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Acute Graft-Versus-Host Disease and Serum Levels of Vitamin D in Patients Undergoing Hematopoietic Stem Cell Transplantation (HSCT)

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Abstract

Background and aims: Patients undergoing hematopoietic stem cell transplantation (HSCT) may present low vitamin D levels because of decreased exposure to sunlight, reduced dietary vitamin D, use of corticosteroids, limited outdoor activity, sunscreen use, and decreased oral intake. Graft-versus-host-disease (GVHD) is a frequent complication in HSCT. The aim of this study is to investigate the association of 25 hydroxy vitamin D (25-OH VD) levels with acute GVHD and engraftment time in patients undergoing HSCT.

Methods: In this cross-sectional study, medical charts of all consecutive patients undergoing HSCT between May 2012 and January 2014, and followed up during the three first months after HSCT, were reviewed. The serum levels of 25-OH VD were measured and registered in the first day of hospitalization, as were anthropometric data. Association of these variables with acute GVHD was examined.

Results: In the study period, of the 72 adult patients admitted for HSCT and included in this study, 15% had acute GVHD diagnosed in the 30 first days of hospitalization, and the majority had vitamin D insufficiency or deficiency. Vitamin D levels varied from 3 ng/ml to 53 ng/ml. Higher vitamin D levels were associated with shorter engraftment time (p<0,005). No significant association between acute GVHD and vitamin D serum levels 40 were found. A statistically significant association between obesity and vitamin D deficiency (p=0.048) was verified.

Conclusions: In this study, no association was found between the serum level of vitamin D in the first day of hospitalization of the patients undergoing HSCT and acute-GVHD, probably due to the low prevalence of acute GVHD in this sample. Higher 45 vitamin D levels were associated to shorter engraftment time (p<0.005).

Keywords: Vitamin D; Hematopoietic stem cell transplantation; Body mass index

Introduction

Vitamin D (VD) may decrease the incidence of chronic graft-versus-host disease (GVHD) and mortality in HSCT. HSCT morbidity and mortality is attributed to infection, organ system toxicity, GVHD and recurrent diseases [1].

VD is a nutrient whose sources can be UVB-dependent endogenous production, supplements and diet intake [2,3]. In the diet, VD is found in natural, non-fortified products, such as fatty fish (salmon, mackerel, sardines, cod liver oil) or some types of mushrooms (Shitake), they have relevant amounts of one of the two major forms, cholecalciferol or ergocalciferol [3].

In the human skin, cholecalciferol is synthesized from 7-dihydrocholesterol when exposed to sunlight (UVB 290-315). Cholecalciferol is biologically inactive and immediately binds to VD binding proteins or albumin. So VD3 is metabolized in the liver to 25-hydroxyVD3, catalyzed by the enzymes CYP2R1 and CYP27A1. In the kidney to its biologically active form, 1,25-dyhydroxyVD3 by the enzyme 1-α-hydrolylase (CYP27B1) which is under strict control of parathyroid hormone and the phosphaturic hormone fibroblast growth factor 23 (FGF-23) [2,3].

VD deficiency (VDD) can cause osteomalacia, bone pain, muscle weakness, fatigue, and increased risk of fracture, and precipitate or exacerbate osteopenia and osteoporosis. It can be caused by reduced skin synthesis, reduced absorption in the gastrointestinal tract, and inherited or acquired disorders of metabolism. Besides that, liver failure and chronic kidney disease can cause decreased synthesis of VD, and anticonvulsants, glucorticoids, and antirejection medications can increase catabolism of VD [4].

The major cause of VD deficiency in adults is inadequate exposure to sunlight [5]. The sunscreen with a sun protection factor of 30 reduces VD synthesis in the skin by more than 95%. People with a naturally dark skin tone have natural sun protection and require at least three to five times longer exposure to make the same amount of VD than people with white skin [5].

Besides that, obesity, malabsorption syndromes, bariatric and gastrointestinal surgeries, medications (such as, anticonvulsants and AIDS/HIV medications), chronic granuloma forming disorders, lymphomas and primary hyperparathyroidism have high risk of VDD [5]. The actions for VD are: [3,6-9]

Mineral Metabolism and Skeletal Health: VD enhances intestinal calcium and phosphate absorption, stimulates osteoclast differentiation and calcium reabsorption from bone and promotes mineralization of the bone matrix.

