



Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org



Supportive Care

Current Practice in Vitamin D Management in Allogeneic Hematopoietic Stem Cell Transplantation: A Survey by the Transplant Complications Working Party of the European Society for Blood and Marrow Transplantation



J. Ros-Soto^{1,*}, J.A. Snowden², N. Salooja³, M. Gilleece⁴, A. Parker⁵, D.M. Greenfield², C. Anthias^{1,6}, A. Alfred⁷, A. Harrington⁸, C. Peczynski⁸, K. Peggs⁹, A. Madrigal¹, G.W. Basak¹⁰, H. Schoemans¹¹, on behalf of the Transplant Complications Working Party of the EBMT

¹ Anthony Nolan Research Institute, Royal Free Hospital, and University College London, London, United Kingdom

² Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

³ Haematology Department, Hammersmith Hospital, Imperial College Healthcare Trust, London, United Kingdom

⁴ Department of Clinical Haematology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

⁵ Haematology Department, Queen Elizabeth University Hospital, Glasgow, United Kingdom

⁶ Department of Haemato-Oncology, The Royal Marsden Hospital, Sutton, United Kingdom

⁷ Photopheresis Unit, The Rotherham NHS Foundation Trust, Rotherham, United Kingdom

⁸ EBMT Data Office, Paris, France

⁹ Department of Clinical Haematology, University College London Hospitals NHS Foundation Trust, London, United Kingdom

¹⁰ Department of Haematology, Oncology and Internal Diseases, Medical University of Warsaw, Warsaw, Poland

¹¹ Department of Haematology, University Hospital Leuven and KU Leuven, Leuven, Belgium

Article history:

Received 12 April 2019

Accepted 15 June 2019

Keywords:

Vitamin D

Hematopoietic stem cell

transplantation

Survey

Supportive care

Post-transplant complications

A B S T R A C T

Beyond its impact on bone health, numerous studies have investigated the immune-regulatory properties of vitamin D and shown how its deficiency can affect outcomes in allogeneic hematopoietic stem cell transplantation (HSCT), particularly in acute or chronic graft-versus-host disease. This survey, carried out by the Transplant Complications Working Party of the European Society for Blood and Marrow Transplantation (EBMT), describes the current clinical practice discrepancies across the EBMT HSCT programs. We therefore recommend the development of evidence-based guidelines to standardize evaluation criteria and to harmonize the management of vitamin D deficiency in patients undergoing allogeneic HSCT.

© 2019 American Society for Transplantation and Cellular Therapy. Published by Elsevier Inc.

INTRODUCTION

Vitamin D deficiency is a global health concern [1] as it has pleiotropic effects on the heart [2], bone metabolism [3], and immune system [4], among others. Risk factors include low sun exposure, age, poor oral intake of vitamin D-enriched alim-ents, and malabsorption [5,6]. In Europe, it affects habitants from different latitudes, including those living in Mediterranean countries [7–10]. It is well known that hematopoietic stem cell transplant (HSCT) recipients are at high risk for vitamin D deficiency and bone abnormalities caused by prolonged hospitalizations (with the subsequent lack of sunshine) and nutritional compromise status [11–13]. Studies carried out within the past decades have contributed to a better

understanding of the immune-regulatory properties of vitamin D and its biological action in the course of HSCT [14–18].

Vitamin D exerts its biologic function through the vitamin D receptor [19], located in cells from the innate and adaptive immunity. It blunts inflammation while enhancing a tolerogenic status, mediating in immune homeostasis [20–22]. In situations of vitamin D deficiency, this balance may be disturbed in favor of an inflammatory status and loss of self-tolerance, leading to conditions such as autoimmune diseases [23,24]. In the allogeneic HSCT setting, it can also affect post-HSCT complications such as graft-versus-host disease (GVHD) [14,15,25], whose pathophysiology shares features of immune dysregulation with autoimmunity [26,27]. Recent studies have proved the association between chronic and acute GVHD and low levels of serum vitamin D in allogeneic HSCT patients, which could be explained by the diminished immune-modulatory effect of vitamin D during the immune reconstitution stage

Financial disclosure: See Acknowledgments on page 2084.

* Correspondence and reprint requests: J. Ros-Soto, MBBS

E-mail address: joserossoto@anthonyolan.org (J. Ros-Soto).

(Table 1) [14-17,25,28-33]. Despite this, clinical guidelines in HSCT have focused only on the role of vitamin D in bone health and mineral metabolism [13,34,35], but there is little recognition of the potential contribution of vitamin D deficiency in post-HSCT complications and subsequently in its outcomes [14-17,25].

To better understand differences in the management of vitamin D deficiency in allogeneic HSCT patients, we have conducted an online survey across the European Society for Blood and Marrow Transplantation (EBMT) affiliate centers.

MATERIALS AND METHODS

HSCT program directors of 326 EBMT affiliate allogeneic transplant centers from 42 countries were invited to participate in an online survey comprising 34 questions, divided in different categories such as diagnosis, prescription of vitamin D replacement, or follow-up.

This survey was carried out from September to November 2018. Each EBMT center was allowed to participate only once in the survey. Data were analyzed descriptively.

RESULTS

Demographics

All the EBMT affiliate centers that perform allogeneic HSCT were approached (n=326). A total of 114 centers from 24 countries completed the questionnaire. The location of the participating centers is displayed in Figure 1, and their characteristics are presented in Table 2.

