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Changes in trabecular bone score and bone mineral density following allogeneic hematopoietic stem cell transplantation

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ABSTRACT

Purpose: It has been demonstrated that bone mineral density (BMD) loss is substantial within the first 12 months after allogeneic hematopoietic stem cell transplantation (alloHSCT). Declines in BMD showed a disproportionate cortical bone loss even though trabecular bone is metabolically more active than cortical bone. This finding suggests a unique mechanism. However, the structural bone deficits after alloHSCT have not been well characterized. The trabecular bone score (TBS) has emerged as a method to assess bone microarchitecture. The aim of this study was to evaluate the changes in BMD and TBS in patients who received alloHSCT with follow-up of two years.

Methods: All patients 18 years and older who received alloHSCT between 2009 and 2015 at Seoul St. Mary's Hospital, Korea were included. They were segregated into a first group (A, n = 24) that was evaluated for BMD at the time of alloHSCT and 12 months posttransplant and a second group (B, n = 44) that was evaluated for BMD at 12 and 24 months following alloHSCT.

Results: Subjects in group A experienced a decrease in BMD at the femoral neck and total hip between the time of transplantation and 12 months posttransplantation: 0.056 ± 0.057 (5.48%) and 0.072 ± 0.063 (6.84%), respectively. Subjects in group B experienced an increase in BMD at the lumbar spine and total hip between 12 and 24 months post-alloHSCT: 0.047 ± 0.064 (4.90%) and 0.017 ± 0.045 (2.16%), respectively. In group A, TBS at 12 months post-alloHSCT decreased 0.028 ± 0.067 (1.92%) from the baseline ($p = 0.086$). In group B, TBS at 24 months post-alloHSCT increased 0.010 ± 0.049 (0.78%) from the 12 months post-alloHSCT evaluation ($p = 0.149$). TBS change was positively associated with BMD changes at all measured sites. The cumulative dose of glucocorticoid therapy was associated with loss of BMD at all measured sites and TBS. In addition, the dose of total body irradiation (TBI) was negatively associated with TBS.

Conclusions: In summary, this study delineated longitudinal microarchitectural changes in bone structure occurring in the context of alloHSCT. TBS change per 12 months was insignificant during the two years following alloHSCT. Therefore, our data represented disproportionate cortical bone loss in the context of the microarchitecture.

1. Introduction

With improved outcome of allogeneic hematopoietic stem cell transplantation (alloHSCT), long-term complications, including osteoporosis with a high risk for fractures, have gained greater importance [1]. Therefore, the temporal sequence of bone loss after alloHSCT has been well reviewed. Dual-energy X-ray absorptiometry (DXA)-based studies have demonstrated substantial bone deficits within the first 6 to 12 months after alloHSCT at all skeletal sites. Risk factors for bone loss after alloHSCT include old age, prolonged immunosuppression [2], hypogonadism [3], low body weight [4], total body irradiation (TBI) [5], and glucocorticoid therapy [4,6,7]. The rapid impairment of bone

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formation and the increase in bone resorption might play a role in post-HSCT bone loss. Shortly after HSCT, the serum carboxy-terminal cross-linked telopeptide of type I collagen increased, and osteocalcin decreased [8]. An increased ratio of the receptor activator of the nuclear factor – κB ligand (RANKL) to osteoprotegerin (OPG) contributed to the pathogenesis of osteoporosis by increasing bone resorption [9].

It is now well established that bone mineral density (BMD) is not the only characteristic of bone that determines its strength and fragility and therefore must be considered when deciding on therapy to prevent new or further osteoporotic fractures [10]. This acknowledgement has led to the recognition that evaluating bone microarchitecture might significantly enhance the accuracy of bone strength evaluations [11,12]. Over the past decade, a new approach to assess trabecular bone microarchitecture has emerged, called the trabecular bone score (TBS) [12–14]. It is noninvasive, requires no further patient testing, and has been repeatedly shown to be a BMD-independent predictor of skeletal strength and fracture risk [15]. Ex vivo data generally support the premise that TBS is able to serve as a surrogate for bone microarchitecture [16]. TBS is derived from the experimental variograms of 2D projection images and is calculated as the slope of the log-log transformation of the 2D variogram, where the slope characterizes the rate of gray-level amplitude [14]. It is reviewed that TBS may be useful for fracture risk assessment in subjects with factors that predispose them to bone loss. TBS has been shown to be associated with fractures in patients with diabetes, primary hyperparathyroidism, rheumatoid arthritis, adrenal incidentaloma, and chronic kidney disease and in individuals on long-term glucocorticoid therapy. Moreover, TBS is reduced in patients with ankylosing spondylitis and improves after the treatment of endocrinological conditions related to reduced bone mass, such as Cushing's disease, and primary hyperparathyroidism [17].

It has been reported that declines in BMD of alloHSCT recipients are greater at the femoral neck, a site rich in cortical bone, than in the lumbar spine, a site rich in trabecular bone. This observation suggests disproportionate cortical bone loss [7,18,19]. This pattern is unlike the predominant decline in spine BMD generally seen in postmenopausal and glucocorticoid-induced osteoporosis [20] and suggests a unique mechanism. Shortly thereafter, recovery begins, initially in the lumbar spine and then a much slower improvement at the femur takes place over a period ranging from months to years [21]. However, the structural bone deficits after alloHSCT have not been well characterized. A previous cross-sectional study showed that compared with reference participants, alloHSCT survivors had substantial deficits in trabecular volumetric bone mineral density (vBMD) and cortical geometry by peripheral quantitative CT (pQCT) [5]. However, information regarding the longitudinal microarchitectural change of bone structure occurring in the context of alloHSCT is limited [19]. In fact, little is known about the TBS changes after alloHSCT. Therefore, we conducted a study that included TBS as an additive marker for bone loss in alloHSCT patients. The aim of this study was to evaluate the changes in BMD and TBS in the patients who received alloHSCT with follow-up of two years.

