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# Factors Related to Decreased Bone Mineral Density in Childhood Cancer Survivors

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The risk of osteoporosis or osteopenia is known to increase after childhood cancer treatment. The purpose of this study was to evaluate patterns of bone mineral density (BMD) and to identify factors related to the decreased BMD in childhood cancer survivors. We studied 78 patients (34 boys, 44 girls) treated for childhood cancer. Twenty (25.7%) patients had lumbar BMD (LBMD) standard deviation score (SDS) lower than -2. Nineteen (24.4%) patients had femur neck BMD (FNBMD) SDS lower than -2. The patients treated with hematopoietic stem cell transplantation had lower LBMD SDS (-1.17 ± 1.39 vs -0.43 ± 1.33, $P = 0.025$). The risk of having LBMD SDS < -2 was higher in the patients treated with glucocorticoid (GC) for graft-versus-host disease (GVHD) (36.6% vs 13.5%; odds ratio [OR], 3.7; $P = 0.020$). In multivariate logistic regression analysis, longer duration of GC treatment for GVHD (OR, 1.12; 95% confidence interval [CI], 1.05-1.20) and lower body mass index (BMI) SDS (OR, 0.59; 95% CI, 0.36-0.95) were associated with decreased LBMD SDS. These findings suggest that prolonged GC use and reduction in BMI are risk factors for decreased BMD in childhood cancer survivors. Anticipatory follow-up and appropriate treatment are necessary, especially for the patients with risk factors.

Key Words: Bone Density; Neoplasms; Glucocorticoids

## INTRODUCTION

The bone mass attained early in life is known to be the most important determinant of lifelong skeletal health (1). In adults and children a reduction of one standard deviation in bone mineral density (BMD) is associated with a doubling of the fracture risk (2). Decreased BMD can lead to fractures, deformity, pain, and considerable financial burden (3). Childhood cancer treatment is a potential etiologic factor for low BMD among children who survive cancer management (4). For example, fracture risk was 6 times higher in children with acute lymphoblastic leukemia (ALL) compared with healthy controls (5).

Multiple possible etiologic factors for decreased BMD in these patients have been proposed: the disease itself, growth hormone (GH) and/or sex hormone deficiency, intensive chemotherapy, low calcium and vitamin D intake, and reduced physical activity (4). Chemotherapy (especially glucocorticoid [GC] and methotrexate) can affect bone formation by altering osteoblastic activity and proliferation. High-dose GC and intrathecal methotrexate, included in nearly all ALL treatment regimens, can affect bone formation, by altering osteoblastic activity and proliferation (6). Radiation-associated damage to the hypothalamic-pituitary axis can result in growth hormone deficiency and hypogonadism, which impair bone growth and mineral acquisition. The suboptimal activity and nutrition during the treatment course reduce bone formation during developmentally critical time periods (7).

The purpose of this study was to evaluate patterns of BMD after cancer treatment and to identify factors related to the decreased BMD in childhood cancer survivors.

## MATERIALS AND METHODS

### Patients

A total 78 childhood cancer survivors (34 boys and 44 girls) were enrolled in this study at the Department of Pediatrics, the Catholic University of Korea, Yeouido St. Mary's Hospital. Clinical information was obtained by a review of medical records and laboratory evaluations. Patients who had growth hormone deficiency or adrenal insufficiency were excluded. Data included primary disease, chronological age at treatment, body mass index (BMI), method of treatment (chemotherapy, radiotherapy), endocrine function, presence of chronic graft-versus-host disease (cGVHD), and relevance of BMD standard deviation score (SDS).