The geographical reference was taken based on the annual sunshine duration: above 50 degrees latitude, there are fewer than 1800 hours of sunlight per year, whereas below this latitude, the number of sunlight hours is higher and therefore cutaneous synthesis of vitamin D varies depending on location [36]. A total of 11 participating countries accounting for 46% (n = 52) of the centers are located above this latitude (northern countries), and 13 countries, including 54% (n = 62) of the centers, are below this latitude (southern countries). Moreover, 58% (n = 66) are dedicated adult centers, 21% (n = 24) are pediatric-only centers, and 21% (n = 24) provide care for adult and pediatric patients (mixed centers). At the time of the survey, 84% (n = 96) centers were located in the European Union.

This survey was completed by 46% of transplant directors, 41% of transplant consultants, 8% of non-consultant grade physicians, 3% of HSCT clinical nurse specialists, and 2% of other health care professionals (1 head of research and 1 dietitian). All of them stated to be highly involved throughout the course of allogeneic HSCT: 85% pre-HSCT, 89% during the ward admission for stem cell infusion and early post-HSCT care, 96% during the first year post-HSCT, and 90% who continued the follow-up beyond the first year (several answers were possible).

Standard Operation Procedures for Assessment of Vitamin D

Local and national guidelines (i.e., Swiss Guidelines, Lombardia Regional Statement [Italy], or the French Paediatric Society Guidelines) are followed by 19% of the centers. Similarly, international guidelines, including the Dietary Reference Intake from the Institute of Medicine of the National Academy of Sciences, the National Institute for Health and Care Excellence (NICE), UK Osteoporosis, and UpToDate recommendations are followed by 18%. In the majority (67%) of the mixed centers, adult and pediatric units follow the same recommendations for management of vitamin D deficiency.

Monitoring of Vitamin D

Before allogeneic HSCT, serum vitamin D is routinely checked by 47% of the centers (Figure 2): 37% in all patients and 10% in only those with risk factors for hypovitaminosis D

(Table 3). However, after allogeneic HSCT, nearly double of the centers (70%) monitor it regularly (Figure 3): 53% in all patients and 17% in only those patients with risk factors for hypovitaminosis D (Table 3). Screening occurs every 3 months (39%), every 6 months (24%), once a year (18%), or at other time points (19%). In this regard, seasonality is not taken into account by the majority of the centers (94%).

Prescription of Vitamin D Replacement

To treat vitamin D deficiency, vitamin D replacement is prescribed by transplant physicians (75%), family physicians (10%), endocrinologists (3%), clinical nurse specialists (3%), and other specialist physicians (physiatrist, rheumatologist, gynecologist) (4%), and in 5% of the centers, patients are advised to buy it over the counter. Vitamin D is prescribed combined with calcium carbonate in 52% and alone in 48%.

For prescribing vitamin D replacement, 83% of the centers use a cut-off of serum vitamin D: ≤ 25 nmol/L (26%), ≤ 30 nmol/L (28%), ≤ 50 nmol/L (37%), ≤ 75 nmol/L (7%), and ≤ 100 nmol/L (2%) (Figure 4). Centers from northern countries have a median cutoff of 50 nmol/L, whereas in southern countries, it is 30 nmol/L.

The main reasons to prescribe vitamin D replacement are depicted in Table 4.

Only 33% of the centers start patients on a “loading dose” as part of the treatment of vitamin D deficiency. Eighty-nine percent of the responders provided the loading dose prescribed. The median daily loading dose is 2,000 IU (range 286-20,000), and its median duration is 6 weeks (range 1-52).

Nearly all the centers (98%) prescribe long-term treatment (“maintenance”) with vitamin D. Eighty-eight percent provided the daily maintenance dose prescribed, with a median of 800 IU (range 67-10,000).

Vitamin D replacement is eventually discontinued by 69% of the centers under the following criteria: when therapeutic vitamin D levels are reached (59%), when the dual-energy X-ray absorptiometry (DEXA) scan returns to normal (12%), with symptomatic improvement (9%), all of the aforementioned criteria (9%), or other (after stopping immunosuppression, after completing 1 year of treatment, or when growth stops in pediatric patients) (11%).

Follow-up

Patients' follow-up occurs mainly in the transplant center (89%), by the primary care physician (1%), or in a mixed model (10%). It is most frequently lifelong (57%), although it has also been reported to last less than 5 years (6%), between 5 and 10 years (21%), more than 10 years (4%), until pediatric patients transition to an adult team (8%), or other follow-up programs (4%).

There is a dedicated osteoporosis service in 69% of the transplant centers, mainly in adult (74%) and mixed centers (79%), and in less than half of the pediatric centers (48%). As part of the follow-up, 80% of the centers usually request a DEXA scan (52% perform it in all patients and 48% in only those with a high risk of osteopenia/osteoporosis), which is covered by health insurance in most countries (92%). Seventy-nine percent prescribe vitamin D following an abnormal DEXA scan result. The main indications are osteopenia (87%) and osteoporosis (13%). After the first DEXA scan, most of the centers repeat it (78%): 40% once a year, 19% every 5 years, 28% depending on the previous DEXA scan results, and 13% using other time points. The DEXA scan is discontinued when bone density increases (11%), normalizes (56%), or stabilizes (33%).

