

Current practice in vitamin D assessment and management across the Adult and Paediatric Haematopoietic Stem Cell Transplant Centres in Europe: a survey by the Transplant Complications Working Party of the EBMT

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ABSTRACT

In recent years numerous studies have proved the immune-regulatory properties of vitamin D, and how it can affect the course of allogeneic haematopoietic stem cell transplantation (HSCT). Its deficiency can potentially lead to complications, particularly acute or chronic GvHD, having a negative impact in post-HSCT outcomes. Despite the evidence gathered so far, current clinical guidelines only focus on the role of vitamin D in bone health and mineral metabolism, neglecting the implications of vitamin D within the immune system. As a consequence, patients may not be routinely assessed for this and treated accordingly.

This survey, carried out by the Transplant Complications Working Party of the European Society for Blood and Marrow Transplantation (EBMT), aims to describe the current clinical practice across the EBMT HSCT Programmes to acknowledge possible discrepancies. It could lead to the development of recommendations to standardise criteria and harmonise the management of vitamin D deficiency in patients undergoing allogeneic HSCT, advocating regular measurement of vitamin D, and supplementation if required, as part of the standard of care of HSCT recipients.

INTRODUCTION

Vitamin D deficiency is a global health concern. Risk factors include age, poor oral intake of vitamin D-enriched aliments and malabsorption^{1,2}. In Europe it affects habitants from different latitudes, including those living in Mediterranean countries³⁻⁶. It is well known that haematopoietic stem cell transplant (HSCT) recipients are at high risk for vitamin D deficiency and bone abnormalities^{7,8}. Vitamin D acts as a hormone with pleiotropic effects on the heart⁹, bone metabolism¹⁰ and immune system¹¹ among others. Studies carried out within the last decades have contributed to a better understanding of the immune-regulatory properties of vitamin D and its biological action in the course of HSCT¹²⁻¹⁶. Despite this, clinical guidelines in

HSCT have only focused on the role of vitamin D in bone health and mineral metabolism^{17–19} but there is little recognition of the potential contribution of vitamin D deficiency in post-HSCT complications such as graft-versus-host disease (GvHD)^{12,13,20}. Because of this clinicians worldwide may be managing patients differently and geographical location, endemic diet and local factors could impact on patients care.

In order to audit the current clinical practice 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 centres. Our results could lead to future development of recommendations to standardise criteria towards a more harmonised process, advocating regular measurement of vitamin D and supplementation, if required, as part of the standard of care of HSCT recipients.

MATERIAL AND METHODS

HSCT programme directors of 326 EBMT affiliate allogeneic transplant centres 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 developed by the authors and, prior to its launch, it was thoroughly reviewed by 7 HSCT specialists and amended accordingly. This survey was carried out from September to November 2018, and data was analysed consequently.

The results are given as frequencies of the responder centres to provide a better understanding of the outcomes.

RESULTS

Demographics

All the EBMT affiliate centres that perform allogeneic HSCT were approached (n=326). A total of 114 centres from 24 countries completed the questionnaire. Participating centres were located in the UK (n=25), Spain (n=19), Italy (n=17), Germany (n=8), Belgium (n=6), France (n=6), Turkey (n=6), Israel (n=3), Poland (n=3), Sweden (n=3), Austria (n=2), Netherlands (n=2), Saudi Arabia (n=2), Switzerland (n=2), Australia (n=1), Belarus (n=1), China (n=1), Czech Republic (n=1), Hungary (n=1), Ireland (n=1), Norway (n=1), Romania (n=1), Russia (n=1) and Slovenia (n=1).

As a geographical reference we took 50 degrees latitude because there is a remarkable difference on sunshine duration (hours per year) above and below it. A total of 46% (n=52) of the centres are located above (*northern* countries) and 54% (n=62) below this latitude (*southern* countries). Moreover, 58% (n=66) are dedicated adult centres, 21% (n=24) paediatric-only centres and 21% (n=24) provide care for adult and paediatric patients (*mixed* centres). At the time of the survey, 84% (n=96) were members of the European Union (EU).

This survey was completed by 46% transplant directors, 41% transplant consultants, 8% non-consultant grade physicians, 3% HSCT clinical nurses specialist (CNS) and 2% of other healthcare professional (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% continued the follow-up beyond the first year.

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 only followed by 19% of the centres. Similarly, international guidelines including the *Dietary Reference Intake* from the *Institute of Medicine* (IOM), the *National Institute for health and Care Excellence* (NICE), *UK Osteoporosis and Up-to-date recommendations* are followed by 18% of them. In 67% of the mixed centres adult and paediatric units follow the same policy for management of vitamin D deficiency.

