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# Impact of a Replacement Algorithm for Vitamin D Deficiency in Adult Hematopoietic Stem Cell Transplant Patients

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Authors' disclosures of conflicts of interest are found at the end of this article.

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## Abstract

Adults undergoing hematopoietic stem cell transplant (HSCT) are at risk for vitamin D deficiency. After HSCT, exposure to sunlight is restricted, and patients may experience poor nutrition and malabsorption from HSCT-related side effects. Vitamin D affects bone health and immunologic processes. The aim of this project is to establish a process for monitoring and treating vitamin D deficiency and to evaluate if therapeutic vitamin D levels are attainable posttransplant using an HSCT vitamin D replacement algorithm. A multidisciplinary group led by advanced practice providers established a workflow for monitoring and supplementing vitamin D and created an HSCT vitamin D replacement guideline. The medical records of 144 adult HSCT patients were reviewed, and the records of another 72 patients were reviewed a year later. Historical baseline data before the intervention found that 81% of patients were vitamin D deficient and 30% received supplementation. Postintervention and at 1-year follow-up, 76% and 65% of patients were vitamin D deficient before transplant and 97.1% and 100%, respectively, received supplementation for vitamin D deficiency. Post-HSCT compliance with monitoring demonstrated that approximately 91% of patients had a vitamin D level checked within 6 months of transplant. After implementation of the algorithm, there was a statistically significant difference ($p < .001$) between deficient vitamin D levels pretransplant (72.9%) and posttransplant (26.4%). Results demonstrate sustained compliance over a 2-year period with monitoring and supplementation of vitamin D pre- and peritransplant. Aggressive vitamin D repletion posttransplant decreased the incidence of vitamin D deficiency in HSCT patients. Further study is needed to investigate the long-term effects of vitamin D repletion on posttransplant complications.

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Patients undergoing hematopoietic stem cell transplant (HSCT) are at high risk for vitamin D deficiency before and after transplant, and more so than the general population (Urbain, Ihorst, Biesalski, & Bertz, 2012; Wallace et al., 2015). The prevalence of vitamin D deficiency has been reported to be as high as 70% before transplant and 90% after transplant (Dahir, Perry, & Jagasia, 2013).

At the Memorial Sloan Kettering Cancer Center, survivorship nurse practitioners noted at early posttransplant visits that patients were vitamin D deficient and needed replacement therapy. A gap in practice was identified in monitoring and treating vitamin D deficiency on the adult HSCT service. A retrospective analysis of a 5-month sample of HSCT patients (N = 184) revealed that 29% of pretransplant patients had a level checked, 81% were vitamin D deficient, and 30% received treatment with supplements. This confirmed that deficiencies in vitamin D levels were not routinely assessed or treated. Workflows in the inpatient and outpatient setting were lacking in standardization. The purpose of this article is to describe the impact of standardizing workflow for monitoring and treating suboptimal 25-hydroxyvitamin D (25(OH)D) levels on the incidence of vitamin D deficiency in adult HSCT patients.

## OVERVIEW OF VITAMIN D

Vitamin D is a steroid hormone known for its role in bone health and recognized for its immunomodulatory properties (Durcan & Petri, 2016). It is a fat-soluble vitamin that is an important micronutrient affecting calcium and bone homeostasis (Sproat et al., 2011; Wallace et al., 2015). Adequate vitamin D is needed to promote the absorption of calcium from the gastrointestinal tract. A low vitamin D level contributes to decreased calcium absorption, leading to a negative calcium balance. This results in a compensatory rise in parathyroid hormone, which can lead to secondary hyperparathyroidism, which then causes excessive bone resorption (Moyer, 2013; Sproat et al., 2011). Vitamin D deficiency may precipitate or contribute to osteopenia and/or osteoporosis (Sproat et al., 2011).

The nonskeletal properties of vitamin D impact the immune system and have been reported to have a protective effect on infection susceptibility and play a role in autoimmunity. The importance of maintaining vitamin D sufficiency has emerged given the role of vitamin D as an immune-modulating agent. Vitamin D receptors are expressed on cells of the immune system. Vitamin D deficiency has been linked to autoimmune disorders, including systemic lupus, multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, and psoriasis (Benrashid, Moyers, Mohty, & Savani, 2012).

