Effects of Hormone Replacement Therapy on Bone Mass After Allogeneic Hematopoietic Stem Cell Transplantation

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Context and Objectives: This study aimed to assess the effects of hormone replacement therapy (HRT) on bone mineral density (BMD) in young women who underwent allogeneic hematopoietic stem cell transplantation (HSCT).

Participants and Methods: This retrospective cohort included 234 female patients with premature ovarian insufficiency (POI) who underwent allogeneic HSCT between April 2009 and April 2016 at Seoul St. Mary's Hospital in Seoul, Korea. Inclusion criteria included adult patients who were age 40 years or younger at the time of transplantation and were followed for at least 3 years after HSCT.

Results: At the first and second years after HRT, there was a significant increase in the BMD of the lumbar spine of the HRT group (n = 170) compared to that of the non-HRT group (n = 64) (P = .033 and P = .047, respectively). The BMD of the lumbar spine significantly increased from baseline by 4.16 ± 4.39% and 5.42 ± 5.86% after 1 and 2 years of HRT, respectively (P = .037 and P = .021). The BMD of the femoral neck and total hip also showed a significant percentage increase from baseline after 2 years of HRT. These changes were significant even in the presence of graft-versus-host disease or steroid exposure. For HRT that was initiated within 12 months after HSCT, the increase in BMD in the lumbar spine was greatest after 2 years of HRT.

Conclusions: These results support that early and active hormonal therapy might be beneficial for BMD in female HSCT recipients with POI. **(*J Clin Endocrinol Metab* 105: 1–10, 2020)**

Freeform/Key Words: bone mineral density, hematopoietic stem cell transplantation, premature menopause, hormone replacement therapy

Allogeneic hematopoietic stem cell transplantation (HSCT) is an important therapeutic modality for treating hematologic malignancies. Long-term survival has increased by virtue of the development of therapeutic techniques, but increased morbidity remains a problem because of complications after HSCT, such as

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Abbreviations: AE, adverse effect; BMD, bone mineral density; BMT, bone marrow transplantation; FSH, follicle-stimulating hormone; GVHD, graft-versus-host disease; HRT, hormone replacement therapy; HSCT, hematopoietic stem cell transplantation; MAC, myeloablative conditioning; POI, premature ovarian insufficiency; RIC, reduced-intensity conditioning.

chronic graft-versus-host disease (GVHD) (1). Survivors are often confronted with various endocrine problems posed by transplantation, including decreased fertility, hyperglycemia, thyroid dysfunction, or bone loss. These posttransplant complications are a major contributor to determining survivors' quality of life. In recent years, there has been increasing interest in quality of life, which is considered a very important aspect of patient management after HSCT (2).

Premature ovarian insufficiency (POI) is the most frequent complication after HSCT in female recipients of childbearing age (3, 4). Secondary amenorrhea is associated with several adverse effects (AEs) on gynecological, bone, cardiovascular, and psychological health. Hormone therapy in postmenopausal women is effective and appropriate for managing various problems associated with menopause (5). Hormone replacement therapy (HRT) has been shown to be effective in improving vasomotor symptoms as well as in preventing bone loss associated with menopause (5, 6).

The aim of this study was to investigate the effect of HRT on bone mineral density (BMD) in young female HSCT recipients who were followed for at least 36 months after HSCT.

Methods

Study participants

This retrospective cohort included 234 female patients with POI who underwent allogeneic HSCT between April 2009 and April 2016 at Seoul St. Mary's Hospital in Seoul, Korea.

Inclusion criteria included adult patients who were age 40 years or younger at the time of transplantation and were followed for at least 3 years after HSCT. Initially, 2920 patients were screened, of whom 2173 patients age younger than 18 years or older than 40 years were excluded. Next, we excluded male patients (n = 382). We further excluded patients as follows: died within 3 years after HSCT (n = 91); lost at the follow-up stage (n = 17); transferred to other institutions after transplantation (n = 8); and had no evidence of POI (n = 15). Thus, 234 patients were enrolled for the analysis (Supplementary Fig. 1) (7). This study was approved by the institutional review board of The Catholic University of Korea (KC20RISI0010).

Bone mineral density measurement

The BMDs of the lumbar spine, femoral neck, and total hip were measured in grams per square centimeter using dual-energy x-ray absorptiometry (Lunar Prodigy, GE Healthcare). The coefficient of variation was 1.0% for the lumbar spine, 1.5% for the femoral neck, and 0.9% for the total hip. Given the broad range of ages, the results are also expressed as the number of SDs from normal values of sex-, age-, and ethnicity-matched controls (z score) to avoid overestimating age-associated bone loss. A z score of –2 or lower for age was defined as below the expected range. The changes in BMD are expressed as the mean ± SD with percentage changes.

Other measurements

Serum estradiol and follicle-stimulating hormone (FSH) were measured from sampled blood after overnight fasting. Assays of hormonal levels were conducted by immunoradiometric methods using commercially available kits (Estradiol, E2-RAI-CT; FSH, FSH-IRAM, DIAsource ImmunoAssays S.A.). Women were considered postmenopausal if their amenorrhea duration was more than 12 months or if their serum FSH level was higher than 40 mIU/mL. 25-Hydroxyvitamin D (25[OH]D) was measured using a UniCel DxI 800 Immunoassay Analyzer (Beckman Coulter, Inc). The average dose of glucocorticoids equivalent to prednisolone after HSCT was evaluated by reviewing the medical records. Breast sonography was performed annually in all participants to monitor the occurrence of breast cancer.