The primary diagnosis included ALL (n = 38, 49%), acute myeloid leukemia (n = 35, 45%), and chronic myeloid leukemia (n = 5, 6%). The mean mid-parental height was 171.72 ± 3.68 in males and 160.62 ± 5.01 in females. The mean chronological age at cancer diagnosis was 7.2 ± 3.8 yr in males and 7.7 ± 3.9 yr



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in females. The mean chronological age at the first BMD evaluation was 11.6 ± 3.4 yr in males and 13.0 ± 3.3 yr in females. The mean chronological age at hematopoietic stem cell transplantation (HSCT) was 8.79 ± 3.30 yr in males and 8.28 ± 4.03 yr in females. The time from initial diagnosis to measurement of BMD was 4.42 ± 2.47 yr in males and 5.36 ± 3.20 yr in females. The mean BMI SDS at diagnosis was 0.21 ± 2.7 in males and -0.11 ± 1.25 in females. Fifty (64%) patients were treated with HSCT and 48 patients (62%) received radiation therapy. Thirty-three (42%) patients were treated with GCs for chemotherapy and 41 (53%) patients were treated with GCs for GVHD. Ten (13%) patients had relapse, twenty (26%) patients had hypogonadism, and one patient had hypothyroidism (Table 1).

**Table 1.** Clinical data of 78 childhood cancer survivors

| Characteristics | Findings |
|---|---|
| No. (%) of patients | 78 |
| Boys | 34 (44) |
| Girls | 44 (56) |
| CA at BMD (yr) | |
| Male | 11.6 ± 3.4 |
| Female | 13.0 ± 3.3 |
| Time from Dx. to BMD (yr) | |
| Male | 4.42 ± 2.47 |
| Female | 5.36 ± 3.20 |
| Diagnosis, No. (%) | |
| ALL | 38 (49) |
| AML | 35 (45) |
| CML | 5 (6) |
| BMI SDS at Diagnosis | |
| Male | 0.21 ± 2.7 |
| Female | -0.11 ± 1.25 |
| HSCT, No. (%) | |
| Performed | 50 (64) |
| Not performed | 28 (36) |
| Radiation, No. (%) | |
| Performed | 48 (62) |
| Not performed | 30 (38) |
| cGVHD, No. (%) | |
| Present | 29 (37) |
| Absent | 49 (63) |
| GC treatment for Chemotherapy, No. (%) | |
| Performed | 33 (42) |
| Not performed | 48 (58) |
| GC treatment for GVHD, No. (%) | |
| Performed | 41 (53) |
| Not performed | 37 (47) |
| Hypogonadism, No. (%) | |
| Present | 20 (26) |
| Absent | 58 (74) |

No., number; CA, chronological age; BMD, bone mineral density; Dx.; diagnosis; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; BMI, body mass index; SDS, standard deviations score; HSCT, hematopoietic stem cell transplantation; GC, glucocorticoid; cGVHD, chronic graft-versus-host disease. Data are mean ± standard deviation.

### Arthropometric parameters

Height was measured using a Harpenden stadiometer (Holtain Ltd., Crymych, UK) at the time of the diagnosis, and every six months thereafter. The height was measured three times to the nearest 0.1 cm and an average of three measurements was taken. Weight in kilogram was measured with a scale. Bone age was determined according to Greulich-Pyle method by a trained pediatric endocrinologist. Conventional roentgenograms of left hand and wrist were taken to determine the bone age. Sex-corrected mid-parental height was calculated by taking the mean of parental height and adding or subtracting 6.5 cm for males and females, respectively. The growth status was evaluated with reference to the most recent growth charts for Korean children and adolescents (8). The pubertal status was determined by the Marshall-Tanner method.

### BMD measurement

BMD (g/cm$^2$) was evaluated using dual-energy X-ray absorptiometry (DEXA) (Delphi, Hologic, Bedford, MA, USA) on the lumbar spine (Lumbar vertebrae L1-L4) and femur neck. Reference data of pediatric BMD was obtained from the manufacturer and expressed in age- and gender-matched z-scores (9).