2. Materials and methods

2.1. Patients

All patients 18 years and older who received alloHSCT between 2009 and 2015 at the Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, Seoul, Korea, were included in the study. Subjects were excluded if they had a history of disease known to affect bone health, including neuromuscular disease, inflammatory bowel disease, sickle cell anemia, active malignancy, or renal dysfunction (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2). In addition, patients who were treated with bisphosphonate or SERM (selective estrogen receptor modulator) were excluded. We retrospectively enrolled those who performed two consecutive bone densitometry examinations with the same DXA; total 80 eligible subjects were identified, and 66 enrolled. They were segregated into a first group (A, n = 24) that was evaluated at the time of alloHSCT and 12 months later and a second group (B, n = 44) that was evaluated at 12 and 24 months following alloHSCT. The institutional review board at the Catholic University of Korea approved this study (no. KC16RISI0832), and informed consent was obtained from all the subjects.

2.2. BMD assessment

The BMD of the lumbar spine, femoral neck, and total hip was measured in grams per square centimeter using DXA (Lunar Prodigy, GE Healthcare, Madison, WI, USA). The coefficient of variation used for precise assessment of the BMD measurements was 1.0% for the lumbar spine, 1.50% for the femoral neck, and 0.90% for the total hip. Given the broad range of ages, the results were expressed as the number of SDs from normal values of sex-, age-, and ethnicity-matched controls (z-score) in order not to overestimate age-associated BMD loss. A low BMD for age was defined as a z-score of −2 or lower at each site. The changes in BMD during 12 months were expressed as mean ± SD with percentage change in BMD.

2.3. TBS calculation

TBS was extracted from anteroposterior DXA images using TBS iNsight Software (Medimaps SA, France). A recent review reported that TBS precision, as the coefficient of variation, ranged from 1.12% to 2.1% [14]. TBS was determined for L1–L4: TBS ≥ 1.35, normal; 1.200–1.350, partially degraded; and < 1.200, degraded trabecular microarchitecture [14,16,22].

2.4. Transplantation procedure

The conditioning regimens consisted of cyclophosphamide (50 mg/kg/day to 60 mg/kg/day for 2 days, total of 100 mg/kg to 120 mg/kg) with fractionated TBI (total of 400–1320 cGy) followed by graft-versus-host disease (GVHD) prophylaxis with tacrolimus or cyclosporine and a short-term course of methotrexate (5 mg/m^2 i.v. bolus on days +1, +3, +6, and +11). Bone marrow stem cells or granulocyte colony–stimulating factor–mobilized peripheral blood stem cells were administered on day 0.

2.5. Other assessments

Weight and height were measured with the participants wearing light clothes at the time of the bone densitometry measurements. The body mass index (BMI) was calculated as body weight (kg) / height (m^2). The total dose of corticosteroid in equivalent of prednisolone received from the date of the first to the second DXA examination was assessed through a review of the medical record. It was summarized as cumulative milligrams (mg), milligrams per kilogram (mg/kg), and average milligrams per day (mg/day). The average steroid dose per day was calculated by dividing the total cumulative steroid dose by the numbers of days. The presence or absence of gonadal insufficiency in women was defined by medical chart review. All female subjects who suffered from gonadal failure were treated with sex hormone replacement therapy by endocrinologists or obstetricians in Seoul St. Mary's Hospital, Seoul, Korea. However, growth hormone was not routinely measured in adult patients. Blood samples were obtained on the day of the first DXA measurement. Fracture was confirmed with physician medical record documentation. Osteoporotic fracture was defined by fracture that results from mechanical forces that would not ordinarily result in a fracture according to National Institute for Health and Care Excellence clinical guidelines [23]. Infection was defined with body temperature at least 38 °C and microbiological or clinical documentation in the medical record [24].

Table 1
Characteristics of allogeneic hematopoietic stem cell transplantation (alloHSCT) recipients.