Transplantation procedure

Patients received either a myeloablative conditioning (MAC) or a reduced-intensity conditioning (RIC) regimen based on the classification by Gyurkocza and Sandmaier (8). Based on our center's treatment strategy, as reported previously, patients received either MAC or RIC after considering the age, donor type, type of hematologic disease, disease risk index, and comorbidity of the participants (9-13). During the HSCT procedures, all patients were treated in a designated room with laminar airflow isolation. Other general supportive care procedures, including administration of granulocyte colony-stimulating factor, prophylaxis of veno-occlusive disease, and administration of prophylactic antibiotics, were performed as described in our previous reports (9-14). All HSCT patients received calcium and vitamin D supplements based on published guidelines (15, 16), and the aim was to maintain their serum 25(OH)D levels above 30 ng/mL. Lifestyle modification, including physical activity, smoking cessation, and fall prevention, was also generally recommended for both groups.

Regimen for hormone replacement therapy

According to the protocol suggested by our center, it is advised that patients with POI after HSCT receive HRT unless it is contraindicated or refused. One of 3 different types of regimens was prescribed for HRT. 1) A combination of estradiol (2 mg, Prognova, Bayer Schering Pharma) with progesterone (200 mg, Utrogestan, Han Wha Pharma. Co., Ltd.) was a sequential regimen. Estradiol was administered for 25 days, and progesterone was administered for the last 12 days. 2) Climen, Bayer Schering Pharma, was a sequential regimen, a combination of estradiol (2 mg) and cyproterone (1 mg). 3) Femoston, JW Pharmaceutical, was another sequential regimen consisting of estradiol (2 mg) and dydrogesterone (10 mg). Climen and Femostone consisted of 28 pills in 1 package, with 1 pill taken daily without discontinuation. The choice of regimen for HRT was granted at the discretion of the physicians, who took into account the patients' preferences and conditions.

Time flow for the evaluation of study participants

The protocol proposed by our center indicates that HSCT survivors be prospectively checked via biochemical tests and

BMD to evaluate bone health at the time of initiating HRT and every year thereafter. Therefore, the baseline values of the present study are those assessed at the time of initiating HRT. Serum FSH, 25(OH)D and BMD were measured before HRT was initiated and then again every year (Supplementary Fig. 2) (7).

Statistical analysis

All the data were analyzed using SPSS version 20.0 for Windows software (IBM Corp). The data are presented as the means ± SD unless otherwise stated. Graphics were produced using GraphPad Prism version 5.0. In the evaluation of clinical features, we used the chi-square test for analysis of categorical variables, and the *t* test was used for the analysis of continuous variables. The mean percentage changes for BMD and other biochemical markers from baseline were analyzed using a repeated-measures analysis of variation and Dunnett method, if appropriate. *P* values of less than .05 were considered to represent statistically significant results for all comparisons.

Results

Baseline characteristics

The baseline characteristics of the study population are summarized in Table 1. The median age at HSCT was 30.8 years (range, 19-40 years). There was no significant difference in baseline between the group that received HRT and the group that did not. The baseline BMD and z score were not significantly different between the groups at any of the measured skeletal sites.

Safety of hormone replacement therapy

In terms of prescription drugs, the estradiol/progesterone regimen accounted for 43.5% of the HRT administered, followed by estradiol/dydrogesterone (Femoston) (31.8%) and estradiol/cyproterone acetate (Climen) (24.7%) (Supplementary Table 1) (7). The median time from HSCT to HRT initiation was

Table 1. Baseline characteristics of the study population[a]

Clinical parameters	HRT (n = 170)	Non-HRT (n = 64)	*P*
Age at transplantation, y	30.1 ± 6.6	31.8 ± 6.4	.386
Body mass index, kg/m^2	21.6 ± 2.6	21.6 ± 3.2	.227
Donor type, n (%)			.896
Matched sibling	71 (41.8%)	29 (45.3%)	
Unrelated	72 (42.3%)	25 (39.1%)	
Haploidentical	19 (11.2%)	8 (12.5%)	
Cord	8 (4.7%)	2 (3.1%)	
Hematologic disease, n (%)			.573
Acute myeloid leukemia	54 (31.8%)	22 (34.3%)	
Acute lymphoblastic leukemia	51 (30.0%)	22 (34.3%)	
Severe aplastic anemia	26 (15.3%)	11 (17.2%)	
Myelodysplastic syndrome	26 (15.3%)	6 (9.4%)	
Others	13 (7.6%)	3 (4.7%)	
Exposure to steroid after transplantation, n (%)	113 (66.5%)	41 (64.1%)	.613
Total body irradiation, n (%)	131 (77.1%)	46 (71.9%)	.142
Conditioning intensity, n (%)			.091
Myeloablative conditioning	118 (69.4%)	35 (54.7%)	
Reduced-intensity conditioning	52 (30.6%)	29 (45.3%)	
Steroid dose per d (mg/d) (n = 154)			
Average (range)	15.3 (5-84)	16.2 (5-91)	.498
Acute GVHD (grades II-IV), n (%)	77 (45.3%)	26 (40.1%)	.181
Chronic GVHD (moderate to severe), n (%)	84 (49.4%)	31 (48.4%)	.457
Median time to HRT after HSCT, mo	15.2 (3.5-60.1)	NA	NA
Baseline FSH, mIU/mL	58.0 ± 31.0	56.3 ± 30.5	.774
Baseline estradiol, pg/mL	48.4 ± 39.4	43.1 ± 37.9	.561
Baseline 25(OH) vitamin D, ng/mL	17.6 ± 8.4	18.1 ± 7.8	.352
Median time to baseline BMD after HSCT, mo	13.1 (3.5-18.3)	13.8 (7.6-16.7)	.629
BMD, g/cm^2			
Lumbar spine	1.033 ± 0.116	1.084 ± 0.153	.181
Femoral neck	0.826 ± 0.121	0.805 ± 0.125	.357
Total hip	0.823 ± 0.115	0.800 ± 0.139	.346
Baseline z score			
Lumbar spine	−1.1 ± 0.9	−0.7 ± 1.2	.136
Femoral neck	−1.7 ± 1.0	−1.8 ± 1.0	.535
Total hip	−1.8 ± 0.9	−1.9 ± 1.1	.394