Development of Diseases: It is associated with cardiovascular diseases, cancer and autoimmune disorders, such as type 1 diabetes mellitus, multiple sclerosis and inflammatory bowel disease.

Regulation of host immune responses and prevention of autoimmunity: VD inhibits DC maturation, polarizes T-cell populations toward the expression of Th2 as compared with Th1 cytokines, and blunts allogeneic T-cell proliferation in response to DC stimulation. VD increases expression of IDO, an enzyme responsible for tryptophan metabolism (upregulated in tolerizing DCs). It can prevent of GVHD.

The VD receptor is expressed on various hematopoietic precursors as well as monocytes, some thymoccytes, and active B and T lymphocytes. And its action is potentiated by retinoic acid receptor/retinoid X receptor binding.

Antineoplasic Therapy in Hematological Diseases: VD can participate in the conversion differentiation-arrested myeloblasts into a mature blood cell, acting mostly in Myelodysplastic Syndrome and Acute Myeloid Leukemia.

Modulatory of Immune Response in Allogeneic Transplant: VD receptor can impact on immune reconstitution after HSCT and decrease risks of infection, 110 graft versus host disease and effects.

Patients undergoing to HSCT may have low 25-OH VD level because of decreased exposure to sunlight, the major cause of VDD [5], from prolonged hospital stays, reduced dietary VD, use of corticosteroids, limited outdoor activity, and sunscreen use, and decreased oral intake caused by gastrointestinal treatment toxicity [4,10]. Besides that gastrointestinal graft-versus-host disease (GVHD) limits absorption of VD. Some medications received during the HSCT can increase the VD catabolism, and change renal and kidney function [4].

GVHD is an important and frequent complication in HSCT that is a major determinant of post transplantation morbidity, quality of life and survival [11]. Acute-GHVD, which develops within the first 3 months of HSCT, is characterized by inflammatory dermatitis, hepatitis, and enteritis [11].

Considering the role of vitamin D in hematological diseases and in HSCT, the hypothesis raised in this study is that low levels of vitamin D could be associated with higher acute-GVHD frequency, as higher levels would be associated with a shorter 125 engraftment time.

Our objective was, thus, to study the serum levels of vitamin D in the first day of hospitalization of patients undergoing HSCT to investigate the association of vitamin D levels with acute-GVHD (a-GVHD) and with time for engraftment.

Methods

Patients

In this observational, cross-sectional study, we analyzed 72 patients undergoing HSCT from May 2012 to January 2014 in the Hematology-Oncology and Bone Marrow Transplantation Center at Albert Einstein Hospital in São Paulo, Brazil, during the first 3 months. The characteristics of the patients who participated in the study were shown in Table 1. The patients who were less than 18 years old were excluded. In our study there were not patients with dark skin, only white skin.

All patients were weighed to the nearest 0.05 kg by calibrated digital scales and height was measured in the nearest 0.1 cm using a stadiometer. Body Mass Index (BMI) was calculated as weight (kg) divided by square height (m).

All patients were divided by BMI (kg/m^2) <65 years old in 4 groups: <18.5 as malnutrition; between 18.4 and 24.9 as normal; 25-29.9 as overweight; >30 as obesity. And patient's ≥ 65 years-old in 3 groups: <21.9 kg/m^2 as malnutrition; 22- 26.9 kg/m^2 as normal; >27 kg/m^2 as obesity [12].

The serum levels of 25-OH VD were measured in the first day of hospitalization of the adult patients (≥18 years) who would be undergoing HSCT. The result of this exam was ready in the second day of hospitalization. All types of HSCT patients were included. As a retrospective study, we did not know the serum levels of 25-OH VD after the treatment.

Serum levels of 25-OH VD

The method used to quantitate 25(OH) D is ECL Roche Diagnostics®. This is an automated competitive immunoassay that includes the sample pretreatment to decouple your vitamin D binding protein. VDD definition used in our study was defined as a 25(OH) D ≤ 20 ng/ml, VD insufficiency of 21-29 ng/ml, and VD normal ≥ 30 ng/ml [5].