Vitamin D is mainly attained from sun exposure, diet, or supplements. It is synthesized in the skin following exposure to sunlight and obtained to a lesser extent from food sources. Fatty fish oils and eggs are a few of the limited foods that are significant sources of vitamin D without fortification (fortified foods include cereal, orange juice, and milk products). The Institute of Medicine (IOM, 2011) has recommended a daily dietary intake of 400 to 600 international units (IU) of vitamin D for adults up to 70 years and 800 IU for adults over 70 years. Individuals at higher risk for vitamin D deficiency may need 2,000 IU or more daily to maintain sufficient levels (Dahir et al., 2013; Holick et al., 2011). Supplements are available in two different forms: cholecalciferol (vitamin $D_3$) is derived from animal sources and produced in the human body, and ergocalciferol (vitamin $D_2$) is derived from plant sources. Ergocalciferol is not as potent as cholecalciferol and may need to be dosed at a higher level to attain sufficient levels (Dahir et al., 2013). Repletion of vitamin D has been shown to have positive health benefits, as patients in the general population who have adequate vitamin D levels have a decreased incidence of fractures and falls (Holick et al., 2011; Simmons et al., 2013).

## VITAMIN D IN THE HSCT PATIENT

Vitamin D deficiency is highly prevalent in HSCT patients due to multiple factors. This population has decreased sun exposure related to long hospitalizations and limited outdoor activity. Patients are counseled to avoid unprotected exposure to sunlight and use sunscreen due to an increased risk of nonmelanoma skin cancer as well as potential activation of chronic graft-vs.-host disease (cGVHD) (Simmons et al., 2013). Poor nutrition and decreased oral intake related to gastrointestinal treatment toxicity may impact some patients.

This includes poor absorption of vitamin D due to medication exposures, diminished intestinal uptake due to gastrointestinal GVHD, and bacterial overgrowth. This may contribute to difficulty absorbing dietary fat and fat-soluble vitamins, including vitamin D (Beebe et al., 2018). Corticosteroids and other immunosuppressants can increase the breakdown of vitamin D, contributing to deficiency. Liver failure and chronic kidney disease can further lead to decreased synthesis of vitamin D (Sproat et al., 2011).

Vitamin D deficiency may be associated with low bone mass and osteoporosis after transplant (Bechard et al., 2015; Benrashid et al., 2012). The risk of decreased bone density worsens during the first 6 to 12 months posttransplant, with variable recovery after this time (Majhail et al., 2012; Simmons et al., 2013). Patients are at risk for bone loss posttransplant due to immunosuppressants, hypogonadism, chemotherapy, radiation therapy, kidney dysfunction, malabsorption, and cytokine therapy (Sproat et al., 2011). This late complication may lead to osteopenia or osteoporosis, with an increased risk of bone fragility and fractures that can result in morbidity, mortality, and affect quality of life (McClune et al., 2011).

Screening for vitamin D deficiency is recommended by the Endocrine Society Clinical Practice Guidelines for high-risk populations and HSCT patients (Dahir et al., 2013; Holick et al., 2011). The major circulating form of vitamin D is 25-hydroxy and most accurately indicates vitamin D status (Dahir et al., 2013). A serum 25(OH)D level is the standard test used to measure vitamin D (Holick et al., 2011). The optimal level of vitamin D has been a source of debate and has not been precisely defined given the relationship between levels and various clinical endpoints (Hansson et al., 2014). In the general population, vitamin D deficiency has been defined by the Institute of Medicine as < 20 ng/mL and insufficiency as 21 to 29 ng/mL (Durcan & Petri, 2016). Expert recommendations include a goal 25(OH)D level within 20 to 50 ng/mL (Dahir et al., 2013). Guidelines have been established regarding the appropriate supplementation of vitamin D because of its important role in many biological processes. Recommendations include maintaining a 25(OH)D level > 30 ng/mL in patients with or at risk for musculoskeletal issues, cardiovascular disease, autoimmune disease, and cancer (Benrashid et al., 2012). Although vitamin D supplements have an excellent safety profile, there is some evidence that levels of 25(OH)D > 50 ng/mL may be associated with potentially adverse effects (Dahir et al., 2013). Serum 25(OH)D level > 150 ng/mL has been associated with a risk of hypercalcemia, hypercalciuria, and calcifications (Durcan & Petri, 2016).

