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25-Hydroxy Vitamin D Deficiency Following Pediatric Hematopoietic Stem Cell Transplant

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Children may be at increased risk for vitamin D deficiency following HSCT because of lack of sun exposure, the recommended use of sunscreen, dietary insufficiency, malabsorption, and the use of certain medications. We prospectively assessed the prevalence of and risk factors for 25-hydroxy (25-OH) vitamin D deficiency in 67 patients transplanted at our institution. 25-OH vitamin D levels were checked during 3 separate 4-week periods in the spring, autumn, and winter. Subjects were <2 years following transplant and/or being treated for chronic graft-versus-host disease (cGVHD). Levels less than 20 ng/mL were considered deficient, and those less than 30 ng/mL were considered insufficient. The mean 25-OH vitamin D level was 22.8 ng/mL (range: 7-46.2). A total of 80.6% (confidence interval [CI] 69.1%-89.3%) of patients had a level less than the lower limit of the institutional normal range. The deficiency rate was 37.3% (CI 25.8%-50%). The mean parathyroid hormone (PTH) level was 77.5 (SD = 80.5). There was no correlation between 25-OH vitamin D and PTH levels. We evaluated potential risk factors for 25-OH vitamin D deficiency including age, season of testing, sun exposure, sunscreen use, use of steroid or calcineurin inhibitor, race, and dairy intake. In multivariate logistic regression, only older age was found to be a risk factor for deficiency ($P = .004$). Patients with deficient levels were treated with 50,000 IU of ergocalciferol once weekly for 6 weeks. A postrepletion 25-OH level was available for 22 patients. The majority of repleted patients had a normal posttreatment level (63.6%). The postsupplementation level corrected into the insufficient range for 31.8% of patients and 4.6% remained deficient. Vitamin D insufficiency and deficiency are common following HSCT. Further investigation into potential risk factors and the appropriate supplementation for these patients is warranted.

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INTRODUCTION

Vitamin D deficiency is a recognized international health issue [1-11]. An adequate supply of vitamin D is needed for skeletal development, and vitamin D deficiency in childhood can interfere with optimal skeletal calcium deposition [12]. Emerging evidence suggests that vitamin D may play a role in immunomodulation, decreasing the risk for certain cancers, and the prevention of multiple chronic illnesses [11,13-29]. Children are potentially at increased risk for vitamin D deficiency following hematopoietic stem cell transplant (HSCT) for multiple reasons. Vitamin D is typically acquired from exposure to sunlight and from dietary sources [11,30]. Following HSCT, children may have decreased exposure to direct sunlight because of hospitalization and convalescence. Additionally, properly applied sunscreen may reduce vitamin D_3 synthesis by 99% [31]. Sunscreen use is commonly recommended posttransplant and, when used as directed, may place patients at greater risk for vitamin D deficiency. Other potentially contributing factors to post-HSCT vitamin D deficiency are decreased bioavailability because of malabsorption, obesity resulting in sequestration of vitamin D in fat, and increased catabolism because of glucocorticoid and calcineurin inhibitor use [11,32,33].

The recommended daily vitamin D intake for healthy children and adolescents is 400 IU [34]. There are many published regimens for the treatment of vitamin D deficiency. Most repletion strategies involve weekly enteral supplementation with high-dose vitamin D, although intramuscular injection and ultraviolet exposure have also been recommended

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[30,35-40]. The appropriate vitamin D repletion and supplementation for children following HSCT is unknown. This prospective study investigated the prevalence of 25-hydroxy (25-OH) vitamin D deficiency in children and adolescents following HSCT. We evaluated potential risk factors for 25-OH vitamin D deficiency and the efficacy of a weekly oral repletion strategy.

