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Applied nutritional investigation

Bone mineral density, vitamin D, and nutritional status of children submitted to hematopoietic stem cell transplantation

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ABSTRACT

Objective: The aim of the study was to evaluate the effect of allogeneic hematopoietic stem cell transplantation (HSCT) on bone mineral density (BMD), serum vitamin D levels, and nutritional status of 50 patients between ages 4 and 20 y.
Methods: We conducted pre-HSCT and 6-mo post-HSCT evaluations. We measured BMD at the lumbar spine (LS) and total body (TB) by dual energy x-ray absorptiometry (DXA); body composition by bioimpedance analysis, and dietary intakes of calcium and vitamin D using the 24-h recall and semiquantitative food frequency questionnaire methods.
Results: We observed a significant reduction in BMD 6 mo post-HSCT. Nearly half (48%) of patients had reductions at the LS (average −9.6% ± 6.0%), and patients who developed graft-versus-host disease (GVHD) had the greatest reductions (−5.6% versus 1.2%, $P < 0.01$). We also found reductions in serum levels of 25-hydroxyvitamin D (25-OHD), from 25.6 ± 10.9 ng/dL to 20.4 ± 11.4 ng/dL ($P < 0.05$), and in body weight. Corticosteroid treatment duration, severity of chronic GVHD, serum 25-OHD levels, and family history of osteoporosis were all risk factors associated with variations in BMD at the LS.
Conclusion: HSCT in children and adolescents negatively effects their BMD, nutritional status, and vitamin D levels. We suggest that early routine assessment be done to permit prevention and treatment.

Introduction

The advancement of scientific knowledge has led to increases in the number of hematopoietic stem cell transplants (HSCTs), as well as in the disease-free survival rate and, consequently, a larger number of patients with HSCT late complications. Endocrine organs are sensitive to the cytotoxic drugs and radiation therapy commonly used during the pre-HSCT conditioning stage, thus, low bone mass, impaired growth, gonadal and thyroid dysfunction, metabolic syndrome, and changes in nutrient metabolism can develop after transplantation [1,2]. Additionally, there is the negative influence of drugs used post-HSCT because cyclosporine and corticosteroids cause muscular atrophy and reductions in bone formation [3,4]. Other factors also can be involved in bone mass reduction post-HSCT, including reduced physical activity and lean body mass, low sun exposure, and vitamin D deficiency, which is a required vitamin in the development and maintenance of bone mass [5].

Reductions in bone mineral density (BMD) are observed both at early (few months) and late stages (up to 10 y) post-HSCT [6–8]. Bone metabolism changes have been more widely studied in adults, but fewer studies have been done with children and adolescents, showing a prevalence of osteopenia and osteoporosis post-HSCT between 24% and 57% [7,9–15]. A prospective study assessing BMD pre- and post-HSCT in young patients found 5% reduction in BMD 6 mo post-HSCT [12].

Children and adolescents are growing and developing their bone mass; by age 20, 95% of bone mineral mass has been acquired [16]. Peak bone mass reached at this stage is inversely

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Table 1
Characteristics of patient and control groups

Variables	Patients (n = 50)	Controls (n = 25)	*P*-value
Age (y)	10.4 ± 4.6	10.2 ± 3.8	NS
Sex (M:F)	1.6:1	1.5:1	NS
Body weight (kg)	35.8 ± 17.1	39.0 ± 18.6	NS
Z score W/A	−0.26 (−3.2 to 2.8)	0.10 (−1.1 to 2.9)	NS
BMI (kg/m^2)	18.1 ± 3.6	18.6 ± 4.1	NS
Z score BMI/A	0.19 (−4.0 to 3.0)	0.28 (−1.0 to 2.5)	NS
Z score H/A	−0.69 (−3.2 to 2.6)	0.25 (−2.2 to 2.2)	<0.01
Lean body mass (kg)	29.2 ± 14.3	31.7 ± 15.2	NS
Diagnosis			
Nonmalignant diseases:	37 (74%)		
Fanconi anemia	17 (34%)		
Severe aplastic anemia	10 (20%)		
Wiskott-Aldrich syndrome	5 (10%)		
Adrenoleukodystrophy	5 (10%)		
Malignant diseases:	13 (26%)		
Acute lymphocytic leukemia	5 (10%)		
Acute myeloid leukemia	3 (6%)		
Chronic myeloid leukemia	2 (4%)		
Myelodysplasia	3 (6%)		
Type of HSCT			
Related allogeneic	25 (50%)		
Unrelated allogeneic	25 (50%)		
Conditioning			
Without radiotherapy	41 (82%)		
Radiotherapy (1320–1440 cGy)	9 (18%)		

BMI, body mass index; BMI/A, BMI-for-age; H/A, height-for-age; HSCT, hematopoietic stem cell transplantation; NS, not significant; W/A, weight-for-age

related to fracture risk in adult life, which is associated with high morbidity and mortality [7,17]. Additionally, children submitted to HSCT have nutrient deficiencies leading to impaired development, cognitive function, and delayed linear growth. Nutrition deficiencies are also associated with early mortality post-HSCT [18,19]. Our hypothesis is that HSCT and its complications lead to reduced levels of 25-hydroxyvitamin D (25-OHD), changes in BMD and significant loss of weight and lean mass.

The objective of this study was to evaluate the effect of allogeneic HSCT on BMD, serum levels of vitamin D, and the nutritional status of children and adolescents.

Methods

Study population

All patients between ages 4 and 20 y receiving allogeneic HSCT between August 2006 and September 2008 at the Bone Marrow Transplant Unit at Hospital de Clínicas da Universidade Federal do Paraná were consecutively included in the study. We excluded those patients with osteometabolic bone disorders before HSCT and those with any impossibility to have a bone densitometry exam performed.

