

Review article

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Low bone mineral density in children and adolescents with cancer

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Maximizing accumulation of bone mass during childhood and adolescence is essential to attaining optimal peak bone mass. Childhood cancer survivors (CCS) have lower bone mineral density (BMD) than the general population. Chemotherapeutic agents including steroids and radiotherapy can affect BMD. Cancer itself, hormonal insufficiency, a poor nutritional state, and a deficit of physical activities during or after treatment also influence BMD in CCS, resulting in failure to achieve appropriate peak bone mass. Low BMD in childhood and adolescence can lead to osteoporosis in adult life and complications such as bone pain, bone deformity, and fractures. Thus, BMD in CCS should be monitored with appropriate intervention. Adequate intake of calcium and vitamin D and an increase in physical activity are recommended. Timely supplements of hormones are needed in some cases. Some publications have reported that bisphosphonate therapies using pamidronate or alendronate were well tolerated in CCS and helped increase BMD.

Keywords: Peak bone mass, Childhood cancer survivors, Bone mineral density

Introduction

As the survival rates of childhood cancer increase, there has been a substantial increase in the number of children and adolescents with chronic complications. Survivors of childhood cancer are at risk for late adverse effects of cancer treatment. Endocrine and metabolic and skeletal sequelae are described in 50% of childhood cancer survivors (CCS).¹⁾ CCS have increased risk of low bone mineral density (BMD) because cancer treatments interfere with gains in BMD. Previous studies have included small numbers of cases, various age groups, heterogeneous treatments, different sites of BMD measurement, and different definitions of low BMD.²⁻⁴⁾ The terminology and definitions of low BMD in CCS are diverse. The World Health Organization's (WHO) definitions of osteopenia and osteoporosis are based on T-scores, which are used to compare patient BMD with the maximum BMD of young adults, applying only to postmenopausal women. Some have defined a z-score < -1.0 as osteopenia (low BMD) and < -2.5 as osteoporosis (significantly low BMD).^{5,6)} The International Society for Clinical Densitometry (ISCD) recommends the use of "low BMD for chronological age" when the BMD z-score is lower than -2.0.⁷⁾ Last updated in 2019, diagnosis of osteoporosis in children and adolescents requires the presence of both a clinically significant fracture history and BMD z-score less than or equal to -2.0. Vertebral compression fractures without local disease or high-energy trauma are also indicative of osteoporosis.⁸⁾ Osteoporosis in adulthood has its origins in childhood and adolescence, which is an important period for optimizing peak bone mass (PBM),⁹⁾ which is the maximum amount of bone a person has during their lifetime and a crucial determinant of osteoporotic fracture risk.¹⁰⁾ A considerable part of PBM is determined by genetic factors. CCS fail to achieve PBM due to cancer itself, chemotherapy, malnutrition, and decreased activity. Low BMD in childhood and adolescents is a risk factor

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for fractures in youth and osteoporosis later in life.¹¹⁾ In this article, we address the causes, prevalence, and management of low BMD in children and adolescents with cancer.

Causative factors of low BMD in children and adolescents with cancer

Cancer itself causes BMD deficits. Low BMD at the time of diagnosis of pediatric cancer was primarily reported in patients with acute lymphoblastic leukemia (ALL)^{12,13)} and neuroblastoma.¹⁴⁾ Leukemic cell proliferation in the bone marrow and cytokine-mediated osteoclast activity are suggested as causes of low BMD.¹²⁾ Patients with primary bone tumors, including osteosarcoma and Ewing sarcoma, have low BMD in the affected sites.¹⁵⁻¹⁷⁾