Preventive measures to reduce fracture risk in adult HSCT patients include adequate supplementation with vitamin D and calcium, although the exact dose and formulation is not well known (Majhail et al., 2012). Monitoring of 25(OH)D levels and higher doses of supplementation of vitamin D may be required in adult HSCT patients with levels < 30 ng/mL (McClune et al., 2011; McClune & Majhail, 2013; Simmons et al., 2013). Correction of vitamin D deficiency alone is not adequate to prevent HSCT-related bone loss. Other strategies that may decrease bone loss include weight-bearing exercises, nutrition, and treatment with bisphosphonates or hormone replacement therapy (Hu, Lu, & Gagel, 2010; McClune & Majhail, 2013).

Bechard and colleagues (2015) reported that serum 25(OH)D levels declined significantly in children after HSCT while treated with standard doses of parental vitamin D. 25(OH)D levels decreased from a baseline of 29.2 ng/mL to 19.7 ng/mL at 30 days and 17.7 ng/mL at 100 days after transplant. Prior studies of vitamin D deficiency in HSCT patients have shown conflicting results, with some reporting decreased survival and an increased risk of GVHD, and others finding no impact on these outcomes (Hansson et al., 2014; Sproat et al., 2011; Urbain et al., 2012; Wallace et al., 2015).

The aims of this quality improvement (QI) project were to establish a workflow for monitoring and treating vitamin D deficiency and to determine if therapeutic vitamin D levels could be achieved posttransplant using an HSCT-specific vitamin D algorithm.

## METHODS

### Phase I

An institutional review board waiver was obtained for a retrospective analysis of a 5-month sample of all adult patients undergoing HSCT at Memo-

rial Sloan Kettering Cancer Center between June and October 2015 (N = 184). The data collected included pretransplant 25(OH)D levels checked and vitamin D supplements prescribed. The analysis revealed that 29% of patients had a 25(OH)D level checked prior to transplant; 81% of them were vitamin D deficient, and of those who were deficient, only 30% received treatment with supplements. This review served as historical baseline data and supported the need for a QI initiative to address the gap in practice surrounding vitamin D monitoring and supplementation on the adult HSCT service.

### Phase II

A project team co-led by advanced practice providers (APPs) was formed to standardize the workflow for monitoring and treating vitamin D deficiency. Multidisciplinary participants (APPs, nurses, clinical pharmacists, physicians, and a quality management nurse) represented practitioners from across the HSCT care continuum.

Based on a comprehensive literature review and expert opinion from the adult transplantation and endocrinology services, an HSCT-specific vitamin D replacement therapy guideline was created and approved for use to guide treatment and follow-up monitoring of 25(OH)D levels. The guidelines recommend aggressive vitamin D dosing for the HSCT population compared to standard dosing for the general population. The guidelines allow flexibility to choose either ergocalciferol (vitamin $D_2$) or cholecalciferol (vitamin $D_3$) based on the level and clinical judgment. The level of vitamin D deficiency guides recommendations for the dosing and frequency of supplementation. To reduce pill burden, ergocalciferol was chosen as the initial supplement of choice over cholecalciferol. Ergocalciferol is dosed less frequently (weekly/every other week) than cholecalciferol (dosed daily), and there is no large-dose version of $D_3$ available. Based on feedback from HSCT providers, revisions were made to initial guidelines to improve clarity and ease of use (Table 1). To increase accessibility to prescribers, guidelines were embedded in the electronic orders and "pop-up" when entering an order for ergocalciferol or cholecalciferol.

An order for a 25(OH)D level was added to the HSCT admission order sets. Advanced practice providers were responsible for following up on results and prescribing supplementation if indicated based on the guidelines.

After this workflow was established, multiple educational sessions were conducted to inform the HSCT nurses, APPs, and physicians about the workflow and the new guidelines. The sessions were held at various times and locations to capture most stakeholders across the care continuum. The presentation used in the educational sessions