MATERIALS AND METHODS

We prospectively measured the 25-OH vitamin D and parathyroid hormone (PTH) levels of post-HSCT patients during 3 separate 4-week periods in the spring and autumn of 2009 and in winter 2010. Patients aged 1 to 21 years were eligible for participation if they were transplanted at our institution and were within 2 years of stem cell infusion at the time of enrollment. Patients who were <2 years from HSCT were eligible for participation if they were receiving immunosuppression for the treatment of chronic graft-versus-host disease (GVHD). We evaluated patients <2 years from transplant and those with chronic GVHD (cGVHD) in an effort to exclude patients less medically impacted by HSCT. Exclusion criteria included having a vitamin D level checked within 6 months of enrollment, as it is the standard at our institution to check no more frequently than every 6 months unless clinically indicated, known vitamin D wasting condition, vitamin D supplementation at enrollment, and the inability to receive enteral vitamin D repletion. 25-OH vitamin D levels ≥30 ng/mL were considered normal, levels 20 to 29 ng/mL were considered insufficient, and levels <20 were considered deficient. Patients who had a 25-OH vitamin D level in the deficient range were given repletion with enteral ergocalciferol at the dose of 50,000 IU once weekly for 6 weeks. A follow-up level was checked within 4 weeks of the completion of repletion. A PTH level was checked at the time of the initial 25-OH Vitamin D level. It was not evaluated following repletion. The institutional normal range for PTH is 10-65 pg/mL.

Demographic information, baseline transplant, and the list of medications prescribed at enrollment were abstracted from the medical record. Demographic data included sex, age at enrollment, and race (Caucasian, African-American, Hispanic, Asian, and mixed ethnicity). Baseline transplant data included the type of transplant, the donor source (unrelated or related), the stem cell source, time from transplant, and the indication for transplantation. A survey administered at the time of enrollment assessed potential risk factors for vitamin D deficiency. Subjects were queried about their intake of vitamin D–containing nutrition or supplements using 24-hour dietary recall. This included the use of parenteral nutrition, the volume of daily consumption of milk (cow and soy) and formula, and the use of any nutritional supplements. Daily exposure to direct sunlight was categorized as <30 minutes per day, between 30 minutes and 1 hour per day, 1 to 2 hours per day, and >2 hours per day. Subjects were asked to categorize their use of sunscreen as almost always/rarely go outside without it; sometimes/used when planning to be outside for more than 1 hour; or rarely/less than once per week.

Statistical Methods

The prevalence's were calculated and presented with 95% exact confidence intervals for binomial parameters. Potential risk factors were evaluated using a multivariate logistic regression. Sun exposure was assessed with the 4-point scale and sunscreen use with the 3-point scale described in the previous section. Dietary intake of vitamin D–containing beverages or supplements was evaluated with a 24-hour dietary recall and was analyzed as a continuous variable. The type of transplant, sex of patient, the absence or presence of active GVHD, and calcineurin inhibitor and steroid use were analyzed as binary variables. The indication for transplantation was analyzed as the categoric variables hematologic malignancy, solid tumor, and nonmalignant condition. Age was analyzed as a continuous variable. The underlying disease was treated as a categoric variable.

To describe the effect of ergocalciferol supplementation once weekly, we report the mean levels with standard deviations (SD) prior to and following treatment. Patients who were prescribed ergocalciferol for repletion, but died before completing the period of repletion, were included in the analysis of prevalence and excluded from analysis of the effect of ergocalciferol supplementation. The mean change in vitamin D levels after supplementation was evaluated using the Wilcoxan signed rank test. The Pearson correlation coefficient was used to assess the linear correlation between vitamin D and PTH levels.

RESULTS

Between May 21, 2009, and February 23, 2010, a total of 67 patients had a 25-OH vitamin D level collected. The seasonal distribution of testing was 41.8% in the spring, 23.9% in the autumn, and 34.3% in the winter. The population was 62.7% male and had a median age at enrollment of 73 months (mean = 94.6 months). The racial composition of the study population was 64.2% Caucasian, 13.4% Hispanic, 11.9% Asian, 7.5% African American, and 3% mixed ethnicity (Table 1). The majority of patients, 82.1%, had an allogeneic HSCT (70.9% unrelated donor). The median duration of time since HSCT was 69 days (mean = 133 days). The majority of patients took a calcineurin inhibitor (68.7%) and/or corticosteroids (38.8%), and 10.4% of the patients had active