Monitoring of vitamin D

Prior to allogeneic HSCT, serum vitamin D is routinely checked by 47% of the centres (**figures 1 and 2**): 37% in all the patients and 10% only in those with risk factors for hypovitaminosis D (**table 1**). However, after allogeneic HSCT nearly double of the centres (70%) monitor it regularly (**figures 3 and 4**): 53% in all the patients and 17% only in those patients with risk factors for hypovitaminosis D (**table 1**). It 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 centres (94%).

Prescription of vitamin D replacement

Vitamin D replacement is prescribed by transplant physicians (75%), family physicians (10%), endocrinologists (3%), CNS (3%), other specialists physicians (physiatrist, rheumatologist, gynaecologist) (4%) and in 5% of the centres, 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 centres 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%) (**figures 5 and 6**). Centres from northern countries tend to have a cut-off equal or greater than 50 nmol/L whereas in those from southern countries it tends to be equal or lower than 30 nmol/L.

The main reasons to prescribe vitamin D replacement are depicted in **table 2**.

Only 33% of the centres start patients on a “loading dose” as part of the treatment with vitamin D, of which 58% are adult, 24% mixed and 18% paediatric centres (**figures 7 and 8**). Eighty-nine percent of the responders provided the loading dose prescribed (the remaining were 3 paediatric centres where the dose is based on patients’ weight, and one adult centre where it is based on serum vitamin D levels). The median loading dose is 2,000 IU per day (286 - 20,000), being 3,200 IU/day in mixed centres, 2,000 IU/day in adult and 1,550 IU/day in paediatric centres. The median duration of the loading dose is 6 weeks (1-52).

Nearly all the centres (98%) prescribe long-term maintenance treatment with vitamin D (**figures 9 and 10**). Eighty-eight percent provided the daily maintenance dose prescribed (8 did not know it, 4 based it on patients’ weight and 1 on serum vitamin D levels): The median daily dose of vitamin D across the different age group centres is 800 UI/day (67 – 10,000).

Vitamin D replacement is eventually discontinued by 69% of the centres under the following criteria: when therapeutical vitamin D levels are reached (59%), when DEXA (dual-energy X-ray absorptiometry) 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 paediatric patients) (11%).

Follow-up

Follow-up occurs mainly in the transplant centre (89%), by the primary care physician (1%) or a mixed model (10%). It is most frequently life-long (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 paediatric patients transition to adults team (8%) or other follow-up programs (4%).

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

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 healthcare professionals in vitamin D deficiency: One was conducted among primary care physicians and midwives in the UK²¹; and the other among primary care physicians in Belgium, wherein some of them had patients institutionalised in nursing homes²². However, we have not found similar reports published in the field of stem cell transplantation.

Vitamin D has a largely studied immune-modulatory effect through the vitamin D receptor²³, located in cells from the innate and adaptive immunity. It blunts inflammation while enhancing a tolerogenic status, mediating in immune homeostasis²⁴⁻²⁶. In situations of vitamin D deficiency, this balance may be disturbed in favour of an inflammatory status and loss of self-tolerance, leading to conditions such as auto-immune diseases^{27,28}. In the allogeneic HSCT setting, it can also impact in post-HSCT complications and subsequently in its outcomes^{12-15,20}.

Currently, clinical guidelines do not include the assessment of vitamin D prior to HSCT^{29,30}. This could explain why less than half of the institutions participating in our study requested it at that time-point. However, this practice nearly doubles following HSCT as guidelines recommend to monitor vitamin D, alongside calcium and phosphorus, to assess bone health, prevent osteoporosis and ultimately bone fractures in high risk patients¹⁷⁻¹⁹. In fact, maintaining bone and mineral metabolism is considered by the majority of the responder centres the main indication for commencing on vitamin D replacement (92%).

The cut-off of serum vitamin D to define vitamin D deficiency is still a matter of debate: It is based on the minimum concentration of vitamin D required to prevent bone disease (rickets and osteomalacia). Nevertheless there is no evidence of the optimal serum vitamin D levels required to foster immune-reconstitution and prevent post-HSCT complications. In our study, the serum vitamin D cut-off ranged from 25 nmol/L to 75 nmol/L (as previously reported in series of allogeneic HSCT patients^{12,20,31,32}) although 50 nmol/L was the most common threshold (also in line with current literature^{13,33-36}). Anecdotally, a small proportion of the centres considered levels below 100 nmol/L as vitamin D deficiency, although there is no

evidence to endorse it. An interesting finding was the trend of northern centres towards higher cut-offs (≥ 50 nmol/L) compared to southern centres (≤ 30 nmol/L). This may be due to the different guidelines followed by these centres although, as we have previously mentioned, evidence-based guidelines for vitamin D management are followed by a minority of institutions (less than 20%).