**Table 1. Adult Hematopoietic Stem Cell Transplant Vitamin D Replacement Therapy Guideline**

| 25-hydroxy vitamin D level (ng/mL) | Replacement prescription Ergocalciferol ($D_2$) Cholecalciferol ($D_3$) | Dose adjustment based on level |
|---|---|---|
| < 20 | $D_2$ 50,000 IU orally once weekly; recheck level in 6 weeks | If < 20 after 6 weeks, increase to $D_2$ 50,000 IU orally twice a week; recheck level in 4 weeks<br>If > 20 after 6 weeks, $D_2$ 50,000 IU every 14 days or $D_3$ 2,000 IU daily; recheck level in 3 months |
| 20–29 | $D_2$ 50,000 IU every 14 days or $D_3$ 2,000 IU daily; recheck level in 6–12 weeks | Continue current regimen; recheck level in 3 months or when deemed clinically appropriate |
| 30–50 | None (continue current supplements, if any) | Recheck in 3 months and then at least annually |
| > 51 | Stop $D_2$ or $D_3$; recheck level in 1 month | |

*Note*. For critically ill patients, consider checking level at 1 month after initiating treatment, and adjust dosing as clinically indicated. Regimen may NOT be advisable in patients with hypercalcemia, recurrent calcium nephrolithiasis, primary hyperparathyroidism, sarcoidosis, or other granulomatous disease. 25-hydroxy vitamin D = 25(OH)D; $D_2$ = ergocalciferol; $D_3$ = cholecalciferol; IU = international units.

was emailed to HSCT staff to serve as a reference document. The education rollout was completed in November 2015, and the workflow changes (QI project intervention) went live thereafter.

Following the intervention, a review of records of the first cohort of adult patients presenting for HSCT from December 2015 to March 2016 was performed. The data collected included patient demographics (e.g., sex, age at transplant), transplant characteristics (e.g., diagnosis, type of transplant, donor source), 25(OH)D levels pretransplant and within 6 months posttransplant, and vitamin D supplements prescribed. This review was to assess compliance with the newly established workflow and the impact of using the guidelines on posttransplant rates of vitamin D deficiency. A year later, review of a second cohort of patients presenting for HSCT between March and April 2017 was performed to assess for sustained compliance with workflow.

Descriptive statistics were used to summarize patient characteristics, rates of monitoring, treatment, and prevalence of vitamin D deficiency. Baseline characteristics of sex, age, disease, and transplant type were assessed by pretransplant 25(OH)D level (< 30 ng/mL vs. ≥ 30 ng/mL) in the postintervention cohort using Wilcoxon rank-sum and Fisher's exact tests. Change in vitamin D levels pre- and posttransplant in the postintervention cohort was evaluated using Fisher's exact test.

## RESULTS

The intervention cohort consisted of 162 patients. Five patients with a diagnosis of germ-cell tumor (managed by a different service) and 13 patients who died before 180 days posttransplant were excluded. The remaining 144 patients were included in the analysis. The distribution of baseline characteristics by pretransplant vitamin D level is presented in Table 2. There was no significant difference found between patients with pretransplant deficient and sufficient 25(OH)D levels with respect to sex, age, disease, or type of transplant. All autologous transplant cell sources were peripheral blood stem cells. Allogeneic transplant cell sources were bone marrow (6%), peripheral blood stem cells (70%), and cord blood (24%).

An evaluation of 144 patients revealed that 96.5% had a pretransplant 25(OH)D level performed, and of those patients tested, 72.9% were vitamin D deficient. Follow-up monitoring of

**Table 2. Distribution of Baseline Characteristics by Pretransplant Vitamin D Level (N = 144)[a]**

| Characteristic, n(%) | Sufficient[b] (N = 34, 24%) | Deficient[c] (N = 105, 76%) | *p* value |
|---|---|---|---|
| *Sex* | | | .11 |
| Male | 15 (44) | 64 (61) | |
| Female | 19 (56) | 41 (39) | |
| *Age* | | | .88 |
| Mean (SD) | 57.4 (11.6) | 56.4 (12.8) | |
| Median (range) | 58.9 (21.2–75.2) | 59.3 (19.1–74.2) | |
| *Disease* | | | .88 |
| Amyloidosis/Multiple myeloma | 11 (32) | 36 (34) | |
| Non-Hodgkin lymphoma/Hodgkin lymphoma | 10 (30) | 35 (33) | |
| Acute leukemia/Chronic leukemia/ Myeloproliferative disease/Other | 13 (38) | 34 (32) | |
| *Transplant type* | | | .56 |
| Autologous | 17 (50) | 59 (56) | |
| Allogeneic | 17 (50) | 46 (44) | |

*Note.* Demographic characteristics of intervention group prior to transplant by vitamin D level (normal vs. deficient).
SD = standard deviation.
[a]5 patients were not tested.
[b]25(OH)D level ≥ 30 ng/mL.
[c]25(OH)D level 0–29 ng/mL.