Table 1. Patient Characteristics and Potential Risk Factors

	Normal (>30 ng/mL)	Insufficient (20-29 ng/mL)	Deficient (<20 ng/mL)
Mean age (months)	84	78	119
Male:female	62:38	55:45	72:28
Underlying malignancy (%)	69	66	60
Allogenic HSCT (%)	77	72	96
Unrelated donor (%)	80	59	78
Mean days from HSCT	46	133	113
cGVHD (%)	4	5	4
• Cutaneous (% of GVHD)	17%	34%	34%
• Oral (% of GVHD)	17%	17%	34%
• Occular (% of GVHD)	0	0	34%
• Pulmonary (% of GVHD)	0	34%	0
Prednisone use (%)	9	15	24
Calcineurin inhibitor use (%)	15	31	38
Mean volume milk/day (oz)	14	10	14
Sunscreen use (%)			
Always	31	31	32
Sometimes	54	59	44
Rarely	15	10	24
Daily time outside (%)			
<30 minutes	70	61	67
30 minutes-1 hour	15	13	8
1-2 hours	15	13	25
>2 hours	0	13	0

HSCT indicates hematopoietic stem cell transplantation; GVHD, graft-versus-host disease.

GVHD at enrollment. Patients with active GVHD were not analyzed as a separate cohort because of the small number of patients with GVHD.

The mean 25-OH vitamin D level was 22.8 ng/mL (median = 23, range: 7-42.6). The prevalence of either vitamin D deficiency or insufficiency was 80.6% (95% confidence interval [CI] 69.1%-89.3%). The prevalence of vitamin D deficiency was 37.3% (CI 25.8%-50%) and insufficiency was 43.3% (CI 31.2%-56.0%). The mean 25-OH vitamin D level was highest in the autumn (28.0 ng/mL) in contrast to the mean values in the spring (21.0 ng/mL) and winter (21.4 ng/mL) ($P = .89$). The 25 patients with 25-OH vitamin D levels in the deficient range were prescribed ergocalciferol and 22 patients completed 6 weeks of repletion. Three patients who were prescribed repletion died of relapsed leukemia prior to follow-up. The mean change in 25-OH vitamin D levels following supplementation was 18.8 (SD = 11.3, range: 8-42). Of the evaluable subjects, 63.6% had a postsupplementation level in the normal range, 31.8% had levels in the insufficient range, and 4.5% remained deficient. The mean presupplementation level in patients with normal postsupplementation values was 15.1 ng/mL (SD = 2.7, range: 8.3-19.3) compared to 11.8 ng/mL (SD = 4.0, range: 7-17.2) in subjects who had abnormal postsupplementation levels ($P = .0699$).

A PTH level at enrollment was available for 63 patients. The mean value was 77.5 pg/mL (SD = 80.5, range: 7.2-450). The correlation coefficient between the vitamin D and PTH levels was −0.0055 ($P = .9647$), and there was not statistical evidence to conclude a correlation.

In multivariate analysis of the age at enrollment, the use of sunscreen, daily sun exposure, the daily milk intake, calcineurin or steroid use, and race, only older age at enrollment was found to be a risk factor for vitamin D deficiency ($P = .004$).

DISCUSSION

Vitamin D insufficiency and deficiency were common in this population of children and adolescents following HSCT in Boston. The mean serum vitamin D level, 22.8 ng/mL (56.9 nmol/L), in this population is lower than mean levels reported in the National Health and Nutrition Examination Surveys (NHANES) 2000-2004, which reported mean 25-OH levels of 76.43 nmol/L in children aged 1 to 5 years; 70.02 nmol/L in children aged 6 to 11 years, and 63.86 nmol/L in adolescents aged 12 to 19 years [41]. The prevalence of deficiency in this study, 37.3%, is higher than the 12.1% reported in healthy infants and toddlers in Boston and is similar to a prevalence of 42% reported in healthy adolescents, defined as age >11 years, living in Boston [2,3]. However, the deficiency rate in the subset of patients in our study aged 11 years or older was 66.7%.

