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Do Bone Density, Bone Microarchitecture, and Body Composition Differ in Recipients of Allogeneic Hematopoietic Stem Cell Transplant? A Cross-Sectional Study from Southern India

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A B S T R A C T

The significant advancements made in the field of allogeneic hematopoietic stem cell transplantation (allo-HSCT) have ensured increased longevity in transplant recipients. However, they do have late effects that may adversely affect the endocrine system, bone health, and body composition. This study was undertaken to evaluate bone mineral density (BMD), trabecular bone score, and body composition in recipients of allo-HSCT and compare them with age, sex, and body mass index (BMI) matched controls. This was a cross-sectional study done in 63 cases and 65 matched controls. The mean femoral neck BMD was found to be lower in cases than in controls (0.777 [0.119] versus 0.846 [0.122] g/cm^2, P = .002). Among cases, the mean BMD at the neck of femur was lower in patients who had received myeloablative conditioning compared with those who had received the nonmyeloablative regimen (0.731 [0.090] versus 0.802 [0.126] g/cm^2, P = .014]. The mean (SD) bone density at the lumbar spine was significantly lower in the group that had received total body irradiation compared with the group that did not (0.930 [0.111] versus 0.993 [0.127], P = .044). Trabecular bone score did not differ between cases and controls (1.383 [0.877] versus 1.389 [0.750], P = .670). The lean mass was significantly lower (15.9 [2.4] versus 18.6 [4.8] kg/m^2, P < .001) and the prevalence of sarcopenia (42% versus 11%, P < .001) significantly higher in cases than in controls. Normal-weight obesity was also noted to be higher among those with sarcopenia than in those without (12/26 versus 5/36; P = .009). The procedure of allo-HSCT may thus cause an impairment of bone health and alterations in body composition well after the cure of the primary disease.

INTRODUCTION

The evolution of allogeneic hematopoietic stem cell transplant (allo-HSCT) as a treatment modality has witnessed the cure of several hematologic conditions such as leukemia, lymphoma, multiple myeloma, myelodysplastic syndromes, thalassemia, and aplastic anemia [1]. The many advances made in this domain and the availability of excellent post-transplant care have ensured increased longevity in recipients of allo-HSCT. It has been demonstrated in previous studies that patients who are disease free at 5 years after HSCT have a 10-year survival rate that exceeds 80% [2].

However, the cure of the primary hematologic disease is not necessarily accompanied by a full restoration of health. HSCT survivors do have "delayed effects" that may adversely affect morbidity, working capacity, and health-related quality of life. Previous studies have also shown their mortality rates to be significantly higher than the general population [2].

In long-term survivors, besides endocrine dysfunction and an adverse cardiovascular and metabolic profile [3], the HSCT procedure appears to have an adverse impact on bone mineralization and bone microarchitecture, which is comparable to almost 15 years of physiological aging [4]. Previous studies have demonstrated an initial phase of bone loss followed by a more gradual recovery over the next 10 to 15 years [5].

Yet, very little is known with regard to the behavior of bone turnover markers like the C-terminal telopeptide (CTX) and the *N*-terminal propeptide of type 1 procollagen (P1NP) in the context of HSCT. Moreover, there has not been any study from India that has assessed the trabecular bone score (TBS) in recipients of allogeneic transplant in comparison to that of healthy controls. Also, there is a paucity of literature with regard to changes in body composition post-HSCT, and thus far, there has not been any reported study from India that has sought to assess body composition in patients following the transplantation procedure.

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Therefore, this study was undertaken to assess bone mineral density (BMD), bone microarchitecture using TBS, bone mineral parameters, and bone turnover markers in recipients of allo-HSCT and to compare them with age, sex and body mass index (BMI) matched controls. This study also assessed the body composition of allo-HSCT recipients in comparison to controls.

METHOD

This was a cross-sectional study conducted between February 1, 2017, and November 30, 2018, wherein study patients included recipients of allogeneic transplant, aged 18 to 45 years, who were recruited from the hematology transplant outpatient department at least 9 months after and not later than 6 years of transplant. At recruitment, they had been off immunosuppressants for at least 6 months. The age, sex, and BMI matched control group was recruited from the local community. Pregnant individuals and those who were outside the defined age limits, were recipients of autologous transplant, had thalassemia major, or had recurrence of the disease were excluded from the study. Ethical clearance was obtained from the Institutional Review Board.