Characteristic	Total (n = 68)	Group A (n = 24)	Group B (n = 44)
Male (%)	40 (58.8)	13 (54.2)	27 (61.4)
Age at HSCT (years)	42 (18–68)	42 (18–64)	42 (18–68)
Height (cm)	165.5 ± 9.4	164.2 ± 8.2	166.2 ± 10.0
Weight (kg)	61.1 ± 12.4	65.4 ± 15.5	58.8 ± 9.9
Body mass index (kg/m^2)	22.26 ± 3.77	24.10 ± 4.53	21.25 ± 2.86
Initial diagnosis (%)			
Acute lymphoblastic leukemia	27 (39.7)	8 (33.3)	19 (43.2)
Acute myeloid leukemia	14 (20.6)	8 (33.3)	6 (1.36)
Severe aplastic anemia	7 (10.3)	3 (12.5)	4 (9.1)
Myelodysplastic syndrome	14 (20.6)	3 (12.5)	11 (25.0)
Non-Hodgkin lymphoma	5 (7.4)	1 (4.2)	4 (9.1)
Type of graft (%)			
Bone marrow	11 (16.2)	5 (20.8)	6 (13.6)
Peripheral blood	52 (76.5)	19 (79.2)	33 (75.0)
Bord blood	5 (7.4)	0 (0)	5 (11.4)
Total body irradiation (TBI) (%)			
Without TBI	25 (36.8)	16 (66.7)	27 (61.4)
Dosage (400–1320 cGy)	963.7 ± 346.1	977.5 ± 371.5	955.6 ± 329.9
Transplant-related complications			
Acute graft versus host disease	44 (64.7)	13 (54.2)	31 (70.5)
Chronic graft versus host disease	41 (60.3)	15 (62.5)	26 (59.1)
Gonadal failure	15 (53.6)	5 (45.5)	10 (58.8)
Osteoporotic fracture	3 (4.4)	3 (12.5)	0 (0)
Any infection	23 (33.8)	17 (70.8)	6 (13.6)
Microbiologically documented infection	4 (5.9)	2 (8.3)	2 (4.5)
Posttransplant steroid therapy (range)			
Steroid dose during the period (mg)	1621 (0–7246)	2416 (412–7246)	1206 (0–6590)
Steroid dose per body weight (mg/kg)	27 (0 − 123)	38 (7–123)	21 (0–119)
Steroid dose per day (mg/day)	15 (0–88)	33 (9–88)	5 (0–38)
Medication which affects bone (%)			
Calcium + vitamin D supplement	35 (51.5)	9 (37.5)	26 (59.1)
Serum biochemical assessment			
Creatinine (mg/dL)	0.81 ± 0.22	0.77 ± 0.22	0.84 ± 0.21
Albumin (g/dL)	4.07 ± 0.45	4.05 ± 0.37	4.08 ± 0.49
Calcium (mg/dL)	8.98 ± 0.47	8.98 ± 0.51	8.98 ± 0.45
Phosphate (mg/dL)	3.87 ± 0.71	4.00 ± 0.74	3.80 ± 0.70
25(OH) vitamin D (ng/mL)	17.90 ± 9.97	19.90 ± 7.71	17.36 ± 10.02

Qualitative data were expressed as count and percentages, and qualitative variables were expressed as the mean ± standard deviation (SD) or median and range. Steroid dose was expressed in prednisolone equivalents.

2.6. Statistical analysis

Statistical analysis was performed with SPSS version 23.0 (SPSS Inc.). Qualitative data were expressed as counts and percentages, and quantitative variables were expressed as the mean ± SD or median and range. A Wilcoxon signed rank test was used to compare changes in BMD or TBS after one year of follow-up. For the analysis of correlations, the Spearman's rank correlation coefficient was used to test the association between continuous variables. For categorical characteristics, statistical testing was conducted with the Mann–Whitney *U* test.

3. Results

3.1. Patients characteristics

Patient's characteristics are shown in Table 1. The median patient age at the transplant was 42. The mean body mass index was 22.26 ± 3.77 kg/m^2. The common diagnoses necessitating alloHSCT were acute lymphoid leukemia (ALL) (22 subjects; 39.7%), acute myeloid leukemia (AML) (14 subjects; 20.6%), and myeloid dysplastic syndrome (MDS) (14 subjects; 20.6%), respectively. The stem cell source for the alloHSCT was peripheral blood, bone marrow, and cord blood in 52 (76.5%), 11 (16.2%), and 5 (7.4%) subjects, respectively. TBI was used as part of the conditioning regimen in 63.2% of patients. Acute and chronic GVHD occurred in 44 (64.7%) and 40 (60.3%) patients, respectively. Fifteen (53.6%) women suffered from gonadal failure. Of 68 subjects, overall 5.9% (n = 4) had experienced a fracture during 12 months study period, all between the baseline and 12 months post-alloHSCT. There were 3 osteoporotic vertebral fractures and one non-osteoporotic fracture in toe arising from major trauma. A total of 23 (33.8%) patients developed infection during 12 months study period. An average dose of glucocorticoid exposure from time of the first DXA examination to the second examination was 15 mg prednisolone equivalent per day. 51.5% of patients received calcium and vitamin D. Mean serum concentration of 25-hydroxyvitamin D (25-(OH) vitamin D) was 17.9 ± 9.97 ng/mL.

3.2. Bone mineral density and trabecular bone score

Mean pretransplant z-score was normal before transplantation at all sites of measurement in group A. However, 15%, 17%, and 8% of patients had a low BMD for age (i.e., z-score ≤ −2SD) at the lumbar spine, femoral neck, and total hip, respectively. In group B, the mean z-score was normal at 12 months after transplantation. However, 25%, 23%, and 32% of patients had BMD below the expected range for age at the lumbar spine, femoral neck, and total hip, respectively. In addition, 29% and 34% of patients had a partially degraded lumbar spine TBS before alloHSCT in group A and at 12 months after alloHSCT in group B, respectively. However, no subject had TBS in the degraded range at the baseline examination (Table 2, Supplementary Table 1).

3.3. BMD and TBS changes

Twelve months post-alloHSCT, the average difference in BMD at the lumbar spine, femoral neck, and total hip was −0.039 ± 0.105 (−3.47%), −0.056 ± 0.057 (−5.48%), and − 0.072 ± 0.063

Table 2
Prevalence of low BMD for age and partially degraded TBS at the time of transplant in group A and one year after transplant in group B.