Effects of chemotherapeutic agents on bone metabolism have been widely studied. The agents most frequently used to treat pediatric cancer are corticosteroids, alkylating agents, antimetabolites, and antibiotics. Corticosteroids inhibit the activity of osteoblasts and osteocytes, resulting in decreased bone formation and repair of microdamaged bones. Moreover, corticosteroids increase osteoclastic bone resorption and inhibit 1 α -hydroxylation of vitamin D.¹⁸⁾ In patients with ALL, those receiving a total corticosteroid dose greater than 9 g/m² were more likely to have decreased BMD that did not recover after completing chemotherapy.¹⁹⁾ In patients with malignant lymphoma, prednisone dose greater than 20 g/m² is a risk factor for osteopenia.⁵⁾

Patients with ovary or testis tumors are at risk of primary hypogonadism, affecting BMD. Alkylating agents, such as cyclophosphamide and ifosfamide, also cause primary hypogonadism and result in BMD deficits.²⁰⁾ Estrogen and androgens influence the growth and maintenance of bone.²¹⁾ Estrogen has a role in attaining PBM in both sexes.²¹⁾ Androgens enlarge the cross-sectional area of long bones and increase mechanical strength.²¹⁾ Doses of alkylating agents are closely related to degree of gonadal impairment. A CCS study developed a method to combine and compare cumulative doses of different alkylating agents using cyclophosphamide equivalent dose (CED).²²⁾ The St. Jude Lifetime Cohort study reported that high-dose alkylating agents (CED \geq 80 g/m²) and ovarian radiotherapy at any dose are associated with premature ovarian insufficiency.²³⁾ For males, testicular radiotherapy at any dose and exposure to alkylating agents (CED \geq 40 g/m²) were independent risk factors for Leydig cell failure, defined as testosterone <250 ng/dL and luteinizing hormone >9.85 IU/L.²⁴⁾ Methotrexate has a cytotoxic effect on the activity of osteoblasts and stimulates osteoclasts recruitment. It has been reported that a total cumulative dose greater than 4 g/m² was associated with failure to recover to a normal BMD after completion of chemotherapy.^{15,19)} In contrast, a recent study demonstrated that methotrexate exposure is not an independent risk factor for a significant decrease in BMD (z -score \leq -2). It is suggested that methotrexate lowers BMD but does not present a significant

risk for z -score \leq -2.²⁵⁾

Hematopoietic stem cell transplantation (HSCT) also affects BMD. Bone loss occurred and continued frequently in the first year following allogeneic HSCT.²⁶⁾ At 6 months after HSCT, nearly 50% of patients had osteopenia (T-score \leq -1) at the femoral neck or lumbar spine.²⁷⁾ Approximately 1/3 of patients who had undergone allogeneic HSCT in childhood had reduced BMD before reaching adulthood, with a high prevalence of asymptomatic vertebral compression fractures.²⁸⁾ Pediatric patients with solid tumors (osteosarcoma, Ewing sarcoma, neuroblastoma) who underwent autologous HSCT showed a significant decrease in whole-body BMD z -score.²⁹⁾ Multiple factors are involved in the pathogenesis of bone loss following HSCT, including impairment of gonadal and pituitary hormone secretion by high-dose chemotherapy, immobilization, poor oral intake, vitamin D deficiency, and use of calcineurin inhibitors and corticosteroids for graft-versus-host disease.²⁶⁾ High-dose chemotherapy for HSCT shows dose-dependent toxicity on bone marrow stromal osteoprogenitors.³⁰⁾ Patients who underwent HSCT at a younger age and allogeneic HSCT had a significantly higher risk of low BMD of the spine.^{31,32)}

Endocrine sequelae resulting from radiotherapy cause a significant decrease in BMD. Negative effects of radiotherapy on BMD have been frequently reported in children with brain tumors. Patients with a tumor in the sellar or suprasellar region such as craniopharyngioma, germinoma, or low-grade glioma are highly likely to develop growth hormone (GH) deficiency or central hypogonadism.²⁰⁾ Radiation at the hypothalamic-pituitary axis and total body irradiation (TBI) can lead to GH deficiency, affecting bone growth and BMD.^{1,2,33)} GH and insulin-like growth factor I are important for maintaining bone mass because both independently contribute to bone remodeling and apposition.³⁴⁾ The severity of GH deficiency depends on patient age, dose, and fraction of radiation. A young age, higher radiation dose (\geq 18 Gy), pretransplant radiation, TBI \geq 10 Gy in a single fraction, and TBI \geq 12 Gy fractionated increase the risk of GH deficiency.³⁵⁾ Gonadotropin deficiency occurs in patients who received TBI \geq 30 Gy at the brain and may occur in those who received lower radiation doses with longer follow-up.³⁵⁾ In addition to hormonal effects, radiation directly affects bone health at the local site of exposure and results in abnormalities in bone growth and an increased risk of fractures.^{36,37)}