Sample Size Calculation

From a previous study that assessed the proportion of low bone mass in allogeneic stem cell transplant recipients compared with matched controls, the difference in proportion of low bone mass in both groups was 0.06 [6]. Using this difference, with a desired confidence level of 95% and a power of 80%, the required sample size was calculated to be 52 in each group.

Assessment of BMD, TBS, Body Composition, and Parameters of Bone Mineral Metabolism

BMD, TBS, and body composition were assessed by a dual-energy x-ray absorptiometry (DXA) scan. The DXA scanner used in this study was a Hologic (Hologic, Inc., Waltham, Massachusetts) DXA machine Discovery A-QDR 4500 series. The coefficient of variation for measurement of BMD at the lumbar spine and femoral neck was 1% to 2% and 2% to 3%,% respectively. TBS is a textural index that evaluates pixel gray-level variations in the lumbar spine DXA image, providing an indirect index of trabecular microarchitecture [7]. TBS (L1 to L4) measurements were performed using TBS iNsight Software version 3 (Med-Imaps, Bordeaux, France). Currently, certain cutoff points proposed by the manufacturers have been used to define normalcy in TBS [8].

Among the bone biochemical parameters, colorimetric methods were used for calcium, and phosphorus was estimated by the phosphomolybdate method. Parathormone (PTH) was measured by chemiluminescent immunoassay, 25 hydroxy vitamin D was analyzed using an electro-chemiluminescent assay, and alkaline phosphatase was measured by the kinetic paranitrophenyl phosphate method. CTX and P1NP were measured using electro-chemiluminescent assay. Serum creatinine was measured using the modified Jaffe method.

Low bone mass for chronological age was defined as a zscore (at lumbar spine, femoral neck, or forearm) that was ≤ -2.0 [9]. Vitamin D deficiency was defined as a level of serum 25 (OH) vitamin D <20 ng/mL [10]. A TBS of ≥ 1.350 was considered normal, TBS between 1.200 and 1.350 was considered partially degraded bone, and a TBS value ≤ 1.200 was considered indicative of degraded bone [8]. Sarcopenia was defined as an appendicular skeletal muscle mass divided by height squared of less than 7.45 kg/m^2 in males and less than 5.23 kg/m^2 in females [11]. Body fat percentage was considered high when total body fat percentage was >30% in females and >20% in males [12]. Normal-weight obesity (NWO) was defined as the presence of high total body fat percentage (>30% in females and >20% in males) in patients with normal BMI (<23 kg/m^2) [12].

Statistical Methods

Data were entered into an electronic database and analyzed using SPSS (version 21; SPSS, Inc, Chicago, IL). Continuous variables were expressed as mean (SD) and categorical variables as frequencies and percentages. Comparison of means of continuous and categorical variables was done using the Student *t*test and chi-square test, respectively. Correlation was expressed using the Pearson or Spearman coefficient as appropriate. Statistical significance was defined by a *P* value that was <.05.

RESULTS

A total of 63 patients, who had undergone allo-HSCT for various hematologic indications, were recruited on fulfilling the eligibility criteria and after having obtained written informed consent. A flowchart showing the recruitment of patients and the variables studied is depicted in Figure 1. The mean (SD) age of the study cohort was 31.3 (7.9) years and

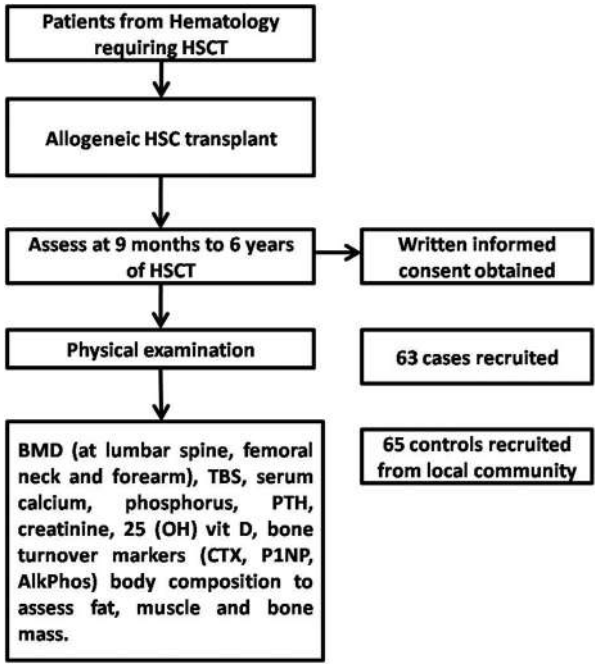

Figure 1. Flowchart showing patient recruitment and variables studied.

consisted of 43 (68.3%) males and 20 (31.7%) females. The duration since transplant ranged from 9 to 64 months, with a mean (SD) of 27.7 (16.6) months.