Table 1
Studies Performed in the HSCT Population to Correlate Vitamin D Serostatus and GVHD

Author	Age Population (n)	Vitamin D Deficiency Cutoff	Timing VD Test	Intervention	Acute GVHD	Chronic GVHD
Beebe et al. [16]	Pediatric (72)	<20 ng/mL	Pre- and post-HSCT	RT provided to 46 patients	No significant differences	No significant differences
Caballero-Velazquez et al. [28]	Adult (150)	<50 nmol/L	NR	CG—no treatment	No significant differences	Lower CI of overall and moderate + severe chronic GVHD at 1 year in LD (37.5% and 19.5%) and HD (42.4% and 27%) compared with CG (67.5% and 44.7%), respectively ($P < .05$)
				LD—1000 IU/d RT		
				HD—5000 IU/d RT		
				From day -5 to day +100		
von Bahr et al. [14]	Adult (166)	<25 nmol/L	Pre-HSCT	No	No significant differences	Strong correlation (RR, 2.66) with 25(OH) D_3 serostatus
Wallace et al. [17]	Pediatric (135)	<20 ng/mL	Post-HSCT	No	No significant differences	No significant differences
Hansson et al. [15]	Pediatric (123)	<50 nmol/L	Pre-HSCT	No	More frequent in patients with sufficient VD (47%) pre-HSCT compared with VDD patients (30%) ($P = .05$)	No significant differences
Campos et al. [29]	Pediatric (66)	<20 ng/mL	Pre- and post-HSCT	All patients received 400 to 800 IU/d of RT during hospitalization and 39 (59%) after discharge for an average of 140 days	No significant differences	No significant differences
Glitzbecker et al. [25]	Adult (53)	<25 ng/mL	Pre-HSCT	No	No significant differences	2-year CI 63.8% in VDD patients compared with 23.8% in sufficient VD patients ($P = .02$) Extensive GVHD at 2 years: 54.5% in VDD patients compared with 14.3% in sufficient VD patients ($P = .009$)
Urbain et al. [30]	Adult (102)	<10 ng/mL	Pre-HSCT	No	No significant differences	NR
Robien et al. [31]	Pediatric + adult (95)	<50 nmol/mL	Post HSCT	200–1000 IU/d (duration NR) in long-term post-HSCT patients	No significant differences	No significant differences
Silva et al. [32]	Adult (12)	NR	NR	Patients with active chronic GVHD on \geq first-line IS + RT caused by bone disease	NR	50% study cohort stopped IS after 6 months on RT (5 CR, 6 PR, 1 NR) compared with 20% of CG
				Compared with CG of 24 patients with chronic GVHD on first-line IS but not on RT		
Kreutz et al. [33]	NR (48)	<25 nmol/L	Pre- and post-HSCT	No	Lower serum levels of 25(OH) D_3 in grade 3 and 4 ($P = .031$)*	NR

VD indicates vitamin D (25(OH) D_3); RT, replacement therapy with 1,25(OH) $_2D_3$; NR, no reported; CG, control group; CI, cumulative incidence; LD, low-dose group; HD, high-dose group; RR, relative risk; VDD, vitamin D deficiency; IS, immunosuppression; CR, complete response; PR, partial response.

* Number patients affected not specified.

DISCUSSION

To our knowledge, this is the first survey addressing differences in the management of vitamin D deficiency in allogeneic

HSCT patients. Two previous studies surveyed the awareness of health care professionals in vitamin D deficiency, but they were conducted among primary care physicians and midwives