Abbreviations: 25(OH) vitamin D, 25-hydroxyvitamin D; BMD, bone mineral density; FSH, follicle-stimulating hormone; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; HRT, hormone replacement therapy; NA, not available.

[a]The values of FSH, estradiol, 25(OH) vitamin D, BMD, and z score were captured at 1 year after HSCT in the non-HRT group and prior to the initiation of HRT in the HRT group.

15.2 months (range, 3.5-60.1 months) for the HRT group. Most patients (92.7%) who received HRT reported withdrawal bleeding after HRT. After 2 years of HRT, serum FSH levels decreased from 54.3 ± 17.2 mIU/mL to 37.9 ± 15.3 mIU/mL in the HRT group, whereas serum FSH levels did not change (56.3 ± 14.7 mIU/mL before vs 55.1 ± 20.9 mIU/mL after) in the non-HRT group (P = .044). Common AEs from HRT, such as nausea (11%) or abdominal pain (9%), headache (8%), and hot flushes (12%), occurred but have been reported to improve over time. No serious AEs that required discontinuation were reported during the study period. Moreover, none of the patients developed breast cancer, ischemic stroke, or deep vein thrombosis during the study period.

Percentage changes in bone mineral density

Changes in BMD during the 2 years of HRT were assessed at each measurement site (Fig. 1, Supplementary Table 2) (7). The BMD of the lumbar spine in the HRT group (n = 170) was significantly increased compared to that in the non-HRT group (n = 64) after the first year of HRT (4.16 ± 4.39% vs 2.61 ± 7.50%, P = .033) and after the second year of HRT (5.42 ± 5.86% vs 3.80 ± 6.00%, P = .047). With HRT, the BMD of the lumbar spine increased from baseline (1.033 ± 0.116 g/cm^2) by 4.16 ± 4.39% and 5.42 ± 5.86% after 1 and 2 years of HRT treatment, respectively (P = .037 and P = .021 from baseline). The femoral neck BMD showed a 1.22 ± 5.04% change from baseline after the first year of HRT and a 2.57 ± 4.27% change from baseline after the second year. In the non-HRT group, femoral neck BMD decreased in the first year (–0.07 ± 6.62%) but increased in the second year (2.13 ± 5.74%). For the total hip, similar results to the femoral neck were observed in terms of BMD changes. We did not find any differences in the effects of HRT on BMD among the regimens (data not shown).

Percentage changes in bone mineral density and conditioning intensity

In both the RIC (n = 52) and MAC groups (n = 118), the lumbar spine was the most dominant site of BMD increase after HRT. In the RIC group, the BMD of the lumbar spine was significantly increased after the first and second years of HRT from baseline (4.57 ± 4.62% and 5.18 ± 4.78%, respectively, both P < .001) (Fig. 2A). In the MAC group, compared to that at baseline, the BMD increase of the lumbar spine after the second year of HRT was significant (3.97 ± 3.96%, P = .043) (Fig. 2C). However, no significant increases in the BMD were found in either the RIC or MAC group, in which participants did not receive HRT (Fig. 2B and 2D).

Percentage changes in bone mineral density and the onset of hormone replacement therapy

In patients with early HRT initiation (n = 39), that is, less than 12 months after transplantation (median 8.4 months [range, 3.5-11.9 months]), the BMD increase after HRT was higher in all measured skeletal sites than in patients with HRT initiation after 12 months (median 19.1 months [range, 12.1-60.1 months]) (n = 131). The lumbar spine BMD increased significantly after 1 year of HRT in patients with early HRT initiation compared to