The baseline demographic characteristics, with primary diagnoses, type of conditioning regimen, use of total body irradiation, and occurrence of graft-versus-host disease (GVHD), is as shown in Table 1. GVHD prophylaxis was given to all patients and used cyclosporine, methotrexate, tacrolimus, or cyclophosphamide. Among the cases, 2 patients who had undergone allo-HSCT for severe aplastic anemia developed avascular necrosis of the femoral head bilaterally (3.2%). One of them underwent total hip replacement for the same.

It was observed that the mean (SD) 25 (OH) vitamin D was lower in cases as compared with controls (21.6 [10.3] versus 26.6 [8.9] ng/mL, $P = .002$), and the proportion of vitamin D deficiency in cases was significantly higher than in the control group (32/62 [52%] versus 17/65 [26%], $P = .004$). Serum calcium was not significantly different between both groups. The mean (SD) PTH level was higher in recipients of allo-HSCT as compared with age and sex matched control patients (64.7 [33.8] versus 43.7 [15.1] pg/mL, $P < .001$).

The mean (SD) serum alkaline phosphatase and P1NP were significantly higher in cases as compared with controls (alkaline phosphatase: 83.6 [34.6] versus 71.9 [18.7] U/L, $P = .002$; P1NP: 78.5 [57.1] versus 56.2 [25.2] ng/mL, $P = .024$). The mean CTX trended higher in post-transplant patients than in controls (562.1 versus 455.7 pg/mL, $P = .086$).

The BMD at the femoral neck, lumbar spine, and forearm; TBS; bone mineral parameters; and bone turnover markers of cases (n = 63) and controls (n = 65) are shown in Table 2. The mean BMD at the femoral neck in post-allo-HSCT patients was significantly lower than in age and sex matched control patients (0.777 [0.119] versus 0.846 [0.122] g/cm^2, $P = .002$). Among cases, on subgroup analysis, the mean femoral BMD was significantly lower in the group that had received myeloablative conditioning as compared with the nonmyeloablative conditioning group (0.731 [0.090] versus 0.802 [0.126] g/cm^2, $P = .014$). The proportion of patients with low bone mass at the

Table 1
Baseline Characteristics of the Transplant Recipients

Variable	No.	Percentage
Sex		
Male	43	68.3
Female	20	31.7
Primary diagnosis		
Malignant	39	61.9
AML	22	34.9
ALL	9	14.3
Hodgkin lymphoma	1	1.6
MDS	4	6.3
CML	3	4.8
Nonmalignant	24	38.1
Severe aplastic anemia	23	36.5
PNH	1	1.6
Conditioning regimen		
Myeloablative	21	33.3
Nonmyeloablative	30	47.6
Reduced intensity	12	19.1
TBI	26	41.3
GVHD	25	40.0
Acute	6	9.5
Grade 2	5	7.9
Grade 3	2	3.2
Grade 4	2	3.2
Chronic	16	25.4
Limited	13	20.6
Extensive	6	9.5
Acute and chronic	3	4.8

AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; PNH, paroxysmal nocturnal hemoglobinuria; TBI, total body irradiation.