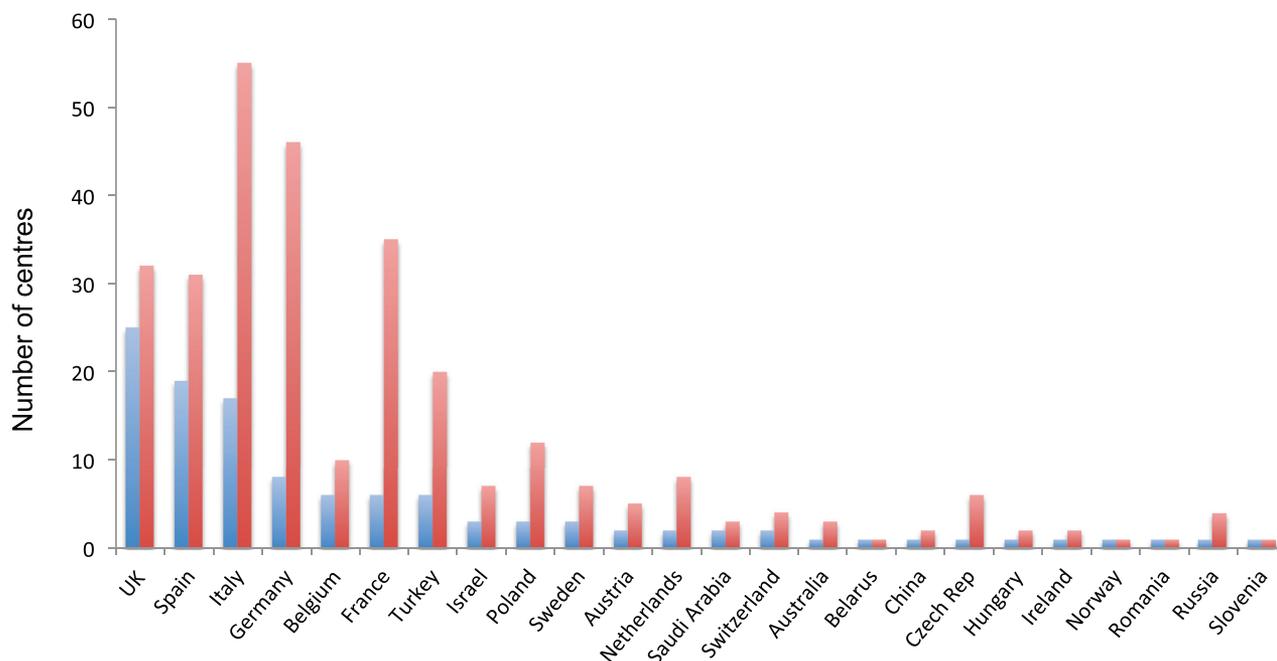


Figure 1. Number of centers participating in the survey (left) compared to the total of EBMT centers that performed allogeneic HSCT per country (right).

in the United Kingdom [37] and among primary care physicians in Belgium [38].

Currently, clinical guidelines do not include the assessment of vitamin D before HSCT [39,40]. This could explain why less than half of the institutions participating in our study request it at that time point. However, this practice nearly doubles following HSCT as guidelines recommend monitoring vitamin D, alongside calcium and phosphate levels, to assess bone health, prevent osteoporosis, and ultimately prevent bone fractures in high-risk patients [13,34,35]. In fact, maintaining bone and mineral metabolism is considered by the majority of the

responder centers the main indication for commencing on vitamin D replacement (92%). Although most of the responders (96%) do not take into account timing for monitoring vitamin D, seasonality has been found to be an important risk factor for vitamin D deficiency [7]. In fact, during the brighter seasons, the increased production of cutaneous vitamin D is associated with lower levels of proinflammatory cytokines (IL-1, IL-6, TNF- α) compared with the darker seasons [41], confirming the immune-modulatory effect of vitamin D [20–22]. Monitoring vitamin D before and after HSCT is strongly recommended, particularly during the darkest months, to identify deficient patients and treat them accordingly.

Only a minority of centers considered that vitamin D has an important role in the pathophysiology of GVHD (17%) or contribution in fostering immune reconstitution after stem cell engraftment (24%). Recent publications have shown the association between vitamin D deficiency with a higher incidence of acute [30,33] and chronic [14,25] GVHD, as well as cytomegalovirus reactivation [14]. However, the impact of vitamin D on HSCT survival is more controversial: some studies showed that vitamin D deficiency is associated with a decrease in overall

Table 2
Characteristics of the Participant Centers

Patient group	Responses (%)
Adult only	58%
Paediatric only	21%
Both adult and paediatric	21%
Location	
European	87%
Non-European	13%
Latitude	
Northern	46%
Southern	54%
Number of allogeneic transplant	
<500	35%
500–1000	37%
1000–1500	13%
>1500	15%
Centers performing allogeneic transplantation since	
< 15 years	8%
15–25 years	21%
> 25 years	71%
JACIE accreditation	
Accredited	43%
Accreditation in Progress	25%
No	32%
Transplant type performed	
Identical Sibling	45%
Unrelated (matched and mismatched)	40%
Haploidentical	6%
Other relative (syngenic, matched and mismatched)	6%
Cord Blood	3%
Gross national income	
High	91%
Middle	9%

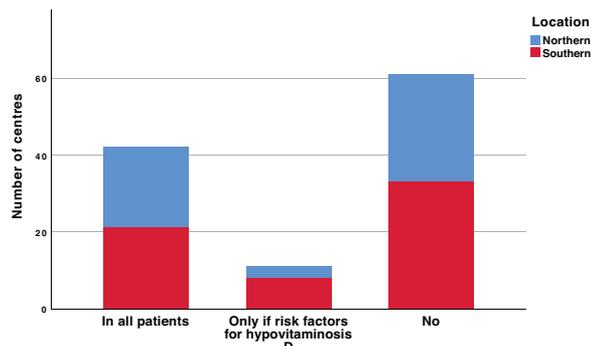


Figure 2. Proportion of centers measuring serum vitamin D before HSCT depending on location.

Table 3
Centers' Responses According to Clinical Indications to Request Serum Vitamin D in Patients Undergoing HSCT (Several Answers Were Possible)

	Pre-HSCT	Post-HSCT
	N (%)	N (%)
Osteopenia/osteoporosis	108 (94%)	100 (86%)
Treatment with steroids	86 (75%)	78 (68%)
Previous fracture	86 (75%)	81 (71%)
Premature menopause	64 (56%)	52 (46%)
Established menopause	57 (50%)	36 (32%)
Total body irradiation	8 (7%)	NR
Low vitamin D levels in serum	7 (6%)	NR
Other*	NR	7 (6%)

* Risk of avascular necrosis of the femur, breastfeeding, total parenteral nutrition.

NR = not reported

survival following HSCT [14–17], whereas others failed to reproduce these findings [11,25,48]. This inconsistency could be caused by small cohorts in the existing studies and differences in population characteristics; thus, further research with a more homogeneous and larger sample size is clearly needed [42].