	Group A (n = 24)	Group B (n = 44)
Low BMD for age		
Lumbar spine 1–4	3 (15%)	11 (25%)
Femoral neck	4 (16.7%)	10 (22.7%)
Total hip	2 (8.3%)	14 (31.8%)
Partially degraded TBS		
Lumbar spine 1–4	7 (29.2%)	15 (34.1%)

The data are presented as numbers and percentages (%).
Low BMD for age: z-score ≤ −2.
Partially degraded TBS: 1.20 ≤ TBS < 1.35.

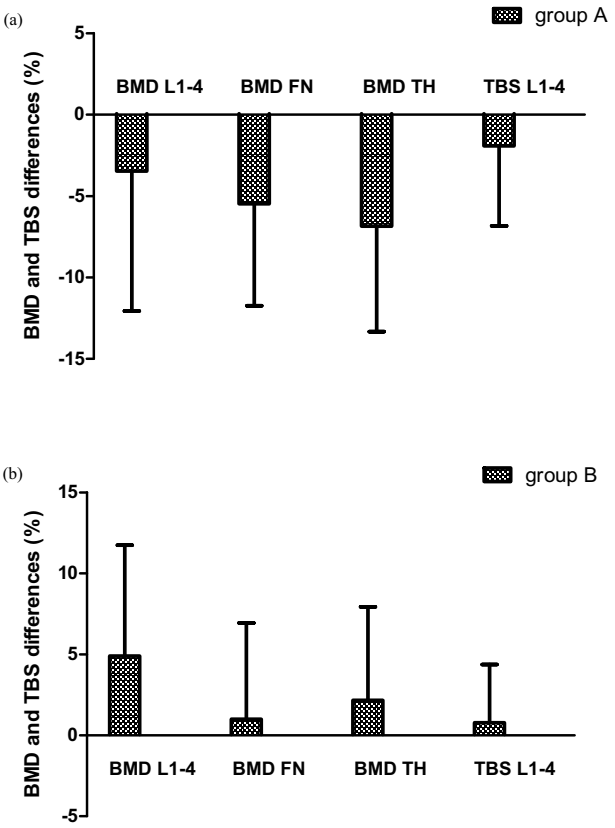

Fig. 1. The average annualized rate of change in BMD and TBS in group A (a) and B (b).
The rate of change in BMD was expressed as an annualized percentage of initial value, i.e., percentage change in BMD per year. The data are presented as the means ± standard deviations (SDs).
BMD: bone mineral density, TBS: trabecular bone score, L1–4: lumbar spine 1–4, FN: femoral neck, TH: total hip.

(−6.84%) from the baseline, respectively. In addition, the average difference in TBS was −0.028 ± 0.067 (−1.92%) per 12 months from the baseline (Fig. 1). Although BMD at the femoral neck and total hip declined from the baseline (all $p < 0.001$), the differences between lumbar spine BMD ($p = 0.076$) and TBS ($p = 0.086$) were not significant (Fig. 2). Between 12 and 24 months post-alloHSCT, the average difference in BMD at the lumbar spine, femoral neck, and total hip was 0.047 ± 0.064 (4.90%), 0.006 ± 0.048 (0.99%), and 0.017 ± 0.045 (2.16%), respectively. In addition, the average difference in TBS was 0.010 ± 0.049 (0.78%) between 12 and 24 months post-alloHSCT (Fig. 1). Although BMD at the lumbar spine ($p < 0.001$) and total hip ($p = 0.004$) was increased compared with the 12 months post-alloHSCT evaluation, the differing values of femoral neck BMD ($p = 0.250$) and

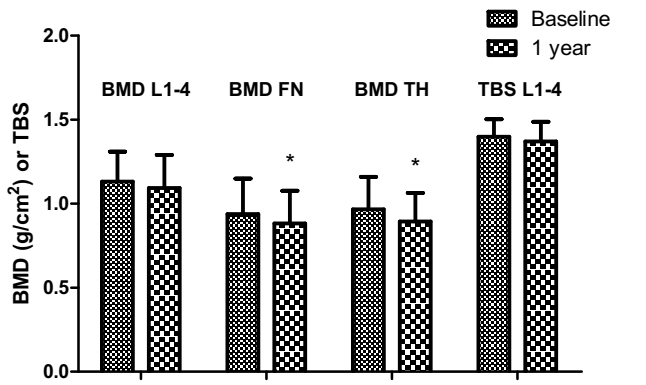

Fig. 2. BMD and TBS at the baseline and 1 year post-alloHSCT in group A.
*: statistically significantly different from the pre-alloHSCT evaluation.
BMD loss during the first year was significant at the femoral neck ($p < 0.001$) and the total hip ($p < 0.001$).
BMD: bone mineral density, TBS: trabecular bone score, L1–4: lumbar spine 1–4, FN: femoral neck, TH: total hip.