The geographical reference was taken based on the annual sunshine duration: above 50 degrees latitude there are less than 1,800 hours of sunlight per year, whereas below this the number of sunlight hours is higher. Coincidentally nearly half of the participant centres were located north (46%) and south (54%) this latitude. Most of the responder centres are located in Western Europe, wherein a large number of transplant centres are based.

In the HSCT setting, some studies have shown the association between low serum vitamin D with complications post-HSCT, including acute^{31,37} and chronic^{12,20} GvHD, as well as CMV disease¹². In addition, the impact of vitamin D in outcomes following HSCT has also been explored, with controversial results: some studies showed that status of vitamin D deficiency may lead to a decrease in the overall survival following HSCT¹²⁻¹⁵, whereas others failed to reproduce these findings^{7,12,20,38}. However, in our study only a small number of centres considered that vitamin D has an important role in the pathophysiology of GvHD (17%) or even that it may contribute to fostering immune reconstitution after stem cell engraftment (24%).

Moreover, serum vitamin D has also been found to contribute to the response to steroids in patients with steroid-resistant asthma^{39,40}. This could be comparable to the steroid-resistant GvHD setting, but it has not been investigated as yet, so it seems reasonable that only 10% of the centres consider this relevant.

Replenishment of vitamin D may be challenging in HSCT patients. Several risk factors cause hypovitaminosis D including malabsorption, low sun exposure secondary to long hospitalisations or concomitant use of immunosuppression^{2,10,41}. To our knowledge, there are not clinical trials that have looked into the impact of a “loading dose” of vitamin D. It is therefore surprising that nearly 1/3 of the centres include it within their regular clinical practice. Reasonably, this loading dose is tailored to the target population and it varies among adult, paediatric and mixed centres. On the other hand, the vast majority of centres prescribe long-term treatment with vitamin D supplements, what we have coined as “maintenance”. In our study, the median maintenance dose was 800 IU per day but it varies greatly in the existing literature: in the general population it ranges from 400 to 4,000 IU per day^{2,42-44} whereas in the HSCT population the range is more remarkable, from 1,000 IU per day to 600,000 IU per week^{14,33,35,36,38,45-47}. Most of the interventional studies in the field of transplantation have been carried out in paediatric patients, where clinicians tailor the dose based on patients’ weight. Nevertheless, in the adult population a fix dose is usually prescribed following the “one-size-fits-all” approach. It may not be accurate and could underestimate the real needs of some patients, requiring a more aggressive treatment to achieve the optimal activity of vitamin D in serum. Due its safe side effects profile^{48,49} and easy administration, high compliance with vitamin D replacement can be achieved.

Anecdotally, a minority of centres prescribe vitamin D therapy to prevent relapse of the disease, as lower levels of serum vitamin D are associated with higher relapse rate and poor prognosis in patients with haematological malignancies^{13,50-52}.

Allogeneic HSCT is an effective cell therapy aiming to cure many diseases. It has gradually increased within the last 2 decades⁵³ and subsequently, the complications derived from this aggressive procedure⁵⁴. Following HSCT, bone health remains a main concern among centres, as we previously stated. Therefore it is not surprising that most of them refer patients to osteoporosis units for assessment and follow-up of bone mineralisation with DEXA scan, as recommended in the literature¹⁷. Although important, DEXA scan results are outweighed by the serum vitamin D levels as reference criteria to discontinue vitamin D therapy.

One of the main strengths of this study is that it has been completed by healthcare professionals with expertise in the field of stem cell transplantation, and highly involved in HSCT patients care. 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.

A weakness of the survey is that despite the large number of centres involved, it only accounts for 1/3 of the institutions approached and therefore the results may not be representative of the current clinical practice across the EBMT centres. Another limitation is that it relies on voluntary self-reporting rather than external validation, which may impact in the accuracy of the responses.

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 centres, including centres from diverse geographical locations and dedicated to patients from different age groups. Monitoring and replacement of vitamin D is neglected in the complex management of HSCT. This may be attributed to the lack of updated HSCT clinical guidelines to provide support to clinicians in the daily clinical practice.

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.

Vitamin D deficiency is a modifiable risk factor of HSCT outcomes with low cost and negligible side effects^{48,49}, that can restore immunological tolerance and prevent post-HSCT complications. This study laid the foundation for the establishment of recommendations to guide healthcare professional in the assessment of vitamin D status and ultimately raise awareness of the importance of vitamin D replacement in the course of HSCT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

JRS lead project design, study management, data analysis and manuscript writing; JAS and HS contributed to project design, study management and manuscript writing; NS, MG, AP, DMG, CA, AA, KP, AM and GWB contributed to project design and manuscript writing; AH contributed to study management and manuscript writing; CP contributed to project design.

APENDIX – Questionnaire

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