All VDD patients were treated with 50.000 UI of vitamin D3 per week and insufficient ones with 10.000 UI per week since the following day of the evaluation of VD serum levels [5].

a-GVHD

The Hematologist Team was responsible for diagnosing a-GHVD in these patients. The diagnosis of the a-GHVD was based on symptoms, exams and/or biopsy [13].

Data Analysis

A descriptive analysis was performed by absolute frequencies and percentages for the qualitative variables and means and standard deviations, quartiles and minimum and maximum values in the case of numerical variables. The association between qualitative variables was evaluated by Chi-square test or Fisher exact tests. The analyzes were performed with SPSS (SPSS Inc. SPSS Statistics 2008 Released in 165 Windows, Version 17.0 Chicago: SPSS Inc.) and level of significance 5%. The estimated minimum sample size was obtained considering the main objective, as well as a range of 95% confidence interval for this estimate. Considering an absolute accuracy of 10% would require 60 patients, at least.

Results

72 adult patients were observed in this study, aged between 18 and 74 years, with the majority (77.8%) aged less than 65 years old. Of the total, 59.7% were men and 41.7% had normal BMI, 30.6% overweight, 25.6% obesity and 2.8% malnourished. (Table1).

		n	%
Elderly	<65 years	56	77.8%
	>=65 years	16	22.2%
	Total	72	100.0%
Sex	Female	29	40.3%
	Male	43	59.7%
	Total	72	100.0%
Type of HSCT	Allogeneic unrelated	14	23.0%
	Allogeneic related	9	14.8%
	Autologous	28	45.9%
	Haploidêntical	10	16.4%
	Total	61	100.0%
BMI (kg/m^2)	Normal	30	41.7%
	Overweight	22	30.6%
	Obese	18	25.0%
	Malnourished	2	2.8%
	Total	72	100.0%
Serum Level of Vitamin D (ng/ml)	>=30: Normal	11	15,5%
	11-29: Insuficiency	48	67,6%
	<10:Deficiency	12	16,9%
	Total	72	100.0%

Table 1: Characteristics of the sample

15% had a-GVHD diagnosed in the 30 first days of hospitalization and 82% did not have it diagnosed in this same time. There was no association between a-GVHD and VD serum levels significantly.

The mean of engraftment was 14.5 days (± 5.3), and was associated with serum levels of vitamin D, higher VD levels were associated with shorter engraftment time (p<0,005).

The most frequent type of Autologous HSCT was 45.9%. As for vitamin D, 67.6% had insufficiency and 16.9% deficiency (Table 1).

As for the change in the value of 25-OH VD, we observe the minimum of 3 ng/ml and maximum of53.0 ng/ml (Table 2).

We observed a statistically significant relationship between obesity and vitamin D deficiency, being that the range deficiency and insufficiency is greater among obese (p=0.048). We found a change in the rates of VDD during 2012 and 2013/2014, while the normal ratio increased, as well as the disabled, and the proportion of patients with insufficient vitamin D decreased (p<0.005– Table 3).

As for types of HSCT, the largest proportion of VDD was observed between the haploidentical and the largest proportion of insufficiency between the autologous (Table 4).

Patients with lymphoma have the highest rate of VDD (41.7%), however 100% had serum levels of 25-OH VD ≤ 20. The patients with myeloma have the highest insufficiency rate (Table 5).

	Median	Maximum	Minimum	1st quartile	3rd quartile
Age(years)	54	74	18	39	64
Weight(kg)	77.6	137.1	35.0	66.2	87.7
BMI (kg/m²)	25.8	39.6	15.5	23.3	29.0
Serum vitamin D level (ng/ml)	19.2	53.0	3.0	13.1	27.0

Table 2: Description of the sample

		Year				p
		2012		2013/2014		
		n	%	n	%	
Vitamin D deficiency	>=30: Normal	1	3.1%	10	25.6%	0.004*
	11-29: Insufficiency	28	87.5%	20	51.3%	
	<10: Deficiency	3	9.4%	9	23.1%	
#: Pearson's Chi-square Test. *: Fisher's exact Test						

Table 3: Evolution of vitamin D deficiency

Discussion

Epidemiological studies have described that higher serum levels of vitamin D are associated with lower incidence rates of cancers, and/or lower incidence rates of grade of severity and/or mortality, such as prostate, breast, colon, ovarium, renal, pancreatic cancer [14].