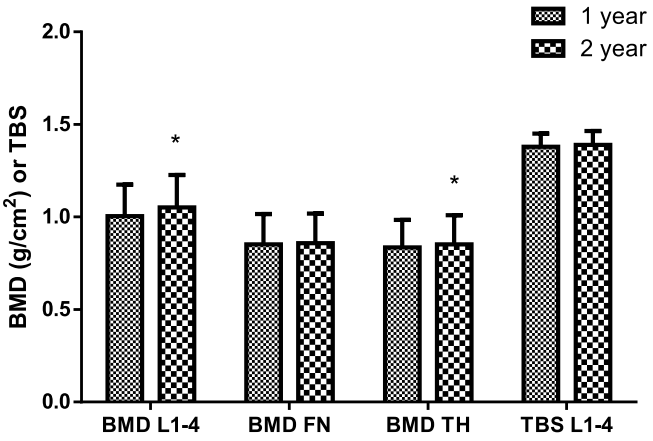

Fig. 3. BMD and TBS at the 1 year and 2 year post-alloHSCT in group B.
*: statistically significantly different from the 1 year post-alloHSCT evaluation.
BMD increase during the second year was significant at the lumbar spine ($p < 0.001$) and the total hip ($p = 0.004$).
BMD: bone mineral density, TBS: trabecular bone score, L1–4: lumbar spine 1–4, FN: femoral neck, TH: total hip.

TBS ($p = 0.149$) were not significant (Fig. 3). The number of subjects who showed BMD increase was larger than that of subjects who showed BMD decrease (Supplementary Fig. 1) in group B. In both groups, TBS change per 12 months was significantly associated with BMD change per 12 months at the lumbar spine (Spearman's rho = 0.399, $p = 0.001$), the femoral neck (Spearman's rho = 0.481, $p < 0.001$), and the total hip (Spearman's rho = 0.463, $p < 0.001$) (Supplementary Table 2).

3.4. Influence of corticosteroid and TBI on bone loss

The cumulative dose of glucocorticoid therapy between the first and the second bone assessments was associated with loss of BMD at all measured sites (all $p < 0.001$) and TBS (Spearman's rho = −0.368, $p = 0.002$). In addition, we could show a clear dose-effect relationship between BMD loss and the cumulative steroid dose per day ($p < 0.001$) or per body weight ($p < 0.001$) applied in both groups. Similarly, TBS degradation after the first bone examination and the cumulative steroid dose per day (Spearman's rho = −0.348, $p = 0.004$) or per body weight (Spearman's rho = −0.353, $p = 0.003$) has a negative dose-effect relationship. However, there was no association between age, height, weight, prevalence of GVHD, intakes of estrogen, calcium and

Table 3
Association between patient characteristics and TBS and BMD changes.

	Lumbar spine 1–4 BMD		Femoral neck BMD		Total hip BMD		Lumbar spine 1–4 TBS	
	Spearman's rho[a]	P^b	Spearman's rho[a]	P^b	Spearman's rho[a]	P^b	Spearman's rho[a]	P^b
Sex	–	0.640	–	0.410	–	0.367	–	0.737
Age at HSCT	−0.315	0.009	−0.137	0.268	−0.238	0.052	−0.081	0.513
Height	0.044	0.719	−0.099	0.427	−0.090	0.467	0.052	0.673
Weight	−0.030	0.808	−0.138	0.266	−0.150	0.226	−0.166	0.177
Initial diagnosis	–	0.631	–	0.746	–	0.753	–	0.555
Total body irradiation dose	0.032	0.798	−0.076	0.542	−0.076	0.540	−0.313	**0.009**
Posttransplant steroid therapy								
Steroid dose during the period	−0.484	**0.000**	−0.498	**0.000**	−0.535	**0.000**	−0.368	**0.002**
Steroid dose per body weight	−0.488	**0.000**	−0.495	**0.000**	−0.628	**0.000**	−0.353	**0.003**
Steroid dose per day	−0.536	**0.000**	−0.546	**0.000**	−0.355	**0.003**	−0.348	**0.004**
Treatment-related complications								
Acute GVHD	–	0.612	–	0.789	–	0.543	–	0.817
Chronic GVHD	–	0.422	–	0.263	–	0.227	–	0.149
Gonadal failure	–	0.195	–	0.864	–	0.136	–	0.829
Osteoporotic fracture	–	**0.035**	–	**0.031**	–	0.056	–	**0.008**
Any infection	–	**0.006**	–	**0.005**	–	**0.001**	–	**0.003**
Microbiologically documented infection	–	0.241	–	0.491	–	0.643	–	0.715
Medication which affects bone								
Estrogen	–	0.277	–	0.186	–	0.347	–	0.264
Calcium + vitamin D	–	0.637	–	**0.048**	–	0.145	–	0.552

Values in bold indicate statistically significant values.
Steroid dose was expressed in prednisolone equivalents.
HSCT = hematopoietic stem cell transplantation.
GVHD = graft versus host disease.
[a] Computed only for covariates that take on continuous values.
[b] Univariate associations between continuous covariates and BMD or TBS change were assessed using Spearman's rank correlation coefficient. For categorical characteristics, statistical testing was conducted with the Mann–Whitney *U* test.

vitamin D and BMD or TBS change. The dose of TBI was negatively associated only with TBS (Spearman's rho = −0.313, $p = 0.009$) (Table 3).

3.5. Treatment related complications and bone loss

The incidence of vertebral osteoporotic fracture was associated with loss of spine BMD, femoral neck BMD, and TBS ($p = 0.035$, 0.031, and 0.008, respectively). In addition, the incidence of infection was associated with loss of BMD at the spine, femoral neck, and total hip ($p = 0.006$, 0.005, and 0.001, respectively) and TBS ($p = 0.003$). However, GVHD or gonadal failure was not statistically associated with TBS or BMD change value (Table 3).