Potential risk factors for vitamin D deficiency are well reported and are inconsistent across studies [2,3,25,42,43]. We investigated multiple potential risk factors and only identified older age as a predictor of vitamin D deficiency. Other studies support an increased risk of vitamin D deficiency in healthy adolescents [8,9]. The underlying cause for the increased risk of deficiency in adolescents and young adults is unclear. Potential contributors include greater intake of nonvitamin D–containing beverages such as soda and juice and less compliance with recommendations to avoid sun exposure. Higher rates of GVHD have been reported in adult patients compared with children [44,45]. We considered the possibility that the adolescent patients had more GVHD and thus more deficiency because of malabsorption and the use of corticosteroid and calcineurin inhibitors. However, in this sample, the rates of GVHD and immunosuppression use were similar between the adolescents and younger children. The impact of suboptimal vitamin D status on the bone and overall health of this population is not known.

Cutaneous absorption of solar ultraviolet B radiation is responsible for the conversion of 7-dehydrocholesterol to previtamin D_3, which is converted to vitamin D_3 [11,30]. People living at higher latitudes have less exposure to UV light during the winter, and seasonal variation of vitamin D levels has been reported [2,8]. Studies of healthy subjects at the end of the winter report prevalence rates of 32% to 48% [10,46]. Season of testing was

not a risk factor for vitamin D deficiency in this study. This is likely explained by the lack of exposure to sunlight even during summer months as 64.2% of patients reported spending <30 minutes per day outdoors. Sunscreen use was common, with 31.3% of patients reporting wearing sunscreen at all times, and 75% of patients who spent greater than 2 hours outdoors per day wearing sunscreen at all times.

We investigated potential risk factors specific to HSCT including type of transplant, donor source, stem cell source, the presence of GVHD, the indication for transplant, steroid use, and calcineurin inhibitor use. None of these factors was found to be a significant risk factor for deficiency, which is likely because of the homogeneity of the transplant population. Patients with insufficient and deficient levels were further from transplant than those with normal levels. The reason for this is unclear, but may be because of the almost universal use of parenteral nutrition replete with vitamin D during the transplant admission.

Previous studies report increased rates of vitamin D deficiency in African American patients when compared to non–African American populations [3,47]. Race (Caucasian, African-American, Hispanic, Asian, or mixed ethnicity) was not a predictor of vitamin D deficiency in our study, which may be because of the lack of ethnic diversity in the study population. Other risk factors reported in healthy populations, but not significant in this population included milk consumption, sunscreen use, and daily sun exposure. Although the lack of a significant impact of any of these factors may be because of the relatively small sample size, an additional explanation may be that underlying risk for deficiency associated with HSCT mitigated the risk factors present in healthy populations.

PTH plays multiple roles in bone metabolism including activation of osteoblasts, stimulation of renal production of 1,25-dihydroxyvitamin, D and augmentation of the renal tubular absorption of calcium [11,13]. In healthy individuals, there is an inverse relationship between vitamin D and PTH levels. There was no correlation between PTH and vitamin D levels in this study, which is unique from studies of deficiency in other populations [2]. The explanation for the lack of correlation is not clear. Hypomagnesemia is a potential contributor, as it is known to blunt the PTH response to low vitamin D levels [48]. However, this likely played a small role in this study as it is our institutional standard to provide magnesium supplementation to patients who receive calcineurin inhibitors, and the majority of patients in this study were treated with calcineurin inhibitors. Despite standardized supplementation, it is common for patients to need additional bolus infusions of magnesium. Another potential contributor is intrinsic parathyroid dysfunction. Bakker et al. [49] reported 35% parathyroid hormone disturbance in children following allogeneic HSCT. PTH disturbances were not found in a study of children following autologous HSCT [50].

The repletion strategy used in this study was adequate, and the majority of patients corrected to a normal posttreatment value. However, 36.4% of patients had insufficient or deficient levels following attempted correction. These patients may have needed a longer period of repletion, and weekly treatment for 8 weeks has been recommended in other studies [11,36]. Repletion occurred in the outpatient setting, and poor compliance with the weekly regimen may have played a role in the lack of normalization for some patients. We advocate repeat testing after attempted repletion for all patients and suggest nutritional consult and continued treatment for those with continued suboptimal levels. If there is concern for difficulty with compliance, then ergocalciferol should be administered in the clinic.