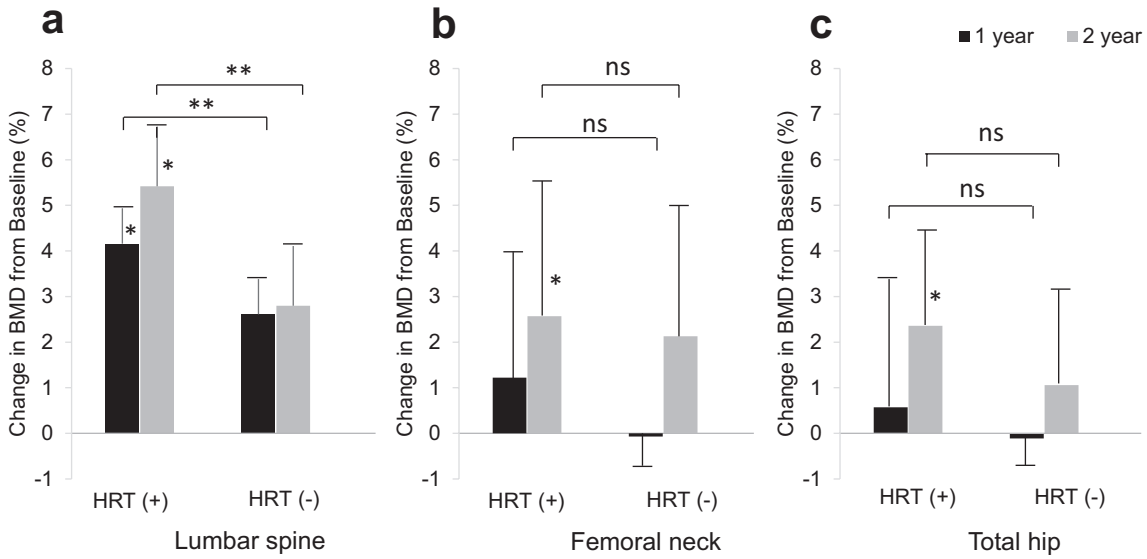

Figure 1. Changes in bone mineral density according to hormone replacement therapy (HRT). Adjusted for variables that affect bone metabolism. A, lumbar spine; B, femoral neck; C, total hip. *P less than .05 compared to baseline. **P less than .05 between the HRT group and the non-HRT group. ns, not significant.

