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# Impaired Bone Mineral Density in Pediatric Patients with Chronic Graft-versus-Host Disease

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A B S T R A C T

Pediatric allogeneic hematopoietic stem cell transplantation (AHSCT) recipients with chronic graft-versus-host disease (cGVHD) are at high risk for endocrinopathies, particularly impaired bone mineral density (BMD). However, rates of BMD impairment in pediatric AHSCT recipients with cGVHD have not been well documented. We report 33 patients with cGVHD who were referred to the National Institutes of Health (NIH) for the Natural History of Clinical and Biological Factors Determining Outcomes in Chronic Graft-versus-Host Disease Study (NCT 0092235) and underwent formal BMD assessment via dual-energy X-ray absorptiometry (DEXA). Not surprisingly, we found much higher rates of BMD impairment than previously reported for pediatric AHSCT recipients who were not stratified by the presence or absence of cGVHD. Most of these patients (73%) had a *z*-score ≤–2 in at least 1 anatomic site. Although we expected the rate to be higher than that observed for pediatric AHSCT recipients in studies that did not analyze patients with cGVHD separately, this rate is nonetheless extremely high. Furthermore, the overall rate of occult vertebral compression fractures (VCFs) in our cohort was 17%, and the rate was 23% in patients with at least 1 *z*-score of ≤–2. The rates of BMD impairment and VCF in our pediatric cohort were significantly higher than those seen in the adult AHSCT recipients who were concurrently enrolled on the same study at the NIH and had similar cGVHD severity. We found that older age at cGVHD diagnosis and a greater number of systemic therapies were associated with occult VCF. Moreover, the intensity of current immunosuppression negatively impacted lumbar spine and total hip BMD in this cohort. Our study, although limited by small patient numbers and lack of a control AHSCT recipient group without cGVHD, indicates that children with cGVHD are at a greater risk for BMD impairment than previously appreciated. Given the rising incidence of cGVHD in AHSCT recipients and our findings, we recommend that pre-AHSCT DEXA be incorporated into routine pediatric pretransplantation screening studies. A baseline DEXA study could facilitate longitudinal monitoring of BMD in children, who may be more susceptible than adults to the negative effects of AHSCT on BMD. In addition, given the high risk of BMD impairment in pediatric AHSCT recipients with cGVHD, such patients should undergo BMD evaluation upon developing cGVHD, with continued monitoring thereafter to allow intervention before progression of the BMD impairment to its severe manifestation, VCF.



## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (AHSCT) has the potential to cure hematologic malignancies, as well as inherited and acquired disorders of hematopoietic cells [1-4]. A significant proportion of AHSCTs are performed in

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children [1,5]. Due to reductions is early transplantation-related mortality (TRM), there is an increasing number of long-term survivors of AHSCT, who are at risk for a multitude of late effects [1,2,4,6]. For pediatric AHSCT recipients in particular, late effects have a significant impact on quality of life, because AHSCT may interrupt growth and development, which may not resume in the post-AHSCT period [1,7-9]. Furthermore, children should have a long life expectancy, and thus the burden of morbidity from a chronic condition, such as chronic graft-versus-host disease (cGVHD), could be greater for pediatric AHSCT recipients. cGVHD is a major cause of nonrelapse mortality following AHSCT for both adult and pediatric patients [2]. Although the incidence of cGVHD is lower in pediatric AHSCT recipients compared with adult recipients, up to 50% of children undergoing AHSCT are affected; however, published rates of cGVHD in the pediatric setting are only estimates, because most studies of AHSCT do not report pediatric data separately [3]. Overall, the combined adult and pediatric cGVHD prevalence is high due to a multitude of factors, including wide use of unrelated donors and peripheral blood-derived stem cells [1,2].

cGVHD, a highly inflammatory state of immune dysregulation, and the immunosuppressive regiments used to treat this condition, can cause damage to many organ systems [1]. First-line treatment for cGVHD continues to be systemic corticosteroids, with duration of therapy frequently extending to several years, often combined with calcineurin inhibitors. Although both of these therapies have been shown to have deleterious effects on bone health in children and adults [4,10,11], the negative impact on bone health can be further enhanced during certain developmental periods of childhood and adolescence, such as puberty [7]. Peak bone mass in adulthood is largely dependent on appropriate bone mineral density (BMD) gain during childhood, and disruptions to this process may have long-lasting effects [8,9].

The negative effects of systemic corticosteroids on bone density are multifactorial, with the primary insult on bone formation [12-14]. This is caused by a reduction in the number of osteoblasts, which is mediated via increased apoptosis of existing osteoblasts coupled with reduced osteoblast replication and precursor differentiation. Moreover, corticosteroids interfere with osteoblast function by inhibiting osteoblast gene transcription. Glucocorticoids also promote bone resorption by enhancing osteoclast activity. In addition, systemic corticosteroids promote renal excretion of calcium and lead to decreased calcium absorption in the gastrointestinal tract. In combination, these processes lead to decreased bone mass [12-14].