There is an inverse association of serum levels of vitamin D and BMI ≥ 30 kg/m², because the body fat kidnaps the fat-soluble vitamin [5]. In our study, we found more VDD in obese patients, for HSCT these groups of patients have more risk of having GVHD [15-17]. The GVHD is the major obstacle to the success of HSCT [18]. Besides that, during HSCT the patients must avoid sun exposure, they have alteration of gastrointestinal absorptive capacity by GVHD or bacterial overgrowth, bile acid and pancreatic enzyme insufficiency, all these factors can bring about VDD [19].

We did not find an association of 25-OH VD serum levels and a-GVHD, however, all our patients were treated since the VDD diagnosis, and for ethical reasons we didn`t have a deficient group without treatment as a control group. Besides that, in our sample we found low prevalence of a-GVHD. Our prevalence of a-GVHD (15%) was lower than other studies (20-50%) [9]. Although the role of VD was better studied in chronic GVHD, maybe VD can have a protection factor in relation to a-GVHD. The patients with higher levels of 25-OH VD had shorter time of engraftment in our study. However, it could be caused for several factors, including the low prevalence of a-GVHD.

We found a high rate of VDD in lymphoma patients in our study, and this association was evaluated in others studies for Hodgkin and Non-Hodgkin lymphoma [20,21].

No studies about the association between VDD and type of HSCT were found, however, in our study, haploidentical and autologous had lower serum levels of 25-OH VD.

There was a significant difference in the serum levels of 25-OH VD in 2012 and 2013/4. Although we didn`t change any protocol of diagnosis and supplementation of vitamin D, all of the members of the HSCT team (hematologists, nurses, dietitians, etc.) were informed about the benefits of high VD levels in patients undergoing HSCT by classes and research protocol. So in 2013/4 more patients had VDD diagnosis and were treated before HSCT, changing the rate of VDD in our sample.

Limitations of this study include the retrospective design and a short follow up, but our objective was to evaluate a-GVHD. And in the first 3 months we were sure about the adhesion of the patients in relation to VD treatment, after that it was not possible any more.

		Type of HSCT								p
		Allogeneic Unrelated		Allogeneic Related		Autologous		Haploidentical		
		n	%	n	%	n	%	n	%	
Serum levels of VD(ng/ml)	>=30: Normal	4	28.6%	1	11.1%	3	11.1%	1	10.0%	0.737*
	29-11: Insufficiency	8	57.1%	6	66.7%	20	74.1%	6	60.0%	
	<10: Deficiency	2	14.3%	2	22.2%	4	14.8%	3	30.0%	
	Total	14	100.0%	9	100.0%	27	100.0%	10	100.0%	
	*: Fisher's exact Test									

Table 4: Relationship between vitamin D deficiency and type of HSCT

		Hematological Disease							
		Leukemia		Lymphomas		Myeloma		Other	
		n	%	n	%	n	%	n	%
Serum levels of VD(ng/ml)	>=30: Normal	5	16.7%	0	0.0%	2	11.1%	4	36.4%
	11-29: Insufficiency	21	70.0%	7	58.3%	14	77.8%	6	54.5%
	<10: Deficiency	4	13.3%	5	41.7%	2	11.1%	1	9.1%
	Total	30	100.0%	12	100.0%	18	100.0%	11	100.0%

Table 5: Vitamin D deficiency by Hematological Disease

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Nonetheless, our low prevalence of a-GVHD was interesting and the associations to obesity, lymphoma and engraftment with 25-OH VD serum levels have the potential to emphasize VDD treatment in HSCT.

Conclusion

In this study, we found that higher levels of VD had shorter time of engraftment. The prevention and treatment of VDD in HSCT patients is easy and cheap, which can improve the transplant outcome and reduce its complications. Our results should stimulate further investigation into the association between VD and a-GVHD.

Conflicts of interest: none.

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