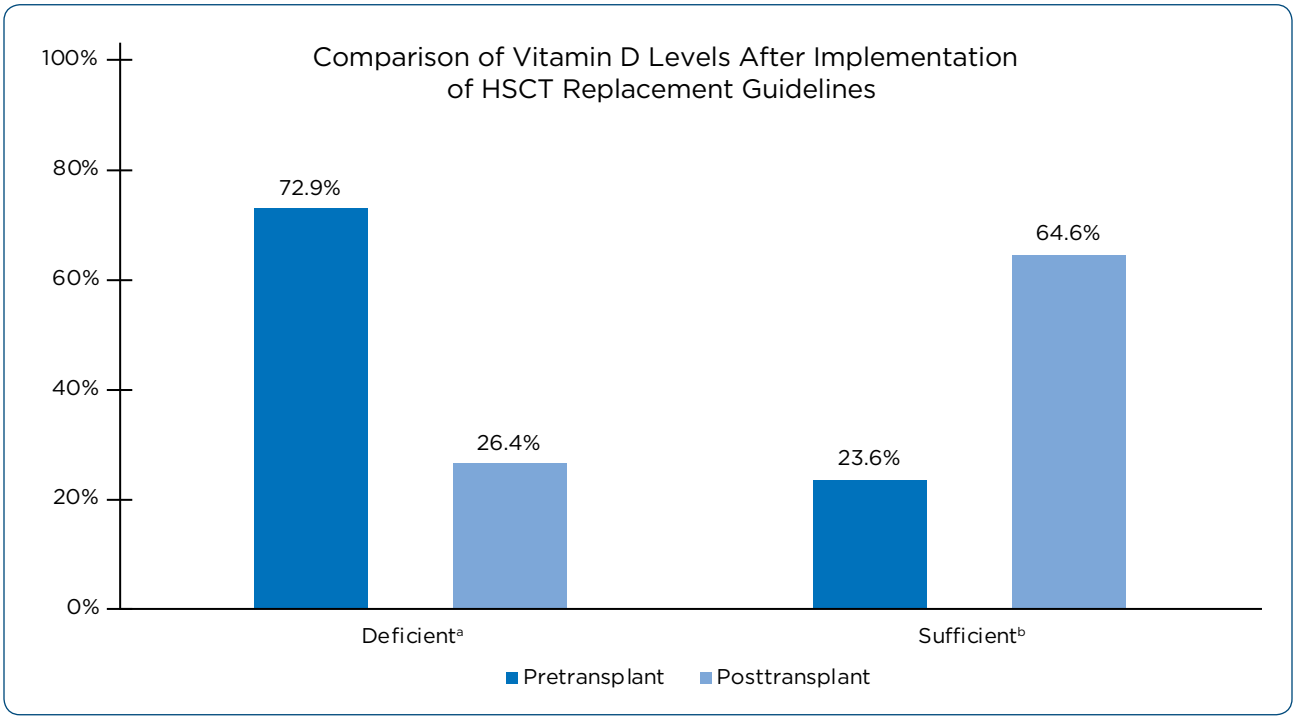


**Figure 1.** Vitamin D levels prior to transplant and within 6 months posttransplant following implementation of the adult HSCT vitamin D replacement therapy guideline. HSCT = hematopoietic stem cell transplant.
[a]25(OH)D level 0–29 ng/mL.
[b]25(OH)D level ≥ 30 ng/mL.

25(OH)D level within 6 months of transplant was performed in 91% of patients and only 26.4% were vitamin D deficient (Figure 1). Serum 25(OH)D levels differed significantly ($p < .001$) between pretransplant and posttransplant measurements after implementation of the HSCT replacement algorithm, as shown in Table 3. The median pretransplant 25(OH)D level was 21 ng/mL, and the 6-month posttransplant median 25(OH)D level was 36 ng/mL. Vitamin D deficiency overall decreased from 72.9% pretransplant to 26.4% posttransplant. In the autologous patients, vitamin D deficiency decreased from 75.6% to 32.1% and in the allogeneic patients from 69.7% to 19.7%. Pre-