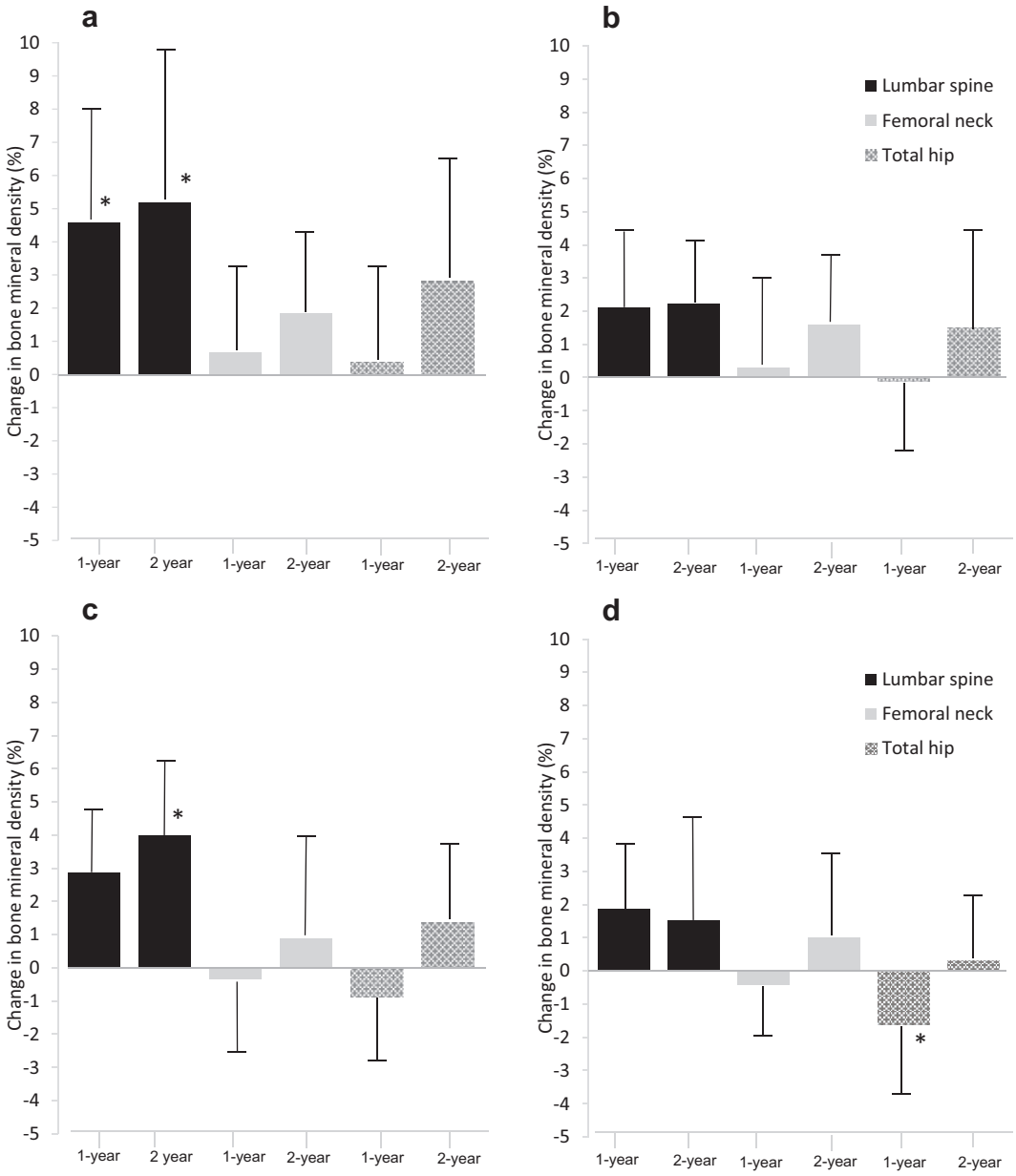

Figure 2. Comparison of bone mineral density changes according to conditioning intensity in a hormone replacement therapy (HRT) group and a non-HRT group. A, Reduced-intensity conditioning (RIC) in the HRT group (n = 52). B, RIC in the non-HRT group (n = 29). C, Myeloablative conditioning (MAC) in the HRT group (n = 118). D, MAC in the non-HRT group (n = 35) *P less than .05 compared to baseline.

those who started HRT after 12 months (5.87 ± 4.15% vs 1.66 ± 4.39%, P = .009). At the second year, the BMD of the lumbar spine and total hip significantly increased in patients with early HRT compared to those who started HRT after 12 months (for the lumbar spine, 6.31 ± 3.89% vs 3.10 ± 4.94%, P = .013; and for the total hip, 3.35 ± 3.99% vs 1.39 ± 3.94%, P = .002) (Fig. 3).

Percentage changes in bone mineral density and steroid exposure

The elevation from baseline of BMD by HRT among patients who did not receive steroids (steroid-unexposed group, n = 57) was significantly higher than that of those who received steroids (steroid-exposed group, n = 113) in all measurable sites during the first and second years of HRT. The lumbar spine was the most elevated site relative to baseline (5.04 ± 4.40%, P < .001) after the second year of HRT in the steroid-unexposed group (Fig. 4A). The BMD of the femoral neck and total hip decreased compared to baseline after the first year of HRT, but the BMD in these sites recovered in the second year in the steroid-exposed group (Fig. 4C). In the steroid-exposed group, the lumbar spine was also the site with the highest increase in BMD relative to baseline after 2 years of HRT (2.61 ± 3.41%, P = .018).

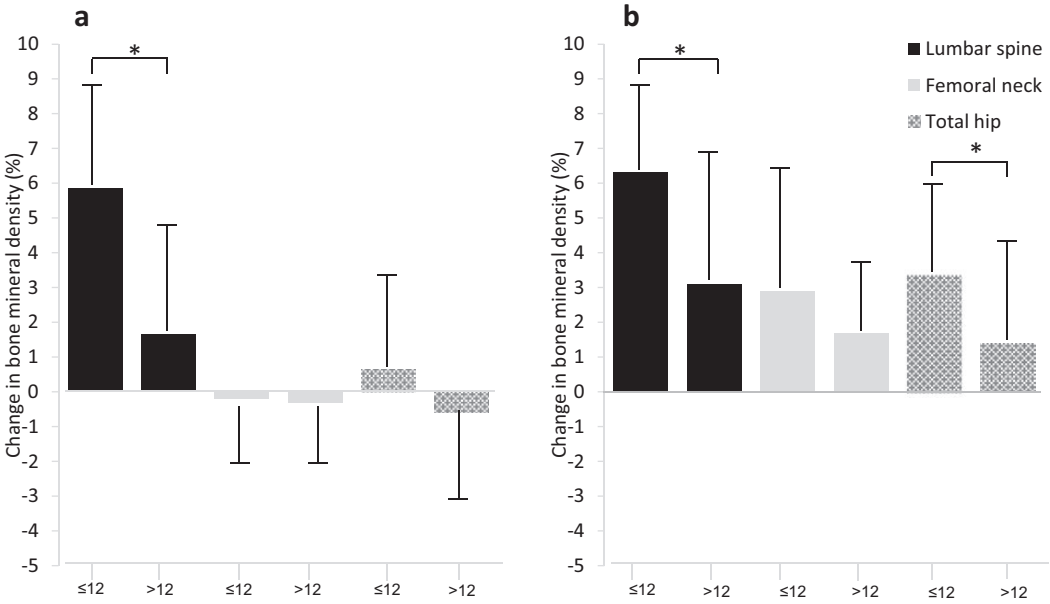

Figure 3. Changes in bone mineral density according to the onset of hormone replacement therapy (HRT) (n = 39 for the initiation of HRT within 12 months post-HSCT, n = 131 for the initiation of HRT after 12 months post-HSCT). A, One-year post-HRT. B, Two-year post-HRT. *P less than .05 between the groups.

However, there was no significant increase in the BMD from baseline at any measurable sites in the non-HRT group (Fig. 4B and 4D). Of note, serious defects of restoration in BMD were observed in the steroid-exposed group compared with those in the steroid-unexposed group in the non-HRT group.