4. Discussion

In this study, we evaluated BMD and TBS changes for a twelve-month period from the time of alloHSCT and from one year later in group A and B, respectively. In group A, BMD of the femoral neck and total hip evaluated at the time of 12 months posttransplant declined from the baseline. In group B, BMD of the lumbar spine and total hip increased between 12 and 24 months post-alloHSCT. In both groups, TBS change was significantly associated with BMD changes at all measured sites. The incidence of fracture, cumulative dose of glucocorticoid therapy, and the dose of TBI were negatively associated with TBS.

In the present study, mean pretransplant z-score was normal before transplantation at all sites of measurement. The majority of the patients showed normal BMD at the spine (85%), femoral neck (83%), and total hip (92%) at the time of transplantation. This result was consistent with earlier studies, which showed that mean BMD was within normal limits before transplantation [7,19]. In addition, no subject had TBS in the degraded range. However, 29% of patients had a partially degraded TBS before alloHSCT.

In this study, subjects in group A experienced a decrease in femoral neck and total hip BMD between the time of alloHSCT and 12 months post-alloHSCT. In contrast, spine BMD decline was not significant. The spine site is predominantly a measure of trabecular bone (66%), while the neck of femur site is predominantly a measure of cortical bone (75%). Trabecular bone is the most metabolically active part of the skeleton, with a high rate of turnover and a blood supply that is much greater than that of cortical bone [25]. Therefore, the bone loss of postmenopausal and glucocorticoid-induced osteoporosis showed a predominant decline in BMD of the trabecular site [20,26]. However, bone loss in alloHSCT recipients in our study shows a unique pattern and is consistent with previous studies. In previous studies, the average annualized bone loss was higher at the femoral neck than at the spine during the two years posttransplantation [4,27]. In particular, our study is consistent with previous studies that showed decrease in proximal femoral BMD despite insignificant change in spine BMD one year posttransplantation. However, other studies that examined BMD at 6 months after alloHSCT showed decrease in lumbar spine BMD [6,7,19]. We assumed that lumbar spine BMD might quickly decline and then start to recover before the following DXA examination at 12 months post-alloHCT. Therefore, we could not demonstrate a significant loss in lumbar spine BMD in group A.

In this study, subjects in group B experienced an increase in lumbar spine and total hip BMD between 12 and 24 months post-alloHSCT. Bone recovery at the spine and total hip, the regions with higher amounts of trabecular bone and higher metabolic activities, was more pronounced, while bone loss at the femoral neck occurred. This observation is consistent with a previous study that showed more significant bone loss at the femoral neck compared to at the spine during the second year of transplantation [7].

Twelve months after alloHSCT, the value of TBS was not significantly reduced, although the value of hip BMD was lower compared to the baseline. Because TBS provides an indirect index of the trabecular microarchitecture [14], disproportionate cortical bone loss is consistently shown not only in the context of macroarchitecture but also in the context of microarchitecture. A potential explanation might be

related to the avascular necrosis (AVN) of the hip. Restriction of vascular profusion at the proximal femur could cause disproportionate cortical bone loss. Further study evaluating the association of microarchitecture at the proximal femur and the incidence of AVN is required.

We could demonstrate several factors were associated with bone loss in alloHSCT recipients. The cumulative dose of glucocorticoid therapy associated with a decrease in BMD at all measured sites. It is postulated that the most important risk factor for osteoporotic fractures might be the long-term use of corticosteroids in association with acute or chronic GVHD in alloHSCT survivors [1]. The greatest effects of glucocorticoids are on bone metabolism, with the result being reduced bone quantity and quality. Reduced bone formation and increased bone resorption results from glucocorticoid-induced inhibition of osteoblasts and increase of osteoclast lifespan [28–30]. It is recognized that glucocorticoids concurrently upregulate RANKL and that they suppress OPG in the osteoblastic cells in vitro [31]. In fact, during the early post-HSCT period, the steroid dose was associated with the RANKL levels and the RANKL/OPG ratio [9].

In addition, the cumulative dose of glucocorticoid therapy associated with a decrease in TBS. This is consistent with a previous study which showed that TBS was reduced in 484 women aged 55–79 years on systemic glucocorticoid treatment compared with healthy controls, even when BMD was similar between the groups [32]. In fact, it is well known that the increase in fracture risk associated with glucocorticoids occurs before BMD loss, which can be measured by DXA [33]. This observation could be related to glucocorticoid-induced changes in bone microarchitecture. In addition, glucocorticoids result in preferential trabecular bone loss with reductions in bone volume fraction, trabecular thickness, and connectivity [20]. Prior studies have demonstrated that the degree of trabecular network disruption correlates with cumulative exposure to oral glucocorticoids [34].

In this study, the dose of TBI was negatively associated with TBS: the lower TBS was associated with a higher dose of TBI exposure. It is well established that TBI exposure is associated with deteriorated bone microarchitecture. In one study, alloHSCT survivors treated with TBI exhibit the markedly increased marrow adiposity, abnormal bone microarchitecture, and abnormal fat distribution [35]. In another study, substantial deficits in trabecular vBMD and cortical geometry by pQCT were more pronounced in survivors with a history of TBI exposure [5]. These deteriorations in bone microarchitecture result from an imbalance of hormone axes. TBI exposure leads to abnormality of the growth hormone/insulin-like growth factor 1 (IGF-1) axis, a major determinant of bone mass [36] in alloHSCT survivors [37]. In addition, TBI exposure leads to gonadal failure in alloHSCT recipients [38]. The bone-sparing effect of estrogen is mainly related to its ability to block bone by decreasing osteoclastogenesis and diminishing resorptive activity of mature osteoclasts [39]. Therefore, a higher dose of TBI-related growth hormone deficiency and hypogonadism may contribute to lower value of TBS in our study. However, in the present study, gonadal failure was not statistically associated with TBS or BMD value. Because our subjects with a diagnosis of gonadal failure were on appropriate hormone replacement at the time of follow-up DXA examination, hormone replacement therapy might inhibit bone loss [40].