Nutrition and physical activity are essential to obtaining PBM.³⁸⁾ In childhood cancer patients, physical activities are decreased due to prolonged periods of hospitalization and surgery, causing bone resorption and negatively affecting BMD.³⁹⁾ In a study with survivors of ALL, reduced exercise capacity was associated with reduced spine BMD.³⁹⁾

Prevalence of low BMD in childhood cancer

The prevalence of low BMD among CCS ranges from 9%–51%.²⁻⁴⁾ Multiple factors contribute to development of low BMD in patients with cancer, as described above. In a collaborative

cohort study of St. Jude and Dutch CCS, shorter height, lower weight, younger attained age, use of alkylating agent, and prior exposure to cranial and abdominal irradiation were closely related with low BMD (z -score \leq -1).⁴⁾ In children with cancer, treatments affect bone health during the first year, causing a significant decrease in BMD. BMD decreased during the first 6 months in patients with leukemia or lymphoma and during the latter 6 months of therapy for those with solid tumors.²⁹⁾ Thus, the prevalence of low BMD depends on subject risk factors and assessment timing of BMD. Nevertheless, decreased BMD is a common finding in survivors of leukemia, lymphoma, brain tumors, solid tumors, and those who undergo HSCT (Table 1).

ALL and lymphoma

At the time of diagnosis, significantly reduced BMD (z -score: -0.60 ± 1.55) was observed at the lumbar spine.¹²⁾ Chemotherapy for ALL includes corticosteroids and methotrexate, and a decrease in BMD occurs during chemotherapy. In a study of childhood leukemia and lymphoma survivors, lumbar spine BMD was low (z -score $<$ -1) in 17.2% of subjects.⁴⁰⁾ Also, 10.8% of survivors aged 15–19 years at diagnosis had very low BMD (z -score $<$ -2), indicating that those of an older age were at high risk for low BMD.⁴⁰⁾ A pharmacogenetic study evaluated the influence of single nucleotide polymorphisms in 4 genes (i.e., vitamin D receptor, collagen type I alpha 1, estrogen receptor 1, and glucocorticoid receptor) on body composition, BMD, and fracture risk. The vitamin D receptor gene (*VDR*) 5'-end (Cdx-2/GATA) haplotype 3 was a risk factor for lower lumbar spine BMD during treatment of pediatric ALL.⁴¹⁾ In children with ALL, skeletal complications, such as bone pain, osteonecrosis, fracture, loss of mobility, bone deformation, and osteopenia, have been frequently reported during or after treatment.⁴²⁾ Osteonecrosis is the best known skeletal complication, but fractures and bone pain are also frequent. In a case series of 122 pediatric patients with ALL, the 5-year incidence of fractures and bone pain was 13.5% and 12.3%, respectively.⁴²⁾

BMD was decreased in long-term survivors of Hodgkin disease and non-Hodgkin lymphoma. A BMD z -score $<$ -1.0 was reported in 41% of patients with Hodgkin disease and 50% of

patients with non-Hodgkin lymphoma at the lumbar spine after 24.1 and 14.1 years of follow-up, respectively.^{5,43)} In addition to high cumulative dose of corticosteroid, mechlorethamine, vincristine, and procarbazine for treating malignant lymphoma also cause low BMD.⁵⁾