Percentage changes in bone mineral density and graft-versus-host disease

A greater BMD increase was observed at all measurable sites in patients without GVHD than in those with GVHD (Fig. 5A). The lumbar spine was the site with a significant increase in BMD relative to baseline in patients without GVHD (4.36 ± 2.03% in the first year, P = .014 and 5.20 ± 2.26% in the second year, P = .031). In the presence of GVHD, the BMD of the femoral neck and total hip decreased relative to baseline after the first year of HRT, but the BMD in these sites increased in the second year. The BMD of the lumbar spine showed the highest increase relative to baseline in the second year (3.13 ± 3.52%, P = .033), but the increase was less than that in the patients without GVHD (Fig. 5C). Again, there was no significant increase in the BMD from baseline at any measurable sites in the non-HRT group (Fig. 5B and 5D).

Discussion

This study analyzed the impacts of HRT on BMD in women of reproductive age who developed POI after allogeneic HSCT. During the study period, BMD increased in all measurement sites in the HRT group, and the lumbar spine was the site with the greatest increase. Compared to patients who did not receive HRT, patients who received HRT for 2 years showed a significant BMD increase in the lumbar spine.

HSCT-related bone loss is multifactorial, and bones undergo various conditions and treatments before and after transplantation. In our previous study, Kang et al explained the cause of bone loss as involving a rapid decrease in bone formation and increase in bone resorption after bone marrow transplantation (BMT) by means of bone turnover markers (17). Lee and colleagues suggested that bone marrow stromal cells are inhibited from osteoblast differentiation after BMT, which may be the cause of post-BMT bone loss (18). After HSCT, progenitor cells in the bone marrow are rapidly reduced, and osteoblast precursors cannot be stored properly because of the degradation of osteogenic cells (19, 20). Glucocorticoids, GVHD, and total body irradiation are well-established risk factors for bone loss associated with HSCT (21-24). Glucocorticoids affect both trabecular bone and the cortical bone. However, bone loss is most prominent in trabecular bone, such as the lumbar spine, because trabecular bone has a large surface area and high metabolic activity (25). In patients with HSCT, the decrease in lumbar spine BMD is marked by steroid administration, but the femur is the site with the greatest decrease (26). Femur BMD rapidly deteriorates during the first 3 months after transplantation and then recovers slowly, depending on other risk factors for bone loss (27). In our study, the BMD