Table 2
Comparison of Bone Mineral Parameters and Bone Mineral Density and Trabecular Bone Score in Cases and Controls

Parameter	Cases (n = 63), Mean (SD)	Controls (n = 65), Mean (SD)	*P* Value
Calcium (mg/dL)	8.9 (0.4)	9.0 (0.5)	.217
Phosphorus (mg/dL)	3.4 (0.7)	3.7 (0.4)	.007
25(OH) vitamin D (ng/mL)	21.6 (10.3)	26.6 (8.9)	.002
Creatinine (mg/dL)	0.6 (0.2)	0.6 (0.2)	.963
PTH (pg/mL)	64.7 (33.8)	43.7 (15.1)	<.001
P1NP (ng/mL)	78.5 (57.1)	56.2 (25.2)	.024
CTX (pg/mL)	562.1 (422.2)	455.6 (209.4)	.086
Alkaline phosphatase (U/L)	83.6 (34.6)	71.9 (18.7)	.002
Femoral neck BMD (g/cm^2)	0.777 (0.119)	0.846 (0.123)	.002
Lumbar spine BMD (g/cm^2)	0.967 (0.124)	0.990 (0.120)	.283
Distal forearm BMD (g/cm^2)	0.745 (0.069)	0.721 (0.106)	.134
Trabecular bone score	1.383 (0.877)	1.389 (0.750)	.670

femoral neck trended higher in post-transplant patients as compared with controls (7/63 [11%] versus 1/65 [2%], $P = .055$). Among cases, the proportion of low bone mass at the femoral neck was higher in the group aged less than 30 years than in those over 30 years of age (86% versus 14%, $P = .05$). The mean BMD at the lumbar spine was not significantly different between cases and controls. The mean (SD) BMD (g/cm^2) at the lumbar spine was significantly lower in the group that had received total body irradiation as compared with the group that did not (0.930 [0.111] versus 0.993 [0.127], $P = .044$). The proportion of patients with low bone mass at the lumbar spine was not significantly different between the case (11/63) and control (8/65) groups (18% versus 12%, $P = .465$).

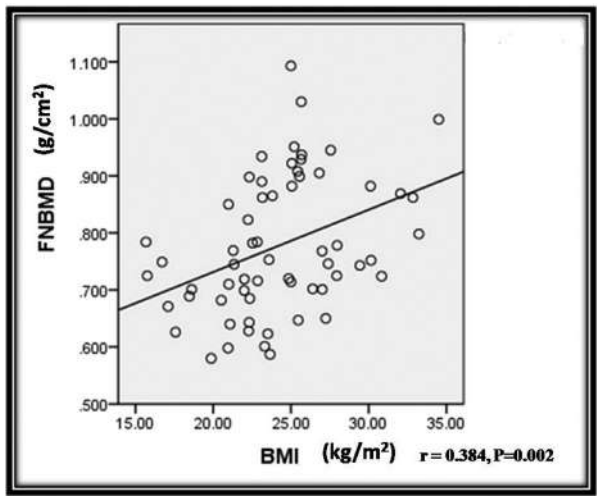

Figure 2. Correlation between BMD at the femoral neck and BMI.

Among post-HSCT recipients, there was a significant positive correlation between BMD at the femoral neck and BMI ($r = 0.384$, $P = .002$) and an inverse correlation with CTX ($r = -0.254$, $P = .050$) and P1NP ($r = -0.318$ $P = .046$) (Figures 2 and 3). The BMD at the lumbar spine in cases had a significant negative correlation with CTX ($r = -0.277$ $P = .032$) (Figure 4). The BMD at the lumbar spine also showed a positive correlation with duration since transplant ($r = 0.246$, $P = .05$), although not statistically significant. Among cases, the BMD at both the femoral neck and lumbar spine had a significant positive correlation with lean mass ($r = 0.447$, $P < .001$ for femoral neck and $r = 0.335$, $P = .008$ for lumbar spine) (Figures 5 and 6).

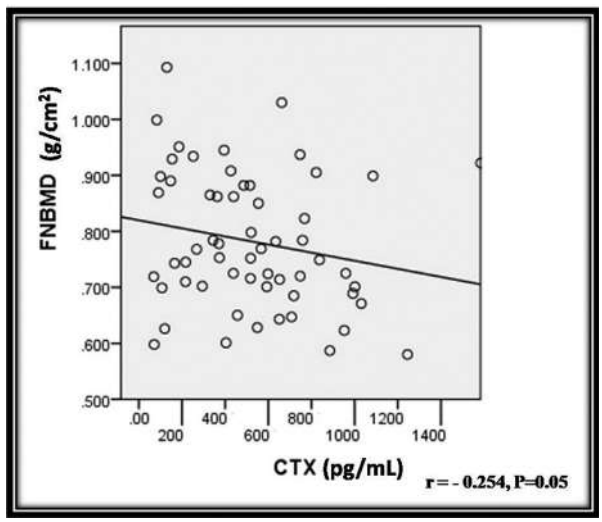

Figure 3. Correlation between BMD FN - femoral neck and CTX.