### Hormone assays

Serum calcium, phosphorus, alkaline phosphatase, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), free thyroxine (T4), and triiodothyronine (T3) were assayed in a single sample at BMD evaluation. Serum calcium, phosphorus, and alkaline phosphatase were measured by automatic chemistry analyzer (Hitachi 7600-100, Tokyo, Japan). The following assay methods were used: immunoradiometric assay using TSH-CTK-3 (DiasorinSpA, Saluggia, Italy) for thyroid stimulating hormone (TSH); radioimmunoassay using fT4-CTK (DiasorinSpA) for free T4; radioimmunoassay using T3-CTK (DiasorinSpA) for T3; immunoradiometric assay using LH-CTK-4 (DiasorinSpA) for luteinizing hormone (LH); immunoradiometric assay using FSH-CTK (DiasorinSpA) for follicle stimulating hormone (FSH); radioimmunoassay using Testosterone RIA CT (RaDIMSpA, Rome, Italy) for testosterone; radioimmunoassay using Estradiol MAIA kit (Adaltis Italia, Reno, Italy) for estradiol; immunoradiometric assay using IRMA IGF-1 kit (IMMUNOTECH, Marseille, France) for Insulin like growth factor -1 (IGF-1); immunoradiometric assay using IGFBP 3 IRMA-CT kit (ImmunoDiagnosticsystems. LTD, USA) for insulin like growth factor binding protein 3 (IGFBP-3).

### BMI

BMI was defined as body weight (kg) divided by the square of height (m). A Z-score for an individual BMI measurement can also be calculated using the age-specific L, M, and S parameters. The LMS technique estimates three parameters: median (M), standard deviation (S), and power in the Box-Cox transformation (L). The formula used to obtain the Z-score is $Z = [(X/M)^L-1]/LS$, where X is the estimated BMI value. Reference val-

ues were obtained from the standard growth chart in 2007 of Korea Centers for Disease Control and Prevention (8).

### Statistical analysis

Data are presented as mean ± standard deviation. *P* value < 0.05 was regarded as statistically significant. SPSS for Window (version 18.0, SPSS Inc. Chicago, IL, USA) was used for statistical analysis. Differences in continuous variables were analyzed using the Student t test. The differences in categorical factors between groups were analyzed by the Pearson's chi-square test and Fisher's exact test, as appropriate. Multivariate logistic regression analysis for decreased lumbar BMD and predictor variables was performed.

### Ethics statement

The study protocol was reviewed and approved by the institutional review board of the Yeouido St. Mary's Hospital (No. SC13-RISI0152). Informed consent was exempted by the board.

## RESULTS

### BMD measurement in male and female subjects

The lumbar BMD (LBMD) SDS and femur neck BMD (FNBMD) SDS at initial BMD measurement were -0.91 ± 1.41 and -1.13 ± 1.79, respectively. The LBMD SDS at initial BMD measurement was -1.04 ± 1.49 in boys and -0.80 ± 1.35 in girls. Twenty (25.7%) patients had LBMD SDS lower than -2. Nineteen (24.4%) patients had FNBMD SDS lower than -2 (Table 2, Fig. 1).

**Table 2.** BMD measurement in subjected boys and girls

| Parameters | Total | Boys | Girls | *P* value |
|---|---|---|---|---|
| Number of subjects | 78 | 34 | 44 | |
| Chronologic age (yr) | 12.4 ± 3.4 | 11.6 ± 3.3 | 13.0 ± 3.3 | 0.062 |
| LBMD SDS | -0.91 ± 1.41 | -1.04 ± 1.49 | -0.80 ± 1.35 | 0.465 |
| FNBMD SDS | -1.13 ± 1.79 | -1.29 ± 1.92 | -1.00 ± 1.70 | 0.480 |
| LBMD SDS < -2 | 20 (25.7%) | 12 (35%) | 8 (18%) | 0.088 |
| FNBMD SDS < -2 | 19 (24.4%) | 9 (26%) | 10 (23%) | 0.707 |

BMD, bone mineral density; LBMD, lumbar bone mineral density; FNBMD, femur neck bone mineral density; SDS, standard deviations score.