Brain and other solid tumors

Low BMD is a common finding among brain tumor patients treated in childhood.^{33,44)} Causes of low BMD are multifactorial, including craniospinal irradiation, GH deficiency, massive corticosteroids doses, and use of alkylating agents. Researchers have found that 23.6%–33% of patients with brain tumors treated in childhood had reduced BMD, with a total body BMD z -score $<$ -2.0.^{33,44)} In a case series of 28 intracranial germ cell tumor survivors, the prevalence of osteoporosis and osteopenia was 25.0% and 42.9%, respectively. In addition to radiation, risk factors included male sex, a low lean mass, and adult GH replacement.⁴⁵⁾

Low BMD was reported in survivors of various other solid tumors. Ten of 48 long-term survivors of highly malignant osteosarcoma were osteoporotic, and 21 of 48 were osteopenic, according to the WHO definition.¹⁵⁾ Reduced lumbar BMD (z -score $<$ -1.0) was also reported in 28.3%–43.6% of survivors of osteosarcoma or Ewing sarcoma.^{16,17)} In a Korean study evaluating the BMD of 9 osteosarcoma patients before and after treatment, 44% showed decreased lumbar BMD and 78% showed decreased femur neck BMD after adjuvant chemotherapy, while all 8 healthy controls showed increased lumbar and femur BMD.⁴⁶⁾ Young age at diagnosis, male sex, and decreased lean mass are risk factors of osteoporosis in long-term survivors of osteosarcoma.⁴⁷⁾ In children with neuroblastoma, three of 27 patients showed low lumbar BMD (z -score $<$ -2.0) at the time of diagnosis, necessitating BMD assessment during the early course of the disease.¹⁴⁾ The incidence of osteopenia (z -score $<$ -1.0) was 27% in long-term survivors of Wilms tumor.⁴⁸⁾

Table 1. Korean data on low BMD in childhood cancer survivors

Cancer type	No. of cases	Sex	Age at cancer diagnosis (yr)	Age at BMD exam (yr)	BMD
Intracranial germ cell tumor ⁴⁵⁾	28	13 M 15 F	11.5 \pm 2.4	23.1 \pm 4.4	Osteoporosis* in 25.0% (n=7) Osteopenia* in 42.9% (n=12)
Osteosarcoma ⁴⁷⁾	40	22 M 18 F	15.9 \pm 3.5 13.9 \pm 5.1	22.4 \pm 4.4 21.2 \pm 6.0	Osteoporosis* in 47.5% (n=19) Osteopenia* in 30.0% (n=12)
Hematologic malignancy & solid tumors ⁵⁸⁾	108	73 M 35 F	8.9 \pm 4.7	20.3 \pm 3.0	z -score $<$ -2.0 in 16.7% (n=18) $-2.0 \leq z$ -score $<$ -1.0 in 26.1% (n=39)
Hematologic malignancy (ALL, AML, CML) ⁵⁹⁾	78	34 M 44 F	7.2 \pm 3.8 7.7 \pm 3.9	11.6 \pm 3.4 13.0 \pm 3.3	z -score $<$ -2 in 25.7% (n=20)

BMD, bone mineral density; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; CML, chronic myeloblastic leukemia. *Definition were as follows; (1) osteoporosis: BMD T-score measured at spine, femur neck, or total body $<$ -2.5 (\geq 20 years), z -score $<$ -2.0 ($<$ 20 years), (2) osteopenia: $-2.5 \leq$ T-score $<$ -1.0 (\geq 20 years), $-2.0 \leq z$ -score $<$ -1.0 ($<$ 20 years).