The most reliable marker of vitamin D status in serum is 25(OH)D₃ as it reflects the cutaneous production and diet intake of vitamin D₃. In the general population, the cut-off of serum 25(OH)D₃ to define vitamin D deficiency is based on the minimum concentration of 25(OH)D₃ required to prevent bone disease [43]. Currently, this is a matter of debate [14,15,25,31,33,44–47]: in the United Kingdom, the NICE guidelines and the Endocrine Society Task Force on Vitamin D define vitamin D deficiency at levels of serum 25(OH)D₃ below 25 nmol/L (10 ng/mL) [48,49], as supported by other publications [5,9,50]. However, the Institute of Medicine in the United States indicates that it should be established at 30 nmol/L (12 ng/mL) [51], whereas Holick [52] recommends setting this threshold at

50 nmol/L (20 ng/mL). In addition, NICE guidelines [48] define vitamin D insufficiency when serum 25(OH)D₃ levels are between 26 and 50 nmol/L, and Holick [52] defines vitamin D insufficiency when these levels are between 50 and 75 nmol/L. The Endocrine Society Task Force on Vitamin D [47] does not mention this concept in its report. Nevertheless, there is no evidence of the optimal level of serum 25(OH)D₃ required to foster immune reconstitution and prevent post-HSCT complications. It is therefore not surprising that in our study, the cut-off mainly ranges from 25 to 75 nmol/L. It is difficult to know which factors influence local practice, but centers are probably led by the existing literature, where studies in allogeneic HSCT have also shown discrepancies in this matter [14,25,33,44]. In addition, the most common threshold for vitamin D deficiency was 50 nmol/L, as also shown in studies exploring outcomes following allogeneic HSCT in both pediatric [15,17,45] and adult [31,46] patients. An interesting finding was the trend of northern centers toward higher cut-offs (≥ 50 nmol/L) compared with southern centers (≤ 30 nmol/L). However, these findings are not always reproduced in the literature and may differ from previous publications [14,28]. Because of the lack of evidence to determine the optimal level of 25(OH)D₃ to favorably affect HSCT, a specific cut-off cannot be recommended, and more studies to confirm this are warranted.

In the general population, a high dose of a short-term course of vitamin D replacement is prescribed to individuals with vitamin D deficiency (“loading dose”), whereas a lower dose of long-term supplementation with vitamin D is recommended to those with vitamin D insufficiency (“maintenance dose”) [48,49]. In our study, we aimed to find out whether both strategies, when combined as replenishment of vitamin D, may be challenging in HSCT. Although there are no clinical trials, to our knowledge, that have looked into the impact of the “loading dose” in the HSCT setting, there are some data published in healthy individuals, with favorable results [53]. Thus, it is expected that centers that include a loading dose within their clinical practice (33%) base their decision on the current evidence in the general population, and this stresses the need for validation of this approach in large clinical trials that focus on HSCT patients.

Moreover, most centers prescribe maintenance with vitamin D supplements. In our study, the median maintenance dose was 800 IU, but it varies greatly in the literature: in the general population, it ranges from 400 to 4000 IU/d [6,48,54,55], whereas in the HSCT population, it encompasses from 1000 IU/d to 600,000 IU/wk [16,28,29,31,32,45,47,56]. The reason for this could be the detrimental effect of additional risk factors for hypovitaminosis D in HSCT patients, such as immunosuppression (cyclosporin or steroids) [43,48] and gut GVHD [11], which

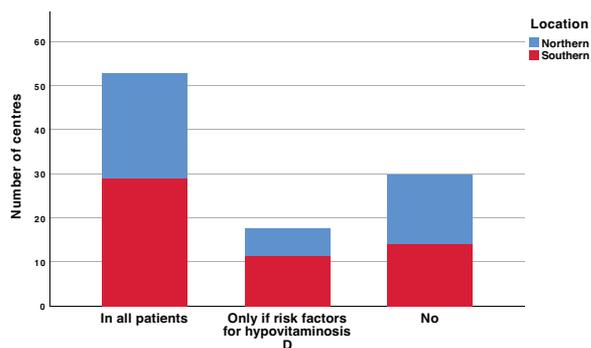


Figure 3. Proportion of centers measuring serum vitamin D after HSCT depending on location.

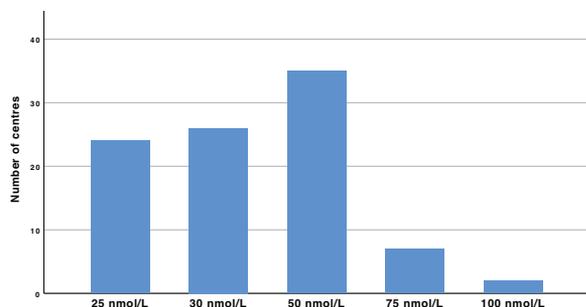


Figure 4. Cut-off values for vitamin D deficiency.

Table 4
Centers' Responses According to Aim for Prescribing Vitamin D Replacement in HSCT Patients (Several Answers Were Possible)

	N	%*
Maintain calcium metabolism and prevent bone loss	105	92%
Enhancement of immune reconstitution post-HSCT	27	24%
Prevent GvHD	19	17%
Enhancement of response to immunosuppression in GvHD	11	10%
Fatigue	2	2%
Reduce relapse risk	2	2%
Depression	1	1%

* % = percentage of the responder centres

could deplete vitamin D storage further, thus requiring a more aggressive approach. Most of the interventional studies in the field of transplantation have targeted pediatric patients, in whom the dose of vitamin D is tailored according to patients' weight [17]. Nevertheless, in the adult population, a fixed dose is usually prescribed following the "one-size-fits-all" approach, underestimating the real needs of these patients. The Scientific Advisory Committee on Nutrition guidelines recommend 400 IU/d in individuals older than 4 years because "this is the average amount needed by 97.5% of the population to maintain a serum 25(OH)D₃ concentration ≥ 25 nmol/L" [49], but this strategy may not be applicable in the HSCT setting for the aforementioned reasons. Therefore, the use of vitamin D therapy is certainly warranted in HSCT patients with vitamin D deficiency/insufficiency, maybe at a higher dose than in the general population.