### Comparison of clinical parameters according to lumbar BMD SDS

Fifty-eight (74.3%) patients had LBMD SDS greater than -2. The mean chronological age at cancer diagnosis was 9.1 ± 3.5 yr in the patients with BMD SDS lower than -2, and 6.9 ± 3.9 yr in the patients with BMD SDS greater than -2. The age at HSCT treatment was older in patients having LBMD SDS lower than -2 (10.2 ± 2.9 vs 7.7 ± 3.8). The mean chronological age at initial BMD measurement was 13.6 ± 3.4 yr in the patients with BMD SDS lower than -2, and 12.0 ± 3.3 yr in the patients with BMD SDS greater than -2. The duration of GC treatment for GVHD was longer in patients with LBMD SDS lower than -2 (21.0 ±

**Table 3.** Comparison of clinical and laboratory parameters according to lumbar BMD SDS

| Parameters | LBMD SDS < -2 | LBMD SDS ≥ -2 | *P* value |
|---|---|---|---|
| Number | 20 (25.7%) | 58 (74.3%) | |
| CA at diagnosis (yr) | 9.1 ± 3.5 | 6.9 ± 3.9 | 0.023 |
| CA at HSCT (yr) | 10.2 ± 2.9 | 7.7 ± 3.8 | 0.026 |
| CA at BMD (yr) | 13.6 ± 3.4 | 12.0 ± 3.3 | 0.076 |
| Time from Dx. To BMD (yr) | 4.4 ± 2.8 | 5.1 ± 3.0 | 0.348 |
| Radiation dose (cGy) | 1,200.0 ± 0.00 | 1,125.0 ± 114.08 | 0.078 |
| GC duration (months) | | | |
| For Chemotherapy | 2.20 ± 1.42 | 2.70 ± 0.94 | 0.171 |
| For GVHD | 21.02 ± 20.80 | 7.39 ± 10.01 | 0.007 |
| BMI SDS | -0.41 ± 1.48 | 0.030 ± 1.34 | 0.058 |
| Calcium (mg/dL) | 9.67 ± 0.53 | 9.37 ± 0.60 | 0.063 |
| P (mg/dL) | 4.08 ± 0.73 | 4.13 ± 0.73 | 0.811 |
| ALP (IU/L) | 525.0 ± 262.2 | 465.53 ± 219.37 | 0.346 |
| IGF-1(ng/mL) | 355.58 ± 195.40 | 409.57 ± 173.92 | 0.285 |

BMD, bone mineral density; SDS, standard deviations score; LBMD, lumbar bone mineral density; CA, chronological age; HSCT, hematopoietic stem cell transplantation; Dx., diagnosis; GC, glucocorticoid; BMI, body mass index; P, phosphorus; ALP, alkaline phosphatase; IGF-1, insulin-like growth factor-1.

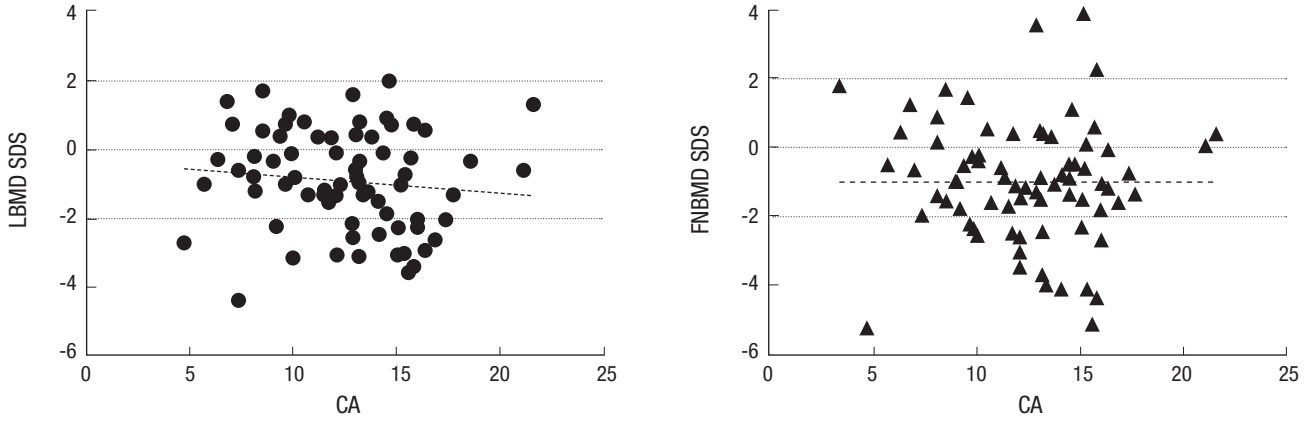


**Fig. 1.** BMD SDS distribution according to chronological age. CA, chronological age; LBMD, lumbar bone mineral density; FNBMD, femur neck bone mineral density; SDS, standard deviation score.