Although children with cGVHD are likely to have high rates of impaired BMD, the prevalence of BMD impairment in this patient population is not known. Current guidelines for monitoring bone-related late effects following AHSCT in children do not include separate recommendations for patients with cGVHD. The recommendations for all AHSCT recipients include dual-energy x-ray absorptiometry (DEXA) or quantitative computed tomography (CT) scan at 1 year post-transplantation [4,15]. In addition, all AHSCT survivors, adults and children alike, are encouraged to maintain adequate calcium and vitamin D intake [4,15]. Endocrine consultations are advised for children with BMD *z*-scores more than 2 standard deviations below the mean for age and those with fractures [15].

Pediatric patients with cGVHD would be expected to have additional risk factors for impaired bone health, given the associated chronic inflammation, long-term use of corticosteroids and calcineurin inhibitors, nutritional and gastrointestinal complications of cGVHD, pubertal delays, poor growth, and decreased physical activity [8]. Based on our clinical experience with moderate and severe cGVHD, we hypothesized that this subset of pediatric patients with cGVHD would have higher rates of BMD impairment than previously suspected, and would be at high risk for occult vertebral compression fractures (VCFs). In this descriptive study, we aimed to measure this cohort's rate of BMD impairment, as well as to investigate clinical features associated with BMD impairment and/or VCF.

## METHODS

### *Patients*

A total of 47 pediatric patients age 2 to 19 years were enrolled on the National Institutes of Health's (NIH) Natural History Study of Clinical and Biological Factors Determining Outcomes in Chronic Graft-versus-Host Disease (NCT 00092235) between February 2005 and June 2016. This study was conducted at the National Cancer Institute (NCI) and was approved by the NCI's Institutional Review Board. Most the patients were referred to the NIH by their extramural primary transplantation team for advice and guidance on management of challenging cGVHD manifestations [16]. Witnessed, signed informed parental or guardian consent, along with patient assent were obtained before study enrollment.

During the week-long participation in this cross-sectional study, patients underwent a multidisciplinary cGVHD evaluation by a transplantation physician, ophthalmologist, dermatologist, dentist, psychologist, physiatrist, occupational therapist, and pain and palliative care specialist, with a pediatric endocrinology consultation for some patients. Organ involvement with cGVHD was assessed and graded in accordance with the NIH cGVHD consensus criteria [16,17].

Among the 47 patients, 8 did not undergo BMD evaluation with DEXA due to age (<8 years); 1 was excluded due to recent contrast administration for a clinically indicated diagnostic CT scan; 1 missed the DEXA appointment, which could not be rescheduled within the week-long study period; and 4 had a recent DEXA performed at an outside institution or at the NIH but more than 3 months after the time of the cGVHD Natural History Study evaluation. The latter patients were excluded from BMD assessments because scans were performed on different equipment, and in the 1 patient who had a scan performed at the NIH, the clinical cGVHD scoring was not performed in temporal proximity to the scan. BMD was evaluated via DEXA at 4 anatomic sites, including the lumbar spine, femoral neck, total hip, and forearm. As stated previously, patients age ≥8 years were scheduled for the scan; however, 6 patients age <8 years were able to undergo DEXA, because they were able to comply with nonsedated imaging. Thus, data on 33 pediatric patients (age range, 3 to 18 years; mean age, 11.5 ± 5.0 years) with DEXA scan measurements were further analyzed with regard to BMD (Figure 1).

### *Clinical Data Collection*

Patient data obtained during the week-long enrollment in the Natural History Study were recorded in the NIH Clinical Center's electronic medical record. Standard demographic data, age and ethnicity, were collected (Table 1).

Available patient records from referring institutions were reviewed and summarized, and included the following parameters: date of AHSCT, indication for AHSCT (primary disease), disease status at AHSCT, conditioning regimen (nonmyeloablative versus myeloablative), use of total body irradiation was used in the conditioning regimen, stem cell source, donor relationship and sex, and degree of HLA match between host and donor (Table 2). Outside records were also reviewed for history of acute GVHD, cGVHD classification (classic, overlap, or late acute), age at cGVHD diagnosis, duration of cGVHD, and number of previous systemic therapies (Table 3). At the time of evaluation at the NIH, the following information was assessed: intensity of current immunosuppression, current prednisone/prednisone equivalent dose, and past and current calcineurin inhibitor therapy (Table 3). Clinical cGVHD scoring [16,18,19] was performed during the patient's visit to the NIH and included the sum of NIH organ scores for skin, mouth, eyes, gastrointestinal tract, liver, lungs, joints and fascia, genital tract in female patients, average NIH organ score, NIH global severity score, chronic GVHD activity assessment, and performance status (Karnofsky score for patients age ≥16 years and Lansky score for patients age <16 years) [20,21] (Table 3). Biochemical data specific to the hypothesis of the study were collected, including serum 25-OH vitamin D, 1,25-$(OH)_2$ vitamin D, and ionized calcium; vitamin D data are provided in Table 1. Information regarding pubertal staging was documented according to the methods of Marshall and Tanner [22] in patients with a pediatric endocrine clinic evaluation (n = 33)