In this study, incident osteoporotic vertebral fracture during the 12 months study period was associated with decrease of BMD and TBS. This observation is consistent with previous studies that showed TBS as a risk factor of fracture [15,17]. However, further study evaluating the association of BMD or TBS change and fracture incidence is required because of insufficient our study period.

In the present study, the incidence of infection is associated with decrease of BMD and TBS. In contrast, a previous study showed higher TBS correlated with a faster drop of the leukocyte count, and higher T-score correlated with a higher risk of infection [41]. Because our recipients experienced profound neutropenia following myeloablative conditioning alloHSCT, bone health could not be associated with drop in the leukocyte count. In addition, glucocorticoids are known to increase the risk of infection by impairing phagocyte function and suppress cell-mediated immunity [42]. Furthermore, the cumulative dose of glucocorticoids was associated with a decrease in BMD and TBS in this study. Therefore, decrease of BMD or TBS correlated with an increased risk of infection, contrast to the previous study [41].

To our knowledge, this is the first original study to assess TBS in adult patients who received alloHSCT. We delineated the longitudinal microarchitectural change of bone structure occurring in the context of alloHSCT. Although this study provided important results, it has some limitations. The first limitation is the retrospective cohort design; therefore, treatment modality including conditioning regimen was heterogeneous. The second limitation is that there are two groups with distinct time point of evaluation after transplantation because of the insufficient (12 months) study period. An additional limitation is the relatively small number of patients and the heterogeneity of the sample in relation to the underlying diagnosis. Finally, the lack of bone marker measurements made it impossible to assess bone remodeling rate or mineralization. Nonetheless, this study establishes the need for further studies of bone microarchitectural deficits in alloHSCT recipients.

4.1. Conclusions

In summary, this study delineated the insignificant loss and recovery of TBS in the two years following alloHSCT. Therefore, we consistently showed a disproportionate cortical bone loss in the context of microarchitecture. In addition, TBS change was positively associated with BMD change and negatively associated with the cumulative dose of glucocorticoid and dose of TBI. Therefore, further longitudinal studies with TBS conducted beyond two years post-alloHSCT are required. The accurate characterization of fracture and identification of risk factors in alloHSCT survivors are also required.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.04.004.

References

[1] A.H. Hautmann, et al., Metabolic bone diseases in patients after allogeneic hematopoietic stem cell transplantation: report from the Consensus Conference on Clinical Practice in chronic graft-versus-host disease, Transpl. Int. 24 (9) (2011) 867–879.
[2] B.N. Savani, et al., Increased risk of bone loss without fracture risk in long-term survivors after allogeneic stem cell transplantation, Biol. Blood Marrow Transplant 13 (5) (2007) 517–520.
[3] M. Le Meignen, et al., Bone mineral density in adult survivors of childhood acute leukemia: impact of hematopoietic stem cell transplantation and other treatment modalities, Blood 118 (6) (2011) 1481–1489.
[4] J.M. Stern, et al., Bone density loss after allogeneic hematopoietic stem cell transplantation: a prospective study, Biol. Blood Marrow Transplant 7 (5) (2001) 257–264.
[5] S. Mostoufi-Moab, et al., Bone density and structure in long-term survivors of pediatric allogeneic hematopoietic stem cell transplantation, J. Bone Miner. Res. 27 (4) (2012) 760–769.
[6] D.J. Campos, et al., Bone mineral density, vitamin D, and nutritional status of children submitted to hematopoietic stem cell transplantation, Nutrition 30 (6) (2014) 654–659.
[7] C. Schulte, et al., Bone loss in long-term survivors after transplantation of hematopoietic stem cells: a prospective study, Osteoporos. Int. 11 (4) (2000) 344–353.
[8] M.I. Kang, et al., The short-term changes of bone mineral metabolism following bone marrow transplantation, Bone 26 (3) (2000) 275–279.
[9] K.H. Baek, et al., Changes in the serum sex steroids, IL-7 and RANKL-OPG system after bone marrow transplantation: influences on bone and mineral metabolism,