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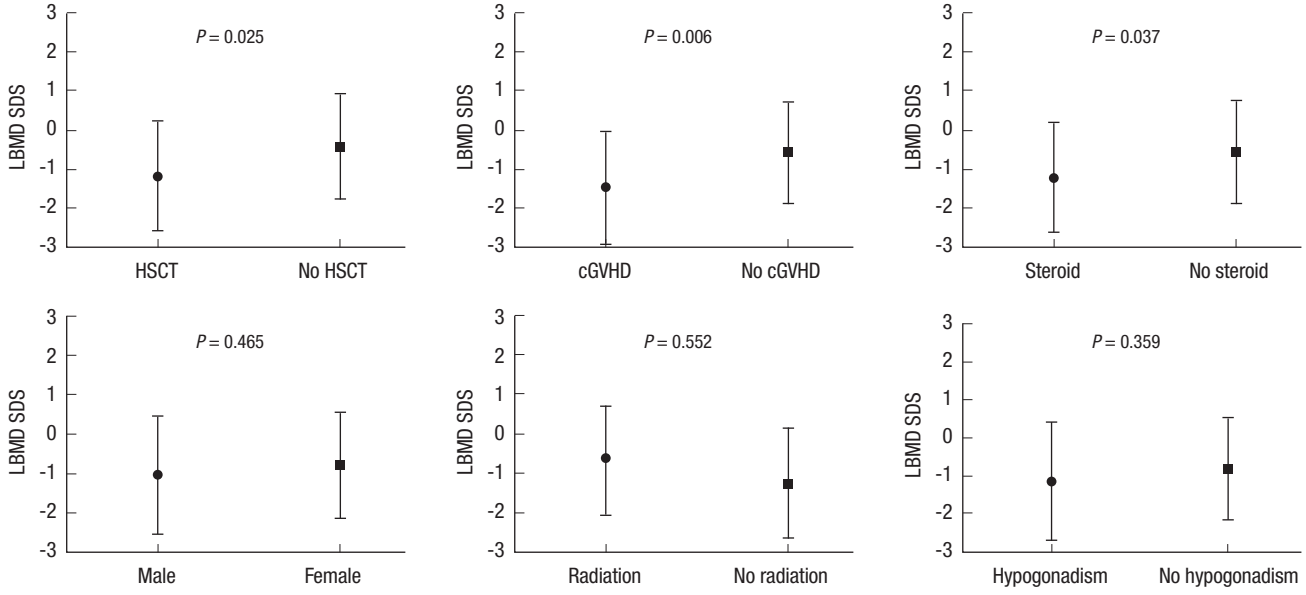


**Fig. 2.** Clinical parameters of childhood cancer survivors with low bone mineral density. LBMD SDS, lumbar bone mineral density standard deviation score; HSCT, hematopoietic stem cell transplantation; cGVHD, chronic graft-versus-host disease.

20.8 vs 7.4 ± 10.0). The duration of GC use for chemotherapy before HSCT, radiation dose, BMI SDS, and IGF-1 were not shown to be statistically significant with regards to LBMD SDS (Table 3).

There were no differences in LBMD SDS and FNBMD SDS among ALL, AML, and other disease groups. The duration of GC treatment before HSCT was significantly longer in the ALL group than other disease groups (2.0 ± 1.5 months vs 0.2 ± 0.7 months vs 0 month, $P < 0.001$). The duration of GC treatment for GVHD was not different among ALL, AML and other disease groups (3.5 ± 9.2 months vs 10.0 ± 16.1 months vs 2.2 ± 1.6 months).