These data must be interpreted in the context of known limitations. The sample size is relatively small and may have been of insufficient size to identify potential risk factors. Furthermore, all subjects were transplanted in the northeastern United States, and the results may not be generalizable to those living in other areas. We did not study vitamin D levels in a non-HSCT control group. It is therefore possible that the low vitamin D levels were because of factors other than transplant. Finally, we did not investigate the effect of suboptimal vitamin D levels on bone or overall health. The implications of vitamin D deficiency on the health of children and adolescents following HSCT remains unknown.

In summary, vitamin D insufficiency and deficiency are common following HSCT, and adolescents appear to be at increased risk for suboptimal levels. We need prospective multicenter trials to examine the prevalence of deficiency in multiple settings and to investigate the effect of suboptimal vitamin D status.

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REFERENCES

1. Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int*. 1997;7:439-443.
2. Gordon CM, DePeter KC, Feldman HA, et al. Prevalence of vitamin D deficiency among healthy adolescents. *Arch Pediatr Adolesc Med*. 2004;158:531-537.
3. Gordon CM, Feldman HA, Sinclair L, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. *Arch Pediatr Adolesc Med*. 2008;162:505-512.
4. Holick MF, Siris ES, Binkley N, et al. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab*. 2005; 90:3215-3224.

5. Marwaha RK, Tandon N, Reddy DR, et al. Vitamin D and bone mineral density status of healthy schoolchildren in northern India. *Am J Clin Nutr*. 2005;82:477-482.
6. McGrath JJ, Kimlin MG, Saha S, et al. Vitamin D insufficiency in south-east Queensland. *Med J Aust*. 2001;174:150-151.
7. Sedrani SH. Low 25-hydroxyvitamin D and normal serum calcium concentrations in Saudi Arabia: Riyadh region. *Ann Nutr Metab*. 1984;28:181-185.
8. Sullivan SS, Rosen CJ, Halteman WA, et al. Adolescent girls in Maine are at risk for vitamin D insufficiency. *J Am Diet Assoc*. 2005;105:971-974.
9. Talwar SA, Swedler J, Yeh J, et al. Vitamin-D nutrition and bone mass in adolescent black girls. *J Natl Med Assoc*. 2007;99: 650-657.
10. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. *Am J Med*. 2002;112:659-662.
11. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357: 266-281.
12. Cooper C, Javaid K, Westlake S, et al. Developmental origins of osteoporotic fracture: the role of maternal vitamin D insufficiency. *J Nutr*. 2005;135:2728S-2734S.
13. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr*. 2004;80(6 Suppl): 1689S-1696S.
14. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc*. 2006;81:353-373.
15. Penna G, Roncari A, Amuchastegui S, et al. Expression of the inhibitory receptor ILT3 on dendritic cells is dispensable for induction of CD4+Foxp3+ regulatory T cells by 1,25-dihydroxyvitamin D3. *Blood*. 2005;106:3490-3497.
16. Gorham ED, Garland CF, Garland FC, et al. Vitamin D and prevention of colorectal cancer. *J Steroid Biochem Mol Biol*. 2005;97:179-194.
17. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer*. 2002;94:1867-1875.
18. Grant WB, Garland CF. Evidence supporting the role of vitamin D in reducing the risk of cancer. *J Intern Med*. 2002; 252:178-179; author reply 179-180.
19. Grant WB, Garland CF. The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. *Anticancer Res*. 2006;26:2687-2699.
20. Holick MF. Calcium plus vitamin D and the risk of colorectal cancer. *N Engl J Med*. 2006;354:2287-2288; author reply 2287-22988.
21. Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. *Am J Public Health*. 2006;96: 252-261.
22. Garland CF, Mohr SB, Gorham ED, et al. Role of ultraviolet B irradiance and vitamin D in prevention of ovarian cancer. *Am J Prev Med*. 2006;31:512-514.
23. Giovannucci E. Calcium plus vitamin D and the risk of colorectal cancer. *N Engl J Med*. 2006;354:2287-2288; author reply 2287-2288.