**Table 3. Comparison of Vitamin D Levels After Implementation of HSCT Replacement Guidelines (N = 144)**

| | Pretransplant | Posttransplant | *p* value |
|---|---|---|---|
| *Vitamin D levels* | | | |
| Mean (SD) | 22.9 (10.4) | 37.4 (13.3) | |
| Median (range) | 21 (5–61) | 36 (11–84) | < .001 |
| *HSCT patients* | | | |
| Sufficient (%)[a] | 34 (23.6) | 93 (64.6) | |
| Deficient (%)[b] | 105 (72.9) | 38 (26.4) | |
| Not tested (%) | 5 (3.5) | 13 (9) | |

*Note.* Pretransplant and posttransplant mean and median vitamin D levels and number of patients sufficient, deficient, or not tested before transplant and within 6 months posttransplant following the implementation of the adult HSCT vitamin D replacement therapy guideline. HSCT = hematopoietic stem cell transplant; SD = standard deviation.
[a]25(OH)D level ≥ 30 ng/mL.
[b]25(OH)D level 0–29 ng/mL.

transplant 25(OH)D levels of autologous patients ranged from 5 to 56 ng/mL with a median of 20 ng/mL. Posttransplant 25(OH)D levels ranged from 12 to 84 ng/mL with a median of 34.5 ng/mL. Similarly, the pretransplant 25(OH)D levels of allogeneic patients ranged from 6 to 61 ng/mL with a median of 22, and posttransplant levels ranged from 11 to 63 ng/mL with a median of 36 ng/mL (Figure 2).

The incidence of pretransplant vitamin D deficiency ranged from 65% to 81%. Following our initiative, compliance with vitamin D level monitoring improved from 29% (historic data) to 97% following the intervention and 100% at 1-year follow-up. Lastly, compliance with supplementation for deficient levels increased from 30% (historic data) to 97% following the intervention and 100% at 1-year follow-up (Figure 3).

## DISCUSSION

This QI project demonstrates that by introducing a new workflow, overall monitoring of pretransplant levels and treatment of vitamin D deficiency increased and was sustained. A review of levels measured after transplant found that 91% of patients had a level checked within 6 months of transplant. This demonstrates that compliance with a standardized work flow positively affected the monitoring and treatment of vitamin D deficiency in this population.

The treatment of vitamin D deficiency was previously not consistently addressed by providers on the HSCT service at this institution. The introduction of a new workflow for standardizing the monitoring and treatment of vitamin D deficiency has increased awareness and treatment of this clinical issue among APPs and other providers. Linking the HSCT vitamin D replacement guidelines to the electronic orders contributes to the sustainability of this practice change.

Pre-HSCT prevalence of vitamin D deficiency at this institution was high, ranging from 65% to 81%, which is consistent with previous reports in the literature (Sproat et al., 2011). This may increase a patient's risk of skeletal, nutritional, and immunologic complications (Benrashid et al., 2012; Wallace et al., 2015). The study by Bechard and colleagues (2015) described a significant decline in 25(OH)D levels through day 100 posttransplant in children treated with standard parenteral vitamin D dosing undergoing HSCT. These results raise the issue of the adequacy of standard parenteral vitamin D dosing for children undergoing HSCT.