The patients treated with HSCT had lower LBMD SDS than those without HSCT (-1.17 ± 1.39 vs -0.43 ± 1.33, $P = 0.025$). The patients diagnosed with cGVHD had lower LBMD SDS (-1.47 ± 1.44 vs -0.57 ± 1.30, $P = 0.006$). The patients who received prolonged GC treatment for GVHD had lower LBMD SDS (-1.22 ± 1.42 vs -0.56 ± 1.32, $P = 0.037$). However, neither radiation therapy nor hypogonadism had a significant impact on BMD difference (Fig. 2).

The risk of having LBMD SDS lower than -2 was higher in patients treated with HSCT (34.0% vs 10.7%; odds ratio [OR], 4.29; $P = 0.024$) and higher in the patients treated with GC for GVHD (36.6% vs 13.5%; OR, 3.7; $P = 0.020$) (Table 4).

**Table 4.** Incidence of decreased lumbar BMD SDS < -2.0 according to clinical parameters

| Clinical parameters | LBMD SDS < -2 No. (%) | LBMD SDS ≥ -2 No. (%) | *P* value | OR (95% CI) |
|---|---|---|---|---|
| Sex | | | 0.086 | |
| Boys | 12 (35.3) | 22 (64.7) | | |
| Girls | 8 (18.2) | 36 (81.8) | | |
| HSCT | | | 0.024 | 4.29 (1.13-16.28) |
| Performed | 17 (34.0) | 33 (66.0) | | |
| Not performed | 3 (10.7) | 25 (89.3) | | |
| Radiation | | | 0.078 | |
| Performed | 9 (18.8) | 39 (81.3) | | |
| Not performed | 11 (36.7) | 19 (63.3) | | |
| cGVHD | | | 0.000 | 6.99 (2.18-20.55) |
| Present | 14 (48.3) | 15(51.7) | | |
| Absent | 6 (12.2) | 43 (87.8) | | |
| GC for GVHD | | | 0.020 | |
| Performed | 15 (36.6) | 26 (63.4) | | |
| Not performed | 5 (13.5) | 32 (86.5) | | |
| Relapse | | | 0.265 | |
| Present | 4 (40.0) | 6 (60.0) | | |
| Absent | 16 (23.5) | 52 (76.5) | | |
| Hypogonadism | | | 0.266 | |
| Present | 7 (35.0) | 13 (65.0) | | |
| Absent | 13 (22.4) | 45 (77.6) | | |

BMD, bone mineral density; SDS, standard deviations score; No., number; OR, odds ratio; CI, confidence interval ; HSCT, hematopoietic stem cell transplantation; cGVHD, chronic graft-versus-host disease; GC, glucocorticoid.

### A multivariable logistic regression model for decreased lumbar BMD SDS

In multivariate logistic regression analysis for decreased lumbar BMD lower than -2 SD after cancer treatment, longer duration of GC treatment for GVHD (OR, 1.12; 95% confidence interval [CI], 1.05-1.20) and lower BMI SDS (OR, 0.59; 95% CI, 0.36-0.95) were associated with decreased LBMD SDS (Table 5).

## DISCUSSION

In this study of childhood cancer survivors, we found that 25.7% of subjects had LBMD SDS lower than -2. The age at cancer diagnosis was 9.1 ± 3.5 yr in patients with BMD SDS lower than -2, and 6.9 ± 3.9 yr in patients with BMD SDS greater than -2.

**Table 5.** A multivariable logistic regression model for decreased lumbar BMD <-2 SD after cancer treatment

| Variables | Odds ratio | 95% CI | *P* value |
|---|---|---|---|
| CA at diagnosis | 1.211 | 0.998-1.469 | 0.053 |
| Disease category* | 0.276 | 0.056-1.374 | 0.116 |
| Duration of GC use for GVHD | 1.124 | 1.052-1.200 | 0.001 |
| BMI SDS | 0.586 | 0.362-0.948 | 0.030 |

*AML in comparison with ALL group. SD, standard deviation; CA, chronological age; GC, glucocorticoid; BMI, body mass index; SDS, standard deviation score.