Anecdotally, a minority of centers prescribe vitamin D to prevent disease relapse. Recent studies have shown that lower levels of serum 25(OH)D₃ are associated with a higher relapse rate and poorer prognosis in patients with hematologic malignancies [15,57–59]. However, there is still little evidence about this, and thus these reports should be considered cautiously.

Moreover, serum vitamin D also has been found to contribute to the response to immunosuppression in patients with steroid-resistant asthma [60,61]. Potentially, it could be comparable to steroid-resistant GVHD, but it has not been investigated yet. Therefore, it is reasonable that only 10% of the responders consider this a clinical indication for vitamin D treatment, as the role of vitamin D in this setting needs to be elucidated.

Finally, following HSCT, bone health remains a main survivorship concern. Majhail et al. [13], for instance, recommend a first evaluation at 1 year after allogeneic transplantation. In our study, most institutions refer patients to osteoporosis units for assessment and follow-up of bone mineralization with a DEXA scan, as also recommended by other publications [34]. Interestingly, DEXA scan results are outweighed by serum 25(OH)D₃ level as reference criteria to discontinue vitamin D therapy, which occurs in the majority of the centers (69%).

One of the main strengths of this study is the large number of centers involved, which accounts for one third of the institutions approached. In addition, our questionnaire covers a broad range of themes related to vitamin D throughout the different stages of allogeneic HSCT and gives a comprehensive overview of the current approaches in vitamin D deficiency in this setting. In addition, it has been completed by health care professionals with expertise in the field of stem cell transplantation and highly involved in HSCT patients' care.

A limitation of the survey is that it relies on voluntary self-reporting rather than external validation, which may affect the accuracy of the responses. Moreover, it is difficult to evaluate clinical practice patterns in the absence of clear

recommendations on vitamin D in the HSCT landscape. Although the contribution of vitamin D within the immune system has been investigated in depth, its effect on stem cells and potentially on engraftment and immune reconstitution is still far from being understood, so further studies are warranted.

CONCLUSIONS

To our knowledge, this is the first survey carried out to provide a comprehensive picture of the current management of vitamin D deficiency in allogeneic HSCT patients. It confirms the highly heterogeneous practice across the EBMT affiliate centers, including those from diverse geographical locations and dedicated to patients of different ages. Vitamin D deficiency is a modifiable risk factor of HSCT outcomes with low cost and negligible side effects [62,63] that might have the potential to restore immunologic tolerance and prevent some post-HSCT complications. This study underlines the need to develop evidence-based recommendations to guide health care professionals in the assessment of vitamin D status and its management in daily practice.

ACKNOWLEDGMENTS

The authors acknowledge the support provided by the British Society of Blood and Marrow Transplantation Clinical Trial Committee and the Transplant Complications Working Party of the EBMT, as well as all the participant centers.

Conflict of interest statement and financial disclosure: There are no conflicts of interest or financial disclosures to report.

Authorship statement: J.R.-S. led project design, study management, data analysis, and manuscript writing. J.A.S. and H.S. contributed to project design, study management, and manuscript writing. N.S., M.G., A.P., D.M.G., C.A., A.A., K.P., A.M., and G.W.B. contributed to project design and manuscript writing. A.H. contributed to study management and manuscript writing. C.P. contributed to project design. All authors accepted the final version of the manuscript.

REFERENCES

- Holick MF. The vitamin D deficiency pandemic and consequences for non-skeletal health: mechanisms of action. *Mol Asp Med*. 2008;29(6):361–368.
- Lee P, Milliken S, Center JR. Hypocalcaemic cardiac failure post BMT secondary to unrecognized vitamin D deficiency. *Bone Marrow Transplant*. 2008;42(5):363–364.
- Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. *Physiol Rev*. 2016;96(1):365–408.
- Provvedini M, Tsoukas CD, Defetos LJ, Manolagas SC. 1,25-Dihydroxyvitamin D₃ receptors in human leukocytes. *Science*. 1983;80:1181–1183.
- Rosen CJ. Vitamin D insufficiency. *N Engl J Med*. 2011;364(14):1379–1380. author reply 1380.
- Food and Nutrition Board I of M. *Dietary Reference Intakes for Calcium, Magnesium, Phosphorus, Vitamin D, and Fluoride*. Washington: Institute of Medicine (US) Standing-Committee on the Scientific Evaluation of Dietary Reference; 1997.