Out of the 80 patients selected, 68 were included. Of those, 17 (25%) died before the sixth-month post-HSCT, and 1 performed only one test. Fifty patients with an average age of 10.4 ± 4.6 y completed the study. Regarding their diagnosis, 37 patients (74%) had non-malignant disorders, and 13 (26%) had malignant disorders (Table 1). Regarding the source of cells, 40 (80%) patients received an infusion of hematopoietic cell transplantation with bone marrow; nine (18%) with umbilical cord blood; and 1 (2%) with peripheral blood stem cells. The conditioning regimens consisted of cyclophosphamide alone in 12 patients (24%), busulfan, cyclophosphamide, and lymphoglobulin in 11 patients (22%); busulfan and cyclophosphamide in 8 patients (16%); cyclophosphamide, fludarabine, and lymphoglobulin in 10 (20%), and 9 (18%) received total body chemoradiotherapy in association with cyclophosphamide and lymphoglobulin in 6 cases or with busulfan in 3. Forty-five patients (90%) received immunoprophylaxis for graft-versus-host disease (GVHD) with cyclosporine and methotrexate, and 5 patients (10%) received cyclosporine and corticosteroids.

Twenty-two patients (44%) developed either acute or chronic forms of GVHD. Eight (16%) used anticonvulsants, and 31 (62%) used corticosteroids after HSCT, with an average cumulative dose of prednisone of 105.0 ± 63.5 mg/kg or 0.97 ± 0.42 mg/kg daily for the first 6 mo after HSCT. Primary graft failure occurred in 4 patients (8%); 2 were submitted to a second HSCT during the study period.

The study population was compared with a group of 25 healthy children, matched for sex, age, and body mass index (BMI), chosen from children of employees of the Hospital de Clínicas. All patients were evaluated pre-HSCT and 6 mo post-HSCT for BMD, serum levels of vitamin D, nutritional status, and dietary intake of calcium and vitamin D. Twenty-five patients had their BMD and nutritional status assessed a third time, 12 mo post-HSCT.

BMD was assessed through dual-energy x-ray absorptiometry (DXA) using Hologic's QDRW 1000 equipment (Hologic, Bedford, MA, USA). The precision, accuracy and stability of the equipment were constantly tested, and its coefficient of variation was 0.46 for the lumbar spine. After standard measurements for children and adolescents, the areas of assessment were the lumbar spine (LS) and the total body (TB), with the head area being excluded for children ages ≤ 10 [8,20,21]. BMD was measured in g/cm^2 and bone mineral content (BMC) was measured in g. BMD at the LS was obtained as the average densities of vertebrae L1 to L4, and the results were expressed as scores in relation to standard values for healthy individuals of the same age group (*Z* score). BMD was classified as "low BMD for chronological age" when the patient had a *Z* score < −2.0 SD at the LS [8,21]. In order to minimize the effect of skeleton size on DXA results, we calculated the estimated volumetric BMD of the LS, defined as apparent BMD (ABMD) based on BMD and the LS area, through this formula: ABMD = BMD/area; the resulting value was expressed in g/cm^3 [22,23]. Serum vitamin D levels (25-OHD) were measured on day of admission into the hospital for HSCT and 6 mo later, by the chemiluminescence method (Liaison kit, Diasorin, Stillwater, MN, USA). Values used to classify vitamin D status were ≤20 ng/mL for vitamin deficiency; 21–29 ng/mL for vitamin D insufficiency, and ≥30 ng/mL for normal state (vitamin D sufficiency) [24,25].

The study was approved by the Hospital de Clínicas-UFPR Human Research Ethics Board. The patients, as well as their parents or legal guardians, were informed about the objectives and study procedures, and signed the Free and Informed Consent Form.

Nutritional status was assessed by a single professional, and consisted of body weight, height, and lean body mass measurements. Body weight, height, and BMI were assessed using scores compared with reference values for healthy individuals of the same sex and age group (*Z* score), and were classified as "low weight-for-age" and "low height-for-age" when the *Z* score was < −1.0 SD, and a "low BMI-for-age" when the *Z* score was < −2.0 SD [26]. Lean body mass was assessed by bioimpedance analysis (BIA) using a tetrapolar RJL Quantum unit, and lean body mass was calculated through predictive equations for each sex and age group [27]. Dietary intake was assessed using the 24-h recall and semi-quantitative food frequency questionnaire methods through an interview conducted by a registered dietitian. Adequacy of vitamin D and calcium intakes were compared with dietary reference intakes (DRIs) of the same sex and age group [28]. Patients were asked about their levels of sun exposure, previous history of falls, and family history of osteoporosis. Systemic corticosteroid use was assessed by data collection from patient files, and was calculated as total dosage used (equivalent to prednisone) during the 6-mo period after HSCT, and the total use in days. The duration of anticonvulsant drug used was also assessed.

Statistical analysis

The variables selected for statistical analysis were initially submitted to the Shapiro-Wilk and Kolmogorov-Smirnov tests, which tested for their symmetrical (normal) distribution. The variables with symmetrical distribution are shown as the average ± SD, whereas the asymmetrical variables are shown as the median, the lowest and the highest values. For comparing the averages, Student's *t* test was used when the variable had a symmetrical distribution, and non-parametric tests when the variable had an asymmetrical distribution. For categorical variables, the Fisher and χ^2 tests were used. For the analysis of correlations, the Pearson and Spearman coefficients were used to test the association between continuous variables of symmetrical and asymmetrical distribution, respectively, and a multiple linear regression analysis was also conducted. For all analyses, we used a two-tailed *t* test, and a minimum level of significance of 5%.

Results

Bone mineral density

In the pre-HSCT stage, 7 patients (14%) reported a previous history of fracture, and 13 (26%) reported a family history of osteoporosis.