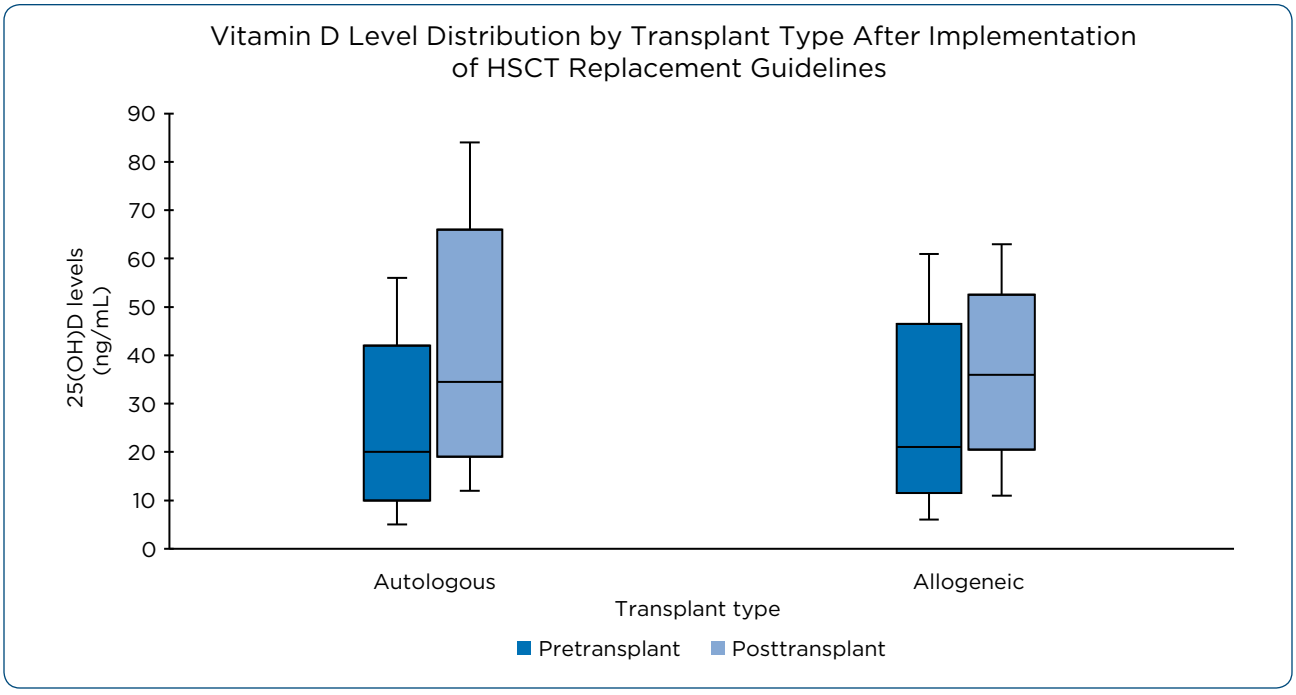


**Figure 2.** Vitamin D level ranges for both autologous and allogeneic transplant types, with 25% to 75% range and median results. HSCT = hematopoietic stem cell transplant.