The characteristics of patients with LBMD SDS lower than -2 were that they had longer duration of GC treatment and lower BMI SDS. In adult cancer survivors, approximately 50% of the patients have osteopenia or osteoporosis (10). Similar to childhood cancer survivors, the risk of osteoporosis and fractures increases with increased GC dose and duration and low body weight in adult cancer survivors (11).

In our study, the risk of low BMD was higher in patients treated with GC. GCs affect bone directly, but also indirectly by altering hormonal axes, intestinal calcium absorption, and renal excretion of calcium (12). GCs decrease bone formation by promotion of apoptosis of osteocytes and osteoblasts, inhibiting osteoblast bone matrix synthesis, and decreasing proliferation and differentiation of periosteal precursor cells (13). GCs have a greater effect on trabecular bone than on cortical bone. Trabecular bone is more metabolically active and has a more rapid rate of turnover than cortical bone: and, thus may be more susceptible to the effects of cytotoxic agents (14). As such, the bone loss is faster, and fractures develop mainly in bones composed of trabecular bone, like vertebrae, ribs, and the ends of long bones. Young people who have a high rate of bone turnover are very susceptible to GC-mediated bone loss. Longitudinal studies have shown that the most rapid rate of bone loss occurs in the first six months of GC treatment and is similar in both the lumbar spine and the femoral neck (15). Furthermore the degree of GC-induced bone loss is related to average GC dose and to the duration of treatment (16). Longer duration of GC use was related to increased risk of fracture (17).

In our analysis, the patients treated with HSCT had a higher risk of having low BMD SDS. BMD is decreased after HSCT from the direct toxic effects of radiation therapy, chemotherapy as conditioning regimen, and gonadal and pituitary hormone secretion (18). While being treated with HSCT, the differentiation of bone marrow stromal cells into osteoblasts is impaired (19), and there is an increase in bone marrow interleukin-6, which is a bone resorption marker (20). After treatment with high-dose chemotherapy and radiation therapy, ovarian insufficiency can occur. Teinturier et al. (21) demonstrated that the high-dose busulfan seemed to be a major cause of ovarian failure even when given in the prepubertal period. High-dose cyclophosphamide shows a dose-dependent toxicity to bone marrow stromal osteoprogenitors and can cause osteopenia by directly damaging the osteoblastic compartment (19). Also, HSCT results in prolonged hospital stay, low activity, and GH deficiency after cranial radiation therapy (22).

Radiation therapy (RT) has important negative effects on skeletal growth in children and adolescents. RT on the central nerve system (CNS) or administered as part of total body irradiation (TBI) before HSCT may result in pituitary hormone deficiencies (23). Decreased growth hormone (GH) of the pituitary hormone leads to a decrease in the IGF-1/IGFBP-3 ratio. These effects of TBI on the somatotrope axis are harmful for bony growth, as the GH/IGF-1 system induces the proliferation of the epiphyseal growth plate until sex hormone-mediated epiphyseal closure occurs (24). The severity of the growth hormone deficiencies are related to the total radiation dose, the number of fractions, the time period of the radiation treatment, and whether the treatment was at early puberty (23). Consequently it is necessary to measure BMD when radiation is given for a longer duration and larger dose, or when treatment is given at early puberty, or rapidly progressing puberty.

Interestingly, in the patients having BMD SDS lower than -2 SD, the age at diagnosis with cancer (9.1 ± 3.5 yr) was close to the age of pubertal onset. Meanwhile, the patients having BMD SDS greater than -2 SD showed significantly younger age at diagnosis (6.9 ± 3.9 yr). BMD shows a rapid increase in adolescents and during puberty; and if bone growth is affected at this age, BMD is reduced rapidly. Also the gonads are more tolerant to chemotherapy and radiation in early childhood. If treated before puberty, the probability of osteoporosis is reduced due to the diminished risk for hypogonadism (25). Estrogen also plays a vital role in achieving maximal bone mass during puberty. If gonadal dysfunction occurs during puberty, the pubertal growth spurt fails to occur, and peak bone mass is reduced (26).