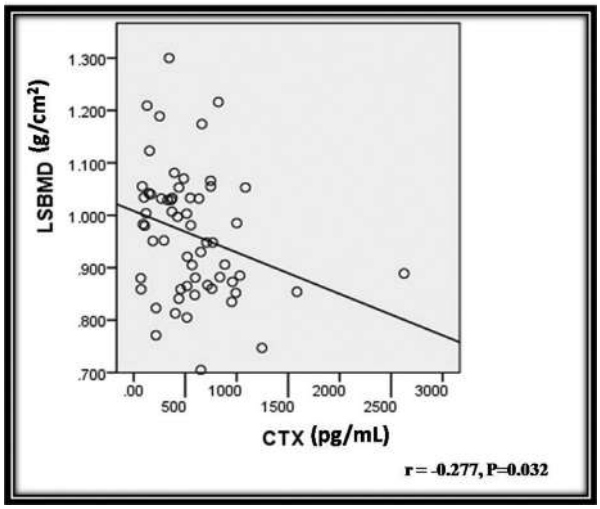

Figure 4. Correlation between BMD LS - lumbar spine and CTX.

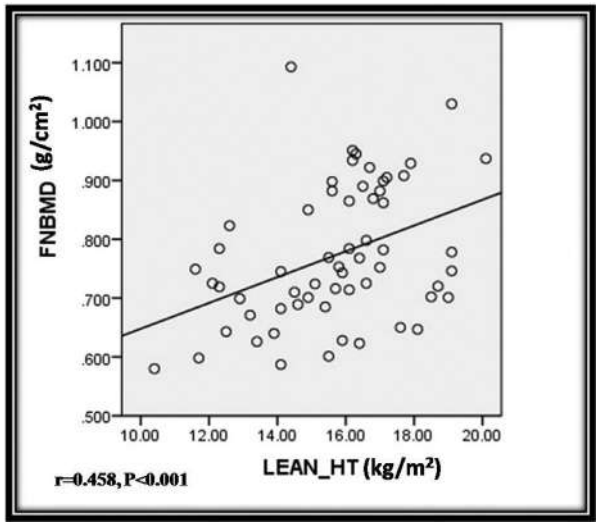

Figure 5. Correlation between BMD (FN) and lean mass.

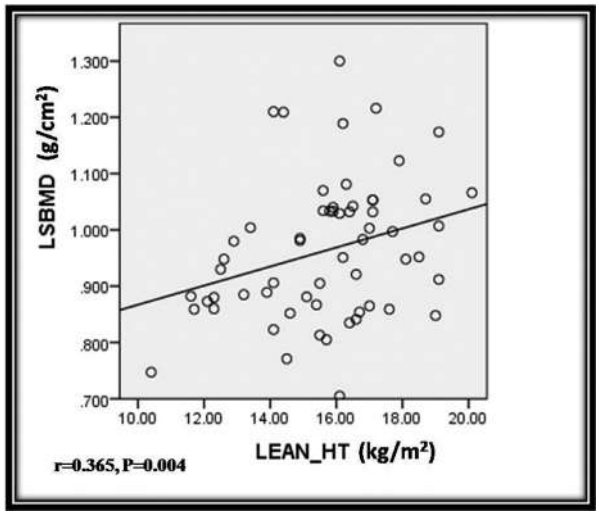

Figure 6. Correlation between BMD (LS) and lean mass.

On performing a univariate logistic regression analysis, it was observed that the use of myeloablative conditioning, BMI <23 kg/m^2, serum vitamin D <20 ng/mL, serum PTH >50 pg/mL, the presence of hypogonadism, and the presence of malignant disease were not significant in predicting low bone mass at the femoral neck or lumbar spine (P = *ns*).

The mean (SD) TBS in cases (1.383 [0.877]) was not significantly different from that of controls (1.389 [0.750], P = .670). Moreover, the proportion of patients with degraded or partially degraded bone was not significantly different between cases and controls (30/63 versus 25/65, P = .375). The proportion of patients with degraded bone microarchitecture was not significantly different on other subgroup analysis.