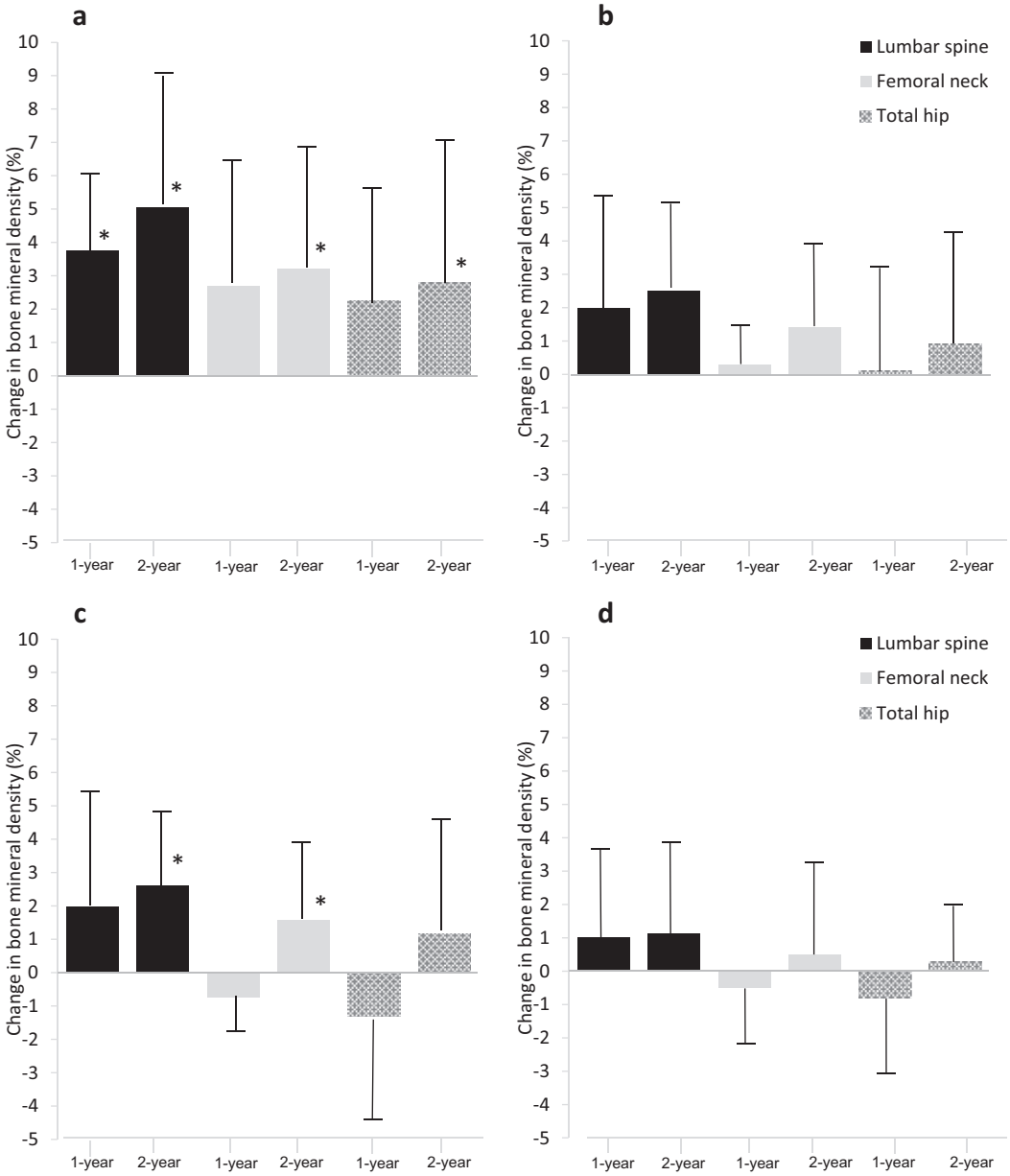

Figure 4. Comparison of bone mineral density changes according to steroid exposure in a hormone replacement therapy (HRT) group and non-HRT group. A, Steroid-unexposed in the HRT group (n = 57). B. Steroid-unexposed in the non-HRT group (n = 23). C, Steroid-exposed in the HRT group (n = 113). D, Steroid-exposed in the non-HRT group (n = 41). **P* less than .05 compared to baseline.

increases in the femoral neck and total hip were observed to be smaller than those of the lumbar spine with HRT. These findings were consistent, even when considering risk factors for bone loss, such as steroids, GVHD, and conditioning regimens.

More than 90% of female patients with allogeneic HSCT experience POI (28). This premature menopause not only causes infertility but also causes significant secondary osteoporosis. Bone strength is determined both by bone mass and bone quality, of which bone mass as estimated by the BMD is an important factor constituting 60% to 70% of bone strength (29, 30). Healthy women in the young age group maintain the anabolic phase until the mid-20s, when peak bone mass is formed. Thereafter, a gradual decline occurs in women until the accelerated period after menopause. On the other hand, in HSCT patients, sudden bone loss occurs because of the abrupt uncoupling of osteoclasts and osteoblasts within 3 months after transplantation, which then slowly recovers (15, 17). This bone physiology is different from the general situation expected at the same age in healthy women. A decrease in bone mass adversely affects bone strength and increases the risk of fractures in the long term; therefore, physicians should pay attention to any BMD changes in this specific patient group.