Nevertheless, the patients having hypogonadism did not show significantly low LBMD SDS (-1.15 ± 1.55 vs -0.18 ± 1.35, $P = 0.359$). It is unclear why BMD is less affected in patients with hypogonadism. As most of our patients with hypogonadism had undergone hormone therapy, the study did not reflect the impact of hypogonadism accurately (data not shown).

In our study, the duration of GC treatment before HSCT in ALL patients was longer than that for other diseases, but there was no difference in the duration of the GC treatment after HSCT among disease groups. In addition, there was no difference in BMD SDS among disease groups, and the disease category did not have a significant effect on decreased BMD SDS in multivariate logistic regression analysis. Therefore, decreased BMD SDS after HSCT was not affected by the duration of GC use before HSCT but rather affected by long-term treatment of GC for GVHD.

Positive correlation between BMD and body weight has been shown in different age groups (27). Likewise in our study, lower


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BMI SDS was associated with decreased LBMD SDS. It is well known low body weight increases the risk of low-energy fracture. Potentially beneficial effects of increased body weight may result from the increased mechanical load exerted on bone, which stimulates osteogenesis (28). Thus, the patients with lower BMI are more susceptible to osteopenia.

Although the effects of lean mass on bone included a strong positive effect on BMD, fat mass had a negative effect or did not affect BMD (29). Childhood obesity can cause various complications including psychosocial problems, hyperlipidemia, hepatic steatosis, and carbohydrate metabolism abnormality (25). As such, it is essential to maintain appropriate body weight and increase lean mass by physical activity and exercise.

Many cancer survivors have the additional risk factors of nutritional deficiency and side effects of treatment that result in altered calcium, 1, 25-dihydroxyvitamin D, and magnesium metabolism, as well as prolonged periods of hospitalization and immobilization (12). Survivors of ALL are less active physically than healthy controls, and lower activity correlates with lower lumbar BMD (4).

Sufficient dietary calcium intake and physical activity are essential to promote bone mineralization (10). Treatments of calcium, vitamin D, and exercise have been shown to have varying degrees of effectiveness. Likewise in our study, the patients treated for hypogonadism with hormone therapy or treated with calcium and vitamin D had less of a decrease in BMD SDS (data not shown). As such, patients with risk factors such as prolonged GC use, HSCT, treatment at puberty and lower BMI SDS should be considered for preventive strategies such as adequate calcium, vitamin D intake and increased weight bearing exercise as tolerated (12). In addition, bisphosphonate therapy has been used in the treatment and prevention of diminished BMD in adults undergoing BMT (10). In a study on children on chronic GC therapy with pathological fractures, pamidronate increased BMD, and decreased skeletal pain (30). Side effects of musculoskeletal pain, vomiting, esophagitis, and severe hypocalcemia must be considered in the use of bisphosphonates. Long-term controlled studies are needed to evaluate the risks and benefits of bisphosphonate treatment in children with osteoporosis (12).

There are some limitations to this study. BMD should be included at the time of initial hematologic diagnosis to see the impact of cancer therapy. Because leukemic cell invasion of bone may destroy the spongiosa (12), BMD at the initial diagnosis is also likely to be lower. Furthermore, in addition to measuring BMD, it is necessary to measure other bone turnover markers, such as type I procollagencarboxyterminal (PICP), aminoterminalpropeptide (PINP), and carboxy-terminal telopeptide of type 1 collagen (β-CTX), in order to observe the precise changes of bone metabolism. Thus, further study which includes BMD at initial diagnosis and evaluation of additional bone turnover markers is necessary.

In conclusion, prolonged GC use and reduction in BMI are risk factors for decreased BMD in childhood cancer survivors. Anticipatory follow-up and appropriate treatment are necessary, especially for the patients with risk factors. Early detection of patients at risk will allow early application of adequate preventive and therapeutic measures which may decrease morbidity.

## DISCLOSURE

The authors have no conflicts of interest to disclose.

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