On analyzing outcomes in 2 groups stratified by time since transplant, it was found that the mean (SD) forearm BMD (g/cm^2) was significantly lower in group 2 (>2 years) as compared with group 1 (≤2 years) (0.724 [0.064] versus 0.761 [0.070], P = .036). Also, the proportion of patients with low bone mass (LBM) at the forearm was significantly higher in group 2 (6/7) as compared with group 1 (1/7); P = .042.

The components of body composition analysis comprising lean mass, total body fat percentage, and visceral adiposity were compared in cases and controls. The results are shown in Table 3. The total body fat percentage (30.5% [8.5%] versus 25.3% [8.7%], P = .001) was significantly higher in post-transplant patients when compared with age, sex, and BMI matched controls. The patients in the post-transplant group had a significantly lower lean mass (corrected for height) as compared with controls (15.9 [2.4] versus 18.6 [4.8] kg/m^2, P < .001). Among cases, the patients who had developed GVHD (n = 25) had a significantly lower lean mass than those who had not developed GVHD (n = 38) (14.9 [2.2] versus 16.5 [2.4] kg/m^2, P = .006). The proportion of patients with sarcopenia was significantly higher in recipients of allo-HSCT (26/62) when compared with age and sex matched controls (7/65) (42% versus 11%, P < .001). The prevalence of NWO among cases (17/62; 27.4%) and controls (11/65; 16.9%) was not significantly different (P = .2). Among cases, NWO was more commonly encountered in patients with sarcopenia as compared with those without (12/26 versus 5/36, P = .009). Other subgroup analysis was not significant.

DISCUSSION

To our knowledge, this is the first Indian study to evaluate the effects of allo-HSCT on BMD, TBS, and body composition in patients who had transplantation in adulthood. In a previously published Indian study, the study population was heterogeneous as patients of all age groups and who had undergone either allogeneic or autologous transplant were included [13]. In patients who had undergone HSCT, femoral neck BMD and lean muscle mass were lower when compared with controls. It

Table 3
Components of Body Composition Analysis in Cases and Controls

Variable	Cases (n = 63), Mean (SD)	Controls (n = 65), Mean (SD)	*P* Value
BMI (kg/m^2)	24.2 (4.1)	24.8 (4.2)	.352
Total body fat (%)	30.5 (8.5)	25.3 (8.7)	.001
Lean mass (kg/m^2)	15.9 (2.4)	18.6 (4.8)	<.001
ASM (kg/m^2)	7.22 (1.72)	8.17 (1.50)	.001
Fat mass (kg/m^2)	7.7 (3.1)	6.7 (3.0)	.075
VAT area (g/cm^2)	75.0 (35.9)	74.8 (30.7)	.967
VAT volume	390.9 (187.3)	389.7 (159.7)	.970

ASM indicates appendicular skeletal mass; VAT, visceral adipose tissue.

was also observed that the mean femoral BMD was significantly lower in the group that received myeloablative conditioning as compared with the group that received nonmyeloablative conditioning. This is probably due to greater toxicity of myeloablative chemotherapy causing damage to the osteoblastic progenitor cells. Further, the proportion of low bone mass at the femoral neck was significantly higher in cases as compared with controls. This is further compounded by the significantly greater prevalence of vitamin D deficiency seen in cases as compared with controls. In a study from northern India, Pandit et al. [13] prospectively evaluated the status of bone health in 50 recipients (both children and adults) of HSCT (allogeneic and autologous). It was observed that at 6 months after transplant, there was a significant decline in BMD from baseline followed by a significant improvement from 6 months to 12 months in the post-HSCT period. In a similar study conducted by Serio et al. [14], the BMD of cases was significantly reduced at the femoral neck and lumbar spine when compared with matched controls. It was also observed that patients who were evaluated at <3 months of transplant had a significantly lower lumbar BMD than patients who were evaluated at >3 months of HSCT. Such differences were not observed in BMD at the femoral neck. This was attributed to greater improvement in mineralization at trabecular sites as compared with sites of cortical bone. The mean TBS of our study patients was not significantly different between cases and controls. In a prospective study by Lim et al. [15], recipients of allo-HSCT were evaluated at 12 and 24 months with BMD and TBS measurements. It was found that, at 12 months, there was a significant decline in femoral neck and hip BMD, with decline in BMD at the spine and TBS that was not significant. The spine is chiefly composed of trabecular bone, which is metabolically more active and is therefore more involved in postmenopausal and glucocorticoid-induced osteoporosis. However, our study, in keeping with previously reported studies, showed a more significant involvement of the cortical bone at the femoral neck than at the spine. This has uniquely been reported with allo-HSCT, and the potential explanation offered is that the lumbar spine BMD might quickly decline and rapidly recover before these changes are evident on DXA scans [15]. The greater involvement of cortical bone as compared with trabecular bone has been exemplified in another study by Pawlowska et al. [16].