7. Valtueña J, González-Gross M, Huybrechts I, et al. Factors associated with vitamin D deficiency in European adolescents: the HELENA study. *J Nutr Sci Vitaminol (Tokyo)*. 2013;59:161–171.
8. González-Gross M, Valtueña J, Breidenassel C, et al. Vitamin D status among adolescents in Europe: the Healthy Lifestyle in Europe by Nutrition in Adolescence study. *Br J Nutr*. 2012;107(5):755–764.
9. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors 1–3. *Am J Clin Nutr*. 2007;85:860–868.
10. Cashman KD, Dowling KG, Gonzalez-Gross M, et al. Vitamin D deficiency in Europe: pandemic? *Am J Clin Nutr*. 2016;103(4):1033–1044.
11. van der Meij BS, de Graaf P, Wierdsma NJ, et al. Nutritional support in patients with GVHD of the digestive tract: state of the art. *Bone Marrow Transplant*. 2013;48(4):474–482.
12. Greenfield D, Boland E, Ezaydi Y, Ross R, Ahmedzai S, Snowden J. Endocrine, metabolic, nutritional and body composition abnormalities are common in advanced intensively-treated (transplanted) multiple myeloma. *Bone Marrow Transplant*. 2014;49:907–912.
13. Majhail NS, Rizzo JD, Lee SJ, Aljurf M, Atsuta Y, Bonfim C. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Biol Blood Marrow Transpl*. 2012;18(3):348–371.
14. von Bahr L, Blennow O, Bjorklund A, Malmberg K-J, Ljungman P, Le BK. Increased incidence of CMV disease in patients with vitamin D deficiency before allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2015;50:S403–S404.
15. Hansson MEA, Norlin A-C, Omazic B, et al. Vitamin D levels affect outcome in pediatric hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2014;20(10):1537–1543.
16. Beebe K, Magee K, McNulty A, et al. Vitamin D deficiency and outcomes in pediatric hematopoietic stem cell transplantation [epub ahead of print]. *Pediatr Blood Cancer*. doi:10.1002/pbc.26817. Accessed August 17, 2017.
17. Wallace G, Jodele S, Myers KC, et al. Vitamin D deficiency and survival after hematopoietic stem cell transplantation. *Biol Blood Marrow Transpl*. 2015;21(2015):S79–S107.
18. Ros-Soto J, Anthias C, Madrigal A, Snowden JA. Vitamin D: is it important in haematopoietic stem cell transplantation? A review. *Bone Marrow Transplant*. 2019;54(6):810–820.
19. Carlberg C. Current understanding of the function of the nuclear vitamin D receptor in response to its natural and synthetic ligands. *Recent Results Cancer Res*. 2003;164:29–42.
20. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. *Curr Opin Pharmacol*. 2010;10(4):482–496.
21. Rosen Y, Daich J, Soliman I, Brathwaite E, Shoenfeld Y. Vitamin D and autoimmunity. *Scand J Rheumatol*. 2016;456:439–447.
22. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. *Chem Biol*. 2014;21(3):319–329.
23. Lopes Marques C. The importance of vitamin D levels in autoimmune disease. *Bras J Rheumatol*. 2010;50(1):67–80.
24. Adorini L, Penna G. Control of autoimmune diseases by the vitamin D endocrine system. *Nat Clin Pract Rheumatol*. 2008;4(8):404–412.
25. Glotzbecker B, Ho VT, Aldridge J, et al. Low levels of 25-hydroxyvitamin D before allogeneic hematopoietic SCT correlate with the development of chronic GVHD. *Bone Marrow Transplant*. 2013;48(4):593–597.
26. Holtan SG, Pasquini M, Weisdorf DJ. Acute graft-versus-host disease: a bench-to-bedside update. 2017;124(3):363–374.
27. Cooke KR, Luznik L, Sarantopoulos S, et al. The biology of chronic graft-versus-host disease: a task force report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant*. 2017;23(2):211–234.
28. Caballero-Velazquez T, Montero I, Sanchez-Guijo F, et al. Immunomodulatory effect of vitamin D after allogeneic stem cell transplantation: results of a prospective multicenter clinical trial. *Clin Cancer Res*. 2016;22(23):5673–5681.
29. Campos DJ, Biagini GLK, Funke VAM, Bonfim CMS, Boguszewski CL, Borba VZC. Vitamin D deficiency in children and adolescents submitted to hematopoietic stem cell transplantation. *Rev Bras Hematol Hemoter*. 2014;36(2):126–131.
30. Urbain P, Ihorst G, Biesalski H-K, Bertz H. Course of serum 25-hydroxyvitamin D3 status and its influencing factors in adults undergoing allogeneic hematopoietic cell transplantation. *Ann Hematol*. 2012;(91):759–766.
31. Robien K, Strayer LG, Majhail N, et al. Vitamin D status among long-term survivors of hematopoietic cell transplantation. *Bone Marrow Transpl*. 2012;46(11):1472–1479.
32. Silva F, Pérez-Simón J, Caballero-Velazquez T, et al. Effect of vitamin D treatment in chronic GVHD. *Bone Marrow Transplant*. 2011;46:1395–1397.
33. Kreutz M, Eissner G, Hahn J, Andreesen R, Drobnik W, Holler E. Variations in 1a,25-dihydroxyvitamin D3 and 25-hydroxyvitamin D3 serum levels during allogeneic bone marrow transplantation Bone. *Bone Marrow Transplant*. 2004;33:871–873.
34. Inamoto Y, Lee SJ. Late effects of blood and marrow transplantation. *Haematologica*. 2017;102(4):614–625.