Bone 39 (6) (2006) 1352–1360.
[10] J.A. Kanis, et al., European guidance for the diagnosis and management of osteoporosis in postmenopausal women, Osteoporos. Int. 24 (1) (2013) 23–57.
[11] N.C. Harvey, et al., Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice, Bone 78 (2015) 216–224.
[12] B.C. Silva, et al., Fracture risk prediction by non-BMD DXA measures: the 2015 ISCD official positions part 2: trabecular bone score, J. Clin. Densitom. 18 (3) (2015) 309–330.
[13] D. Hans, et al., Correlations between trabecular bone score, measured using anteroposterior dual-energy X-ray absorptiometry acquisition, and 3-dimensional parameters of bone microarchitecture: an experimental study on human cadaver vertebrae, J. Clin. Densitom. 14 (3) (2011) 302–312.
[14] B.C. Silva, et al., Trabecular bone score: a noninvasive analytical method based upon the DXA image, J. Bone Miner. Res. 29 (3) (2014) 518–530.
[15] D. Hans, E. Stenova, O. Lamy, The trabecular bone score (TBS) complements DXA and the FRAX as a fracture risk assessment tool in routine clinical practice, Curr. Osteoporos. Rep. 15 (6) (2017) 521–531.
[16] N. Binkley, W.D. Leslie, Clinical application of spine trabecular bone score (TBS), Clin. Rev. Bone Miner. Metab. 14 (1) (2016) 14–25.
[17] F.M. Ulivieri, et al., Utility of the trabecular bone score (TBS) in secondary osteoporosis, Endocrine 47 (2) (2014) 435–448.
[18] W.Y. Lee, et al., The effect of bone marrow transplantation on the osteoblastic differentiation of human bone marrow stromal cells, J. Clin. Endocrinol. Metab. 87 (1) (2002) 329–335.
[19] C.M. Schulte, D.W. Beelen, Bone loss following hematopoietic stem cell transplantation: a long-term follow-up, Blood 103 (10) (2004) 3635–3643.
[20] L. Dalle Carbonare, et al., Comparison of trabecular bone microarchitecture and remodeling in glucocorticoid-induced and postmenopausal osteoporosis, J. Bone Miner. Res. 16 (1) (2001) 97–103.
[21] B.L. McClune, N.S. Majhail, Osteoporosis after stem cell transplantation, Curr. Osteoporos. Rep. 11 (4) (2013) 305–310.
[22] J.T. Schousboe, et al., Association of trabecular bone score (TBS) with incident clinical and radiographic vertebral fractures adjusted for lumbar spine BMD in older men: a prospective cohort study, J. Bone Miner. Res. 32 (7) (2017) 1554–1558.
[23] National Clinical Guideline, C, National Institute for Health and Clinical Excellence, Guidance, in Osteoporosis: Fragility Fracture Risk: Osteoporosis: Assessing the Risk of Fragility Fracture, Royal College of Physicians (UK) National Clinical Guideline Centre, London, 2012.
[24] E.A. Engels, et al., Early infection in bone marrow transplantation: quantitative study of clinical factors that affect risk, Clin. Infect. Dis. 28 (2) (1999) 256–266.
[25] Woolf, et al., What is osteoporosis? Osteoporosis: An Atlas of Investigation and Management, 2008, p. 5.
[26] A.D. Woolf, K. Åkesson, Epidemiology, risk, and risk factors, Osteoporosis: An Atlas of Investigation and Management, Clinical publishing, Oxford, 2008.
[27] N. Buchs, et al., Allogeneic bone marrow transplantation is associated with a preferential femoral neck bone loss, Osteoporos. Int. 12 (10) (2001) 880–886.
[28] L.C. Hofbauer, C. Hamann, P.R. Ebeling, Approach to the patient with secondary osteoporosis, Eur. J. Endocrinol. 162 (6) (2010) 1009–1020.
[29] R.S. Weinstein, Clinical practice. Glucocorticoid-induced bone disease, N. Engl. J. Med. 365 (1) (2011) 62–70.
[30] C.A. O'Brien, et al., Glucocorticoids act directly on osteoblasts and osteocytes to induce their apoptosis and reduce bone formation and strength, Endocrinology 145 (4) (2004) 1835–1841.
[31] L.C. Hofbauer, et al., Stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin production by glucocorticoids in human osteoblastic lineage cells: potential paracrine mechanisms of glucocorticoid-induced osteoporosis, Endocrinology 140 (10) (1999) 4382–4389.
[32] M.A. Paggiosi, N.F. Peel, R. Eastell, The impact of glucocorticoid therapy on trabecular bone score in older women, Osteoporos. Int. 26 (6) (2015) 1773–1780.
[33] J.A. Kanis, et al., A meta-analysis of prior corticosteroid use and fracture risk, J. Bone Miner. Res. 19 (6) (2004) 893–899.
[34] R.I. Gafni, et al., Recovery from osteoporosis through skeletal growth: early bone mass acquisition has little effect on adult bone density, FASEB J. 16 (7) (2002) 736–738.
[35] S. Mostoufi-Moab, et al., Adverse fat depots and marrow adiposity are associated with skeletal deficits and insulin resistance in long-term survivors of pediatric hematopoietic stem cell transplantation, J. Bone Miner. Res. 30 (9) (2015) 1657–1666.
[36] A. Giustina, G. Mazziotti, E. Canalis, Growth hormone, insulin-like growth factors, and the skeleton, Endocr. Rev. 29 (5) (2008) 535–559.
[37] S.M. Shalet, B.M. Brennan, Growth and growth hormone status after a bone marrow transplant, Horm. Res. 58 (Suppl. 1) (2002) 86–90.
[38] A.C. Couto-Silva, et al., Factors affecting gonadal function after bone marrow transplantation during childhood, Bone Marrow Transplant. 28 (1) (2001) 67–75.
[39] J.P. Bilezikian, L.G. Raisz, T.J. Martin, Mechanisms of estrogen action in bone, Principles of Bone Biology, 2008.
[40] J.A. Cauley, et al., Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial, Jama 290 (13) (2003) 1729–1738.
[41] F. Schyrr, et al., Correlation study between osteoporosis and hematopoiesis in the context of adjuvant chemotherapy for breast cancer, Ann. Hematol. 97 (2) (2018) 309–317.
[42] M. Cutolo, et al., Use of glucocorticoids and risk of infections, Autoimmun. Rev. 8 (2) (2008) 153–155.