded proteins) in male patients who receive allogeneic stem cell transplant form female donors [60,61]. These HY antibodies are detected in about 80% of chronic GVHD patients who are males and have received the transplant from female donors [62]. The second class of antibodies among chronic GVHD patients are the ones directed against the nonpolymorphic autoantigens. The example includes antibodies directed against the platelet-derived growth factor receptor leading to fibrosis in systemic sclerosis and in chronic GVHD [63—65]. B cells also contribute to chronic GVHD by antibody-independent mechanisms, such as via production of cytokines and chemokines, antigen presentation, and by working as regulatory cells [59]. T cells also play an important role in chronic GVHD. The immunological mechanisms in chronic skin GVHD demonstrate upregulation of TH1/TH17/cytokines, chemokines, and elevation of IFN-gamma and IL-17 producing CD8 T cells [65,66]. Studies have also reported that patients with active chronic GVHD have low levels of CD4 T cells when compared with the non-chronic GVHD cases [67,68]. Thus, research suggests the complex involvement of both T and B cells in the pathology of chronic GVHD.

Vitamin D and hematological malignancies-role in GVHD

It has been mentioned in the literature that patients with HSCT are deficient in vitamin D [69]. Several reasons behind low vitamin D levels include avoiding sun exposure (to reduce the risk of skin cancer, because of their immunosuppressed state after transplant), receiving immunosuppressive medications, inadequate intake, and organ system complications [69]. In addition to that, the deficiency of vitamin D in these patients has also been linked with increased incidence of GVHD. Several studies have supported this association. A study by Sproat et al. [69] conducted at the Cleveland Clinic (Cleveland, OH, USA) reports a positive association between low vitamin D levels and increased incidence of GVHD, corticosteroid use, and elevated parathyroid hormone levels after HSCT transplant. The study was conducted on a total 289 acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) patients after HSCT. Vitamin D levels were measured in 58 (20%) patients. Out of these, 52 (89.7%) patients had low vitamin D level and 6 (10.3%) had normal level. Most of the patients with low levels of vitamin D were suffering from GVHD (94.8%) and were taking corticosteroids (98.3%) [69].

There are studies that do not support the correlation of low vitamin D levels and GVHD. For example, Perera et al. [70] reviewed 492 patients with HSCT and reported a reduction in overall survival among patients with low vitamin D levels [<50 nmol/L; hazard ratio (HR) = 1.5, $p = .013$]. No significant differences were noted between GVHD and low vitamin D level. However, a positive inverse association was found between low vitamin D levels and mortality in patients with HSCT [70]. One salient study in showing a positive association between low vitamin D levels and development of chronic GVHD is by Glotzbecker et al. [71] In their retrospective cohort study, 53 patients underwent HSCT. The median serum vitamin D level was 21.9 ng/mL [71]. The cumulative incidence of chronic GVHD on Day 100 after HSCT was found to be 53.1% in patients with vitamin D levels < 25 ng/mL compared with 33.3% patients suffering from chronic GVHD with vitamin levels $\geq$ 25 ng/mL ($p = .13$). After 2 years, the cumulative incidence of chronic GVHD in patients with vitamin D < 25 ng/mL was 63.3%

compared with 23.8% with vitamin D levels $\geq$ 25 ng/mL (p = .009) [71]. The study further reports an increased risk of chronic GVHD in patients with low pre-transplant vitamin D levels (HR = 5.26, p = .02) [71]. Another study supports these findings by studying 12 patients with chronic GVHD having vitamin D deficiency. Eleven of these patients showed improvement after 6 months (5 complete responses and 6 partial responses) in symptoms of chronic GVHD after vitamin D supplementation was initiated [72]. A study by Rosenblatt et al. [73] in Boston, highlighted vitamin D's role in alloreactive immunological reactions. The author reports a case of a 26-year-old patient suffering from chronic GVHD (after HSCT for ALL). The patient was partially responsive to methyl prednisone, photophoresis, and mycophenolate mofetil, but showed dramatic clinical recovery and improving liver function tests once the deficiency of vitamin D was corrected [73]. The patient was then tapered off on steroids and performed well without revival of GVHD symptoms. Another case described in the same paper is that of a 47-year-old patient after HSCT for AML [73]. The patient was suffering from acute GVHD of the skin and gastrointestinal tract, and subsequently progressing to chronic GVHD of skin and liver. He was found to be deficient in vitamin D, and showed improvement in GVHD symptoms once the vitamin D therapy was commenced. This study interestingly reports clinical improvement in steroid refractory chronic GVHD cases after the correction of vitamin deficiency [73]. Ganestky et al. (Abramson Cancer Center, Philadelphia, PA, USA) conducted a study on 54 patients after HSCT. Patients with severe deficiency of vitamin D on Day 30 after HSCT (median, 20 ng/mL; range, 6—50) showed inverse correlation with acute skin GVHD (hazard ratio = 0.27, p < .001) [74]. These vitamin D deficient patients also showed 4-fold higher levels of CCR4 receptor (on the skin) on peripheral T lymphocytes. However, deficiency of vitamin D on Day 30 after HSCT did not show significant association with gastrointestinal symptoms of GVHD (HR = 2.16, p = .15), chronic GVHD, or overall mortality [74]. On the contrary, the retrospective cohort study on 116 patients from Sweden by von Bahr et al. [75] reported a high incidence of chronic GVHD in vitamin D-deficient patients after HSCT and not for acute GVHD [75]. The 2-year cumulative incidence of 56% was found in patients with chronic GVHD with vitamin D deficiency (<25 nmol/L) versus 31% in patients with vitamin D insufficiency (26—49 nmol/L), and 21% in the vitamin D sufficient group ($\geq$50 nmol/L) (p = .01) [75].

The above literature strongly supports the low levels of vitamin D prior to HSCT and a significant increase incidence of GVHD. Owing to the role of vitamin D in immunological processes, it is important that adequate levels of vitamin D should be maintained during the post-transplantation period [75]. The longer hospital stays, and avoidance of sun exposure because of increased risk of skin cancer likely result in severe vitamin D deficiency in patients who underwent HSCT [76]. Therefore, under these circumstances, it becomes increasingly important to replenish vitamin D stores via supplementation prior to and during immune reconstitution period. The higher doses of vitamin D (about 4000—6000 IE daily) would be necessary to keep the levels in normal range and reduce the risk of acute and chronic GVHD in stem cell transplant recipients [77].

Conclusion

The deficiency of vitamin D in the oncology setting is an important issue. The high prevalence of vitamin D deficiency among hematopoietic transplant recipients, its crucial role as an antiangiogenesis, anticancer agent, highlights the fact that standardized screening and supplementation of vitamin D is important in this patient population. Both acute and chronic GVHDs are the major cause of morbidity and mortality among BMT recipients. So far, an efficacious and straight clinical approach in prevention of GVHD is not available. The in-depth role of vitamin D in the prevention and treatment of acute and chronic GVHD is also not very clear. More research is necessary to understand the concepts of Vitamin D in immunology and its effect on expression of T lymphocytes, and to understand whether vitamin D deficiency causes early onset of GVHD and increases the severity of acute and chronic GVHD.

Conflict of interest

The authors declared that there is no conflict of interest.

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