35. Bhatia S, Armenian SH, Landier W. How I monitor long-term and late effects after blood or marrow transplantation. *Blood*. 2017;130(11):1302–1315.
36. Engelsen O, Brustad M, Aksnes L, Lund E. Daily duration of vitamin D synthesis in human skin with relation to latitude, total ozone, altitude, ground cover, aerosols and cloud thickness. *Photochem Photobiol*. 2005;81(6):1287.
37. Jain V, Raychaudhuri R, Barry W. A survey of healthcare professionals' awareness of vitamin D supplementation in pregnancy, infancy and childhood: midwives, GPs and health visitors have their say. *Arch Dis Child*. 2011;96(suppl):A16–A18.
38. Buckinx F, Reginster JY, Cavalier E, et al. Determinants of vitamin D supplementation prescription in nursing homes: a survey among general practitioners. *Osteoporos Int*. 2016;27(3):881–886.
39. Elsayy M, Sorror ML. Up-to-date tools for risk assessment before allogeneic hematopoietic cell transplantation. *Bone Marrow Transpl*. 2016;51(10):1283–1300.
40. Sorror ML. How I assess comorbidities before hematopoietic cell transplantation. *Blood*. 2017;121(15):2854–2864.
41. Khoo AL, Chai LYA, Koenen HJPM, et al. Regulation of cytokine responses by seasonality of vitamin D status in healthy individuals. *Clin Exp Immunol*. 2011;164(1):72–79.
42. Binkley N, Krueger D, Gemar D, Drezner MK. Correlation among 25-hydroxy-vitamin D assays. *J Clin Endocrinol Metab*. 2008;93(5):1804–1808.
43. Hewison M. An update on vitamin D and human immunity. *Clin Endocrinol (Oxf)*. 2012;76:315–325.
44. Myers KC, Howell JC, Wallace G, et al. Poor growth, thyroid dysfunction and vitamin D deficiency remain prevalent despite reduced intensity chemotherapy for hematopoietic stem cell transplantation in children and young adults. *Bone Marrow Transplant*. 2015;33(4):395–401.
45. Duncan CN, Vrooman L, Apfelbaum EM, Whitley K, Bechard L, Lehmann LE. 25-Hydroxy vitamin D deficiency following pediatric hematopoietic stem cell transplant. *Biol Blood Marrow Transplant*. 2011;17(5):749–753.
46. Sproat L, Bolwell B, Rybicki L, et al. Vitamin D level after allogeneic hematopoietic stem cell transplant. *Biol Blood Marrow Transplant*. 2009;17(7):1079–1083.
47. Wallace G, Jodele S, Myers KC, et al. Vitamin D deficiency in pediatric hematopoietic stem cell transplantation patients despite both standard and aggressive supplementation. *Biol Blood Marrow Transplant*. 2016;22(7):1271–1274.
48. Wood CL, Cheetham TD. NICE guideline—vitamin D: increasing supplement use among at-risk groups. *Arch Dis Child Educ Pract Ed*. 2014;101(1):1–51.
49. Prentice A. Vitamin D and health. *Sci Adv Commun Nutr*. 2016;7(1):56–116.
50. Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. *Br Med J*. 2010;340(1):b5664.
51. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. *Dietary Reference Intakes Calcium and Vitamin D*. Washington: The National Academies Press; 2010.
52. Holick MF. Vitamin D: evolutionary, physiological and health perspectives. *Curr Drug Targets*. 2011;12(1):4–18.
53. Van Groningen L, Opdenoordt S, Van Sorge A, Telting D, Giesen A, De Boer H. Cholecalciferol loading dose guideline for vitamin D-deficient adults. *Eur J Endocrinol*. 2010;162(4):805–811.
54. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes 1–3. 2006;25:18–28.
55. Talwar SA, Aloia JF, Pollack S, Yeh JK. Dose response to vitamin D supplementation among postmenopausal African American women. *Am J Clin*. 2007;86(6):1657–1662.
56. Wallace G, Jodele S, Myers KC, et al. Single ultra-high-dose cholecalciferol to prevent vitamin D deficiency in pediatric hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2018;24:1856–1860.
57. Kulling PM, Olson KC, Olson TL, Feith DJ, Loughran Jr. TP. Vitamin D in hematological disorders and malignancies. *Eur J Haematol*. 2016;98:187–197.
58. Bittenbring T, Neumann F, Altmann B, Achenbach M, Ziepert M. Vitamin D deficiency impairs rituximab-mediated cellular cytotoxicity and outcome of patients with diffuse large B-cell lymphoma treated with but not without rituximab. *J Clin Oncol*. 2017;32(29):3242–3248.
59. Radujkovic A, Kordelas L, Krzykalla J, et al. Pretransplant vitamin D deficiency is associated with higher relapse rates in patients allografted for myeloid malignancies. *J Clin Oncol*. 2019;35(27):3143–3152.
60. Xystrakis E, Kusumakar S, Boswell S, et al. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. *J Clin Invest*. 2006;116(1):146–155.
61. Nanzer AM, Chambers ES, Ryanna K, et al. The effects of calcitriol treatment in glucocorticoid-resistant asthma. *J Allergy Clin Immunol*. 2014;133(6):1755–1757.
62. Autier PM, Gandini SP. Vitamin D supplementation and total mortality. *Arch Intern Med*. 2007;167(16):1730–1737.
63. Spiller HA, Good TF, Spiller NE, Aleguas A. Vitamin D exposures reported to US poison centers 2000–2014: temporal trends and outcomes. *Hum Exp Toxicol*. 2016;35(5):457–461.