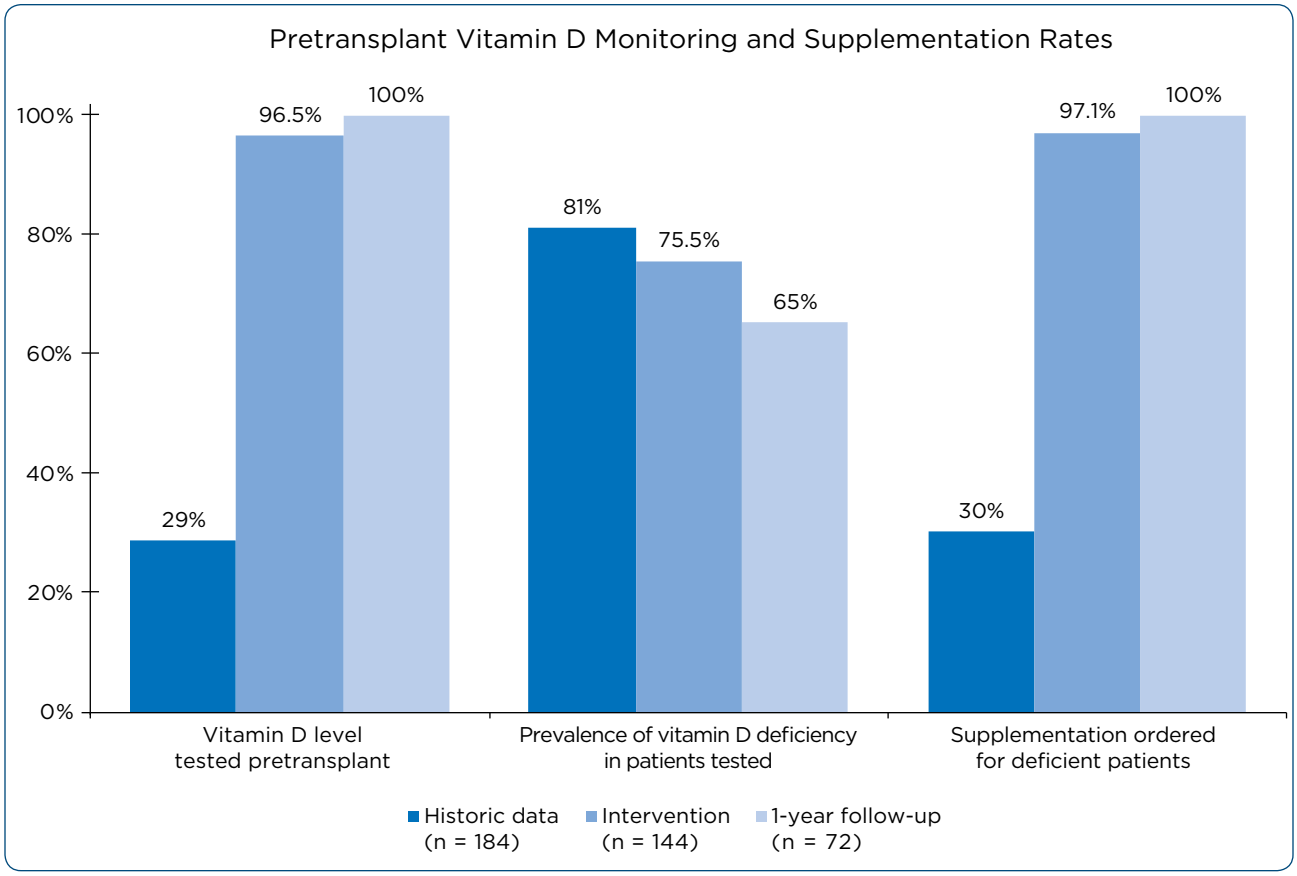


**Figure 3.** Comparison of historic, intervention, and 1-year postimplementation follow-up data on rates of vitamin D testing, vitamin D deficiency, and supplementation orders.

There is a paucity of literature addressing the adequacy of standard and aggressive dosing of vitamin D supplementation in the adult HSCT population. The finding of a statistically significant decrease in vitamin D deficiency from 72.9% to 26.4% within 6 months posttransplant with the use of an HSCT-specific vitamin D guideline is of interest. Although compliance with monitoring and repletion of vitamin D was high, 26% of patients remained deficient. This may reflect variability in the absorption or metabolism of vitamin D, which was not controlled for in this project. Results suggest that aggressive vitamin D supplementation pre- or posttransplant may mitigate vitamin D deficiency in the early posttransplant period. These findings provide the basis for further investigation of the effect of an aggressive vitamin D replacement algorithm pre- and posttransplant on the incidence of vitamin D deficiency. These results are notable considering previous reports have found worsening vitamin D deficiency posttransplant when no supplementation was given and with the use of standard-dose vitamin D supplementation (Bechard et al., 2015; Beebe et al., 2018; Dahir et al., 2013). Based on the results of this project, the adult HSCT service continues to employ this algorithm.

## IMPLICATIONS FOR THE ADVANCED PRACTICE PROVIDER

The current recommendations for daily vitamin D supplementation in the United States may not be adequate to meet the needs of the HSCT population (McClune et al., 2011). The implications for practice include recommendations for pre- and posttransplant screening with 25(OH)D levels and aggressive supplementation based on specific vitamin D replacement guidelines for adult HSCT patients (Table 1). The appropriate level of vitamin D supplementation given various clinical situations remains unknown and can be guided by the measurement of 25(OH)D levels.

This QI project demonstrates that pre- and posttransplant monitoring and treatment of vitamin D deficiency is relatively easy to implement. Vitamin D deficiency remains a long-term issue for this population that is counseled to reduce the risk of secondary skin malignancy by limiting unprotected sun exposure. In the HSCT setting, vitamin D deficiency is a potentially modifiable risk factor that is correctable and may positively impact outcomes. More aggressive replacement of vitamin D with higher dosing than recommended for the general population may be indicated in this population given the population's reduced sun exposure, medications that interfere with the metabolism of vitamin D, malabsorption of vitamin D due to gastrointestinal GVHD, and impaired renal and hepatic function posttransplant. Maintaining vitamin D sufficiency pre- and posttransplant may decrease HSCT-associated morbidity and improve long-term outcomes and quality of life for survivors. Advanced practice providers in oncology have a unique opportunity to impact practice and patient outcomes in this setting. Further investigation is warranted to determine the impact of long-term effects of early repletion of vitamin D on posttransplant complications of bone loss and GVHD. ●

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## Disclosure

The authors have no conflicts of interest to disclose.

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