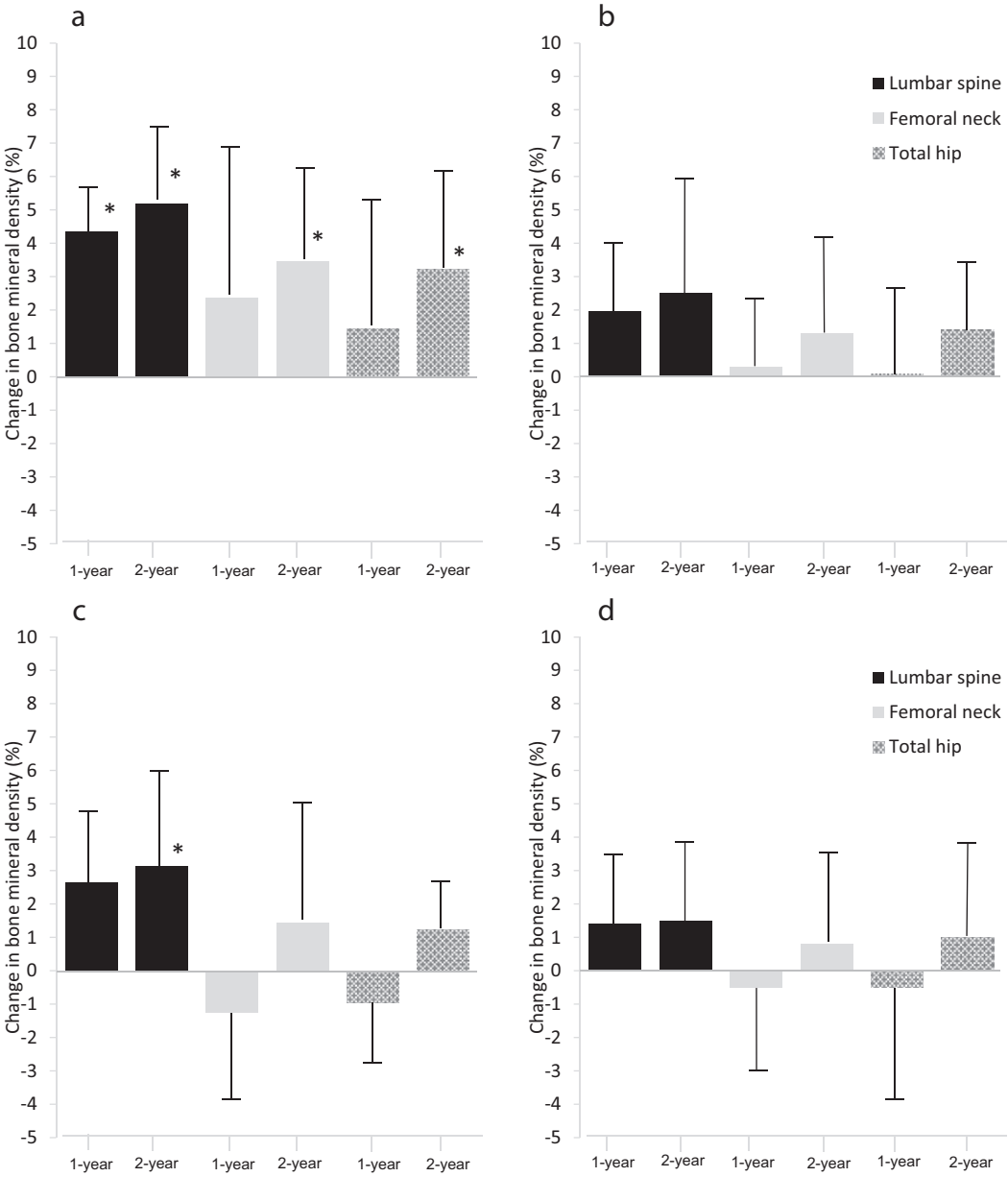

Figure 5. Comparison of bone mineral density changes according to the presence of graft-versus-host disease (GVHD) in a hormone replacement therapy (HRT) group and a non-HRT group. A, Absence of GVHD in the HRT group (n = 86). B, Absence of GVHD in the non-HRT group (n = 33). C, Presence of GVHD in the HRT group (n = 84). D, Presence of GVHD in the non-HRT group (n = 31). **P* less than .05 compared to baseline.

The risk of fractures associated with low BMD increases with continued exposure to steroids or immunosuppressants for post-HSCT management. Recent research by Pundole et al reported an up to 8 times higher risk of fractures in HSCT recipients than in the general population (31). In 2013, updated guidelines for management following HSCT suggested specific guidelines for bone management in this special group of patients (16). In addition to basic recommendations, such as increasing calcium intake, vitamin D supplementation, and exercise, the guidelines specifically recommend the use of bisphosphonates. However, the authors questioned the efficacy of HRT alone for managing bone loss after HSCT because HRT research did not provide consistent data on bone loss after HSCT (15).

HRT is recommended in allogeneic HSCT recipients presenting with POI to prevent serious systemic and psychological effects associated with estrogen deficiency (4). Although there is consensus that HRT is generally effective for improving the symptoms related to POI, there is still insufficient consensus on the effects of HRT on bone loss after HSCT. In our study, the BMD of the lumbar spine increased up to 5.4% during 2 years of HRT, and there was a 3.1% to 5.2% increase even when considering risk factors for bone

loss, such as steroid administration or the presence of GVHD. In the subgroup analysis, although the MAC group showed delayed recovery of BMD in all measurement sites compared to the RIC group, a significant increase in lumbar BMD compared to baseline was observed after 2 years of HRT. Patients who were exposed to steroids or had GVHD were less likely to recover from baseline than those who did not, but those who continued HRT for 2 years also achieved an increase in BMD relative to the corresponding baseline at all measurable sites. The early start of HRT (within 12 months after transplantation) resulted in up to a 6.3% increase in BMD in the lumbar spine, suggesting that the effect of increasing BMD is greater when HRT is started early. This is consistent with the recent consensus that recommends early management of bone loss after HSCT (15).

After HSCT, most of our patients underwent supplementation with elemental calcium and vitamin D and were recommended regular weight-bearing exercise regardless of HRT. As a result, 25(OH)D levels after 2 years of HRT were maintained above 30 ng/mL in our study participants (33.7 ± 6.8 ng/mL in the HRT group and 31.4 ± 7.1 ng/mL in the non-HRT group, $P = .614$). In our study, a small BMD gain was also observed in the non-HRT group, suggesting that general recommendations for improving bone health, such as regular exercise and calcium/vitamin D supplementation, are appropriate for improving bone health in this specific group of patients. To maintain bone health after transplantation, we recommend at least 30 minutes of daily physical exercise and more than 30 minutes of sunlight exposure twice a week.

The strength of this study is that these results provide physicians with important information about the clinical effects of HRT on bone mass in young female survivors with POI after HSCT, and these results were obtained from an analysis with a sufficient number of participants. In addition, all patients underwent daily supplementation with elemental calcium and vitamin D according to the guidelines. However, our study has some limitations. This study was not a randomized controlled trial and followed a retrospective cohort design, which did not consider the various situations that may have occurred during the treatment process. However, because all patients underwent BMD assessments annually under the long-term follow-up program of our center, the data were prospectively collected. The second limitation is that current data present only the results of the first 2 years of HRT. Long-term data on changes in BMD or the incidence of fractures are necessary. The lack of analysis of bone turnover markers is another limitation. Assessment of bone quality by analyzing bone turnover markers is another intriguing area of study.

The present study supports that early and active hormonal therapy might be beneficial for BMD in female HSCT recipients with POI. In the future, a large-scale randomized controlled trial could confirm the effects of HRT on BMD.

Acknowledgments

Part of this study was accepted for an oral presentation at the Endocrine Society's Annual Meeting, ENDO 2020, March 28 to 31, 2020, in San Francisco, California, USA (No. OR29). The first author of the study, J. Ha, was selected as an Outstanding Abstract Award for ENDO 2020. Although the meeting was canceled because of the COVID-19 pandemic, the abstract was published in the supplement issue of the *Journal of the Endocrine Society*.

Additional Information

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Disclosure Summary: The authors have nothing to disclose.

Data Availability: The data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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