Avascular necrosis of the femur is a debilitating skeletal complication following HSCT reported in 3% to 24% of patients after HSCT [17]. In our study, 2 patients (3.1%) developed avascular necrosis of the femoral head on both sides, and one of them required bilateral total hip replacement. Both patients had undergone allogeneic HSCT for severe aplastic anemia. In the study by Serio et al. [14], avascular necrosis of the femoral head occurred in 12% of the patients after allogeneic transplant and in 4% of patients after autologous transplant. The occurrence of avascular necrosis is triggered by local vascular damage, leading to disruption of blood supply, an increase in intraosseous pressure, and mechanical stress leading to demineralization and collapse [18].

Our study demonstrated a significant positive correlation between lean mass and bone mineral density at both the femoral neck and the lumbar spine. This was consistent with the findings from a previous meta-analysis that included 20,226 men and women from 44 studies, in which lean mass was shown to contribute greater to BMD than fat mass. The correlation between lean mass and BMD suggests that increased mechanical loading of the skeleton results in an increase in BMD [19]. This finding also underscores the importance of physical activity in building muscle mass.

The lean mass was significantly lower and the total body fat significantly higher in cases as compared with controls in the present study. It was also observed that the mean lean mass was lower in patients with GVHD than in those without. Also, the prevalence of sarcopenia was higher in post-HSCT recipients than in age and sex matched controls. Sarcopenia is commonly encountered in post-HSCT patients, especially in the presence of chronic GVHD. When associated with low BMD, it can predispose to fractures and can adversely affect the patient's quality of life. In a study conducted by DeFilipp et al. [20] that included 315 patients with lymphoma, it was found that there was an increased incidence of sarcopenia in patients who had undergone allo-HSCT as compared with autologous HSCT. Furthermore, patients who were subjected to both allogeneic and autologous HSCT experienced an increase in total body fat over time. In a study done by Greenfield et al. [21] on 32 patients with multiple myeloma who had undergone at least 1 HSCT procedure, the prevalence of sarcopenia was 26%. The higher proportion of sarcopenia in our study is probably related to the fact that all patients had undergone allogeneic HSCT, unlike the abovementioned study in which the majority had undergone autologous HSCT. In a study by Mostoufi-Moab et al. [22], an analysis of body composition in 54 survivors of allo-HSCT (aged 5 to 25 years) and 894 controls revealed a significantly lower lean mass/height^2 and significantly higher fat mass/height^2 in cases as compared with controls ($P < .001$). These findings were replicated in our study.

The present study also demonstrated a higher prevalence of NWO in patients with sarcopenia. The coexistence of sarcopenia and obesity has been shown to increase cardiovascular risk as compared with obesity alone. Moreover, the presence of obesity may trigger the development of sarcopenia through the release of inflammatory mediators like TNFα and IL-6. These lead to decreased synthesis of muscle protein and increased myofibrillar protein breakdown, resulting in lower muscle mass. In patients with GVHD, the process of inflammation is closely linked with obesity and sarcopenia; this results in recipients of allo-HSCT being highly predisposed to this condition [15].

Our study is limited by its small sample size and cross-sectional design, and changes in BMD have not been assessed prospectively. The observed changes in body composition may predispose to metabolic syndrome and premature atherosclerotic cardiovascular disease. It is therefore imperative to follow up these patients prospectively to detect the development of adverse risk factors and initiate treatment appropriately and in a timely manner.

CONCLUSION

Impaired bone health and alterations in body composition may occur as delayed effects of allo-HSCT. Ensuring adequate calcium and vitamin D supplementation may be necessary to prevent further deterioration of bone health following transplantation. During follow-up of HSCT recipients, it might be prudent to consider graded strength training interventions to build muscle mass and reduce the adverse consequences of sarcopenia.

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