24. Giovannucci E. The epidemiology of vitamin D and colorectal cancer: recent findings. *Curr Opin Gastroenterol*. 2006;22: 24-29.
25. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst*. 2006;98:451-459.
26. Giovannucci E, Liu Y, Stampfer MJ, Willett WC. A prospective study of calcium intake and incident and fatal prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2006;15:203-210.
27. McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med*. 1996;125:353-359.
28. McGrath J, Selten JP, Chant D. Long-term trends in sunshine duration and its association with schizophrenia birth rates and age at first registration—data from Australia and the Netherlands. *Schizophr Res*. 2002;54:199-212.
29. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension*. 1997;30(2 Pt 1): 150-156.
30. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest*. 2006;116:2062-2072.
31. Osterwalder U, Herzog B. Sun protection factors: world wide confusion. *Br J Dermatol*. 2009;161(Suppl 3):13-24.
32. Lo CW, Paris PW, Clemens TL, et al. Vitamin D absorption in healthy subjects and in patients with intestinal malabsorption syndromes. *Am J Clin Nutr*. 1985;42:644-649.
33. Sato T, Fukagawa M, Uchida K, et al. 1,25-Dihydroxyvitamin D synthesis after renal transplantation: the role of fibroblast growth factor 23 and cyclosporine. *Clin Transplant*. 2009;23: 368-374.
34. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics*. 2008;122:1142-1152.
35. Shah BR, Finberg L. Single-day therapy for nutritional vitamin D-deficiency rickets: a preferred method. *J Pediatr*. 1994;125: 487-490.
36. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet*. 1998;351:805-806.
37. Thacher TD, Fischer PR, Pettifor JM, et al. A comparison of calcium, vitamin D, or both for nutritional rickets in Nigerian children. *N Engl J Med*. 1999;341:563-568.
38. Markestad T, Halvorsen S, Halvorsen KS, et al. Plasma concentrations of vitamin D metabolites before and during treatment of vitamin D deficiency rickets in children. *Acta Paediatr Scand*. 1984;73:225-231.
39. Chel VG, Ooms ME, Popp-Snijders C, et al. Ultraviolet irradiation corrects vitamin D deficiency and suppresses secondary hyperparathyroidism in the elderly. *J Bone Miner Res*. 1998;13: 1238-1242.
40. Tangpricha V, Turner A, Spina C, et al. Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. *Am J Clin Nutr*. 2004;80:1645-1649.
41. Looker AC, Pfeiffer CM, Lacher DA, et al. Serum 25-hydroxyvitamin D status of the US population: 1988-1994 compared with 2000-2004. *Am J Clin Nutr*. 2008;88:1519-1527.
42. Rovner AJ, O'Brien KO. Hypovitaminosis D among healthy children in the United States: a review of the current evidence. *Arch Pediatr Adolesc Med*. 2008;162:513-519.
43. Rovner AJ, Stallings VA, Kawchak DA, et al. High risk of vitamin D deficiency in children with sickle cell disease. *J Am Diet Assoc*. 2008;108:1512-1516.
44. Atkinson K. Chronic graft-versus-host disease. *Bone Marrow Transplant*. 1990;5:69-82.
45. Zecca M, Prete A, Rondelli R, et al. Chronic graft-versus-host disease in children: incidence, risk factors, and impact on outcome. *Blood*. 2002;100:1192-1200.
46. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr*. 2002;76:187-192.
47. Looker AC, Dawson-Hughes B, Calvo MS, et al. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. *Bone*. 2002;30:771-777.
48. Sahota O, Mundey MK, San P, et al. Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency. *Osteoporos Int*. 2006;17:1013-1021.
49. Bakker B, Oostdijk W, Bresters D, et al. Disturbances of growth and endocrine function after busulphan-based conditioning for haematopoietic stem cell transplantation during infancy and childhood. *Bone Marrow Transplant*. 2004;33:1049-1056.
50. Frisk P, Arvidson J, Stridsberg M, Gustafsson J. Normal long-term parathyroid function after autologous bone marrow transplantation in children. *Pediatr Transplant*. 2007;11:205-208.