Management of CCS with low BMD

1. Children's Oncology Group guideline

The 2018 Children's Oncology Group guideline defined reduced BMD as a z-score > 2.0 standard deviation (SD) below the mean in survivors < 20 years old or a T-score > 1.0 SD below the mean in survivors ≥ 20 years old.³⁵⁾ It is recommended that patients at risk of reduced BMD undergo baseline BMD evaluation at entry into long-term follow-up (Table 2). Including those at risk, all CCS should undergo prophylaxis for bone loss and fractures. Adequate intake of calcium (500–1,200 mg/day

depending on age), vitamin D (at least 400 units), and physical activities are suggested as measures to improve bone health of CCS.³⁵⁾ Regular weight-bearing exercise, such as brisk walking, dancing, hopping, jogging, and jumping, and adequate sunlight exposure are also recommended to improve BMD.³⁵⁾ In a 1-year prospective study, a significant increase in total body BMD was observed in children with ALL during the first 3 years after completion of therapy, suggesting the positive effect of long-term completion therapy and increase in physical activity.⁴⁹⁾ However, most Korean children and adolescents are not achieving the recommended dietary intake of calcium and vitamin D.⁵⁰⁾ Thus, lifestyle modification should be encouraged

Table 2. Long-term follow-up guideline for childhood cancer survivors who are at risk of reduced BMD

Therapeutic exposure	Potential late effects	Periodic evaluation
Chemotherapy		
Methotrexate IV (high* or low dose)/IM/PO	Reduced BMD	Bone density evaluation (DXA) Adjust for height-age z-score in survivors < age 20 years Baseline at entry into long-term follow-up, repeat as clinically indicated.
Corticosteroids Dexamethasone Prednisone		
Hematopoietic stem cell transplantation		
Radiotherapy		
Head/brain Total body irradiation	GH deficiency	History Assessment of nutritional status (every 6 months until growth is completed, then yearly) Physical Tanner staging (every 6 months until sexually mature) Height/weight/BMI (every 6 months until growth is completed, then yearly)
	Gonadotropin deficiency	History Onset and tempo of puberty Sexual function Medication use (yearly) Physical Tanner staging until sexually mature Testicular volume (yearly) Monitor growth until mature (yearly)
Testis	Testicular hormonal dysfunction	History Onset and tempo of puberty Sexual function Medication use (yearly) Physical Tanner staging until sexually mature Testicular volume (yearly) Monitor growth until mature (yearly)
Pelvis Spine (whole/sacrum) Total body irradiation	Ovarian hormone deficiency	History Onset and tempo of puberty Menstrual history Sexual function Menopausal symptoms Medication use (yearly) Physical Tanner staging until sexually mature Monitor growth until mature (yearly)

BMD, bone mineral density; IV, intravenous; IM, intramuscular; PO, peroral; DXA, dual energy x-ray absorptiometry; GH, growth hormone; BMI, body mass index.

*Any single dose ≥ 1 g/m².

in CCS.

2. Bisphosphonates in pediatric cancer patients

Bisphosphonates (BPs) inhibit bone resorption and have been used to treat osteoporosis. The efficacy of BPs was demonstrated in pediatric patients with osteogenesis imperfecta, quadriplegic cerebral palsy, and juvenile rheumatoid arthritis. As in adults, CCS with low BMD are candidates for BPs therapy. For children receiving chemotherapy, the safety and efficacy of BPs are particularly important. Several case series reported the efficacy of BPs on osteoporosis or osteopenia in children with cancer (Table 3). Intravenous infusion of pamidronate increased bone mineral content and alleviated bone pain of pediatric patients with osteosarcoma⁵¹⁾ and ALL.⁵²⁻⁵⁴⁾ Pamidronate was well tolerated, with few episodes of fever, pain, or symptomatic hypocalcemia. However, the biggest concern is possible interaction of BPs with chemotherapeutic agents. Pamidronate administered with standard chemotherapy was reported to be safe and effective in pediatric patients with ALL and non-Hodgkin lymphoma.⁵²⁻⁵⁴⁾ The Memorial Sloan Kettering Cancer Center conducted a clinical trial testing the efficacy and safety of pamidronate for osteosarcoma patients.⁵⁵⁾ Pamidronate was administered with combination chemotherapy comprising high-dose methotrexate, cisplatin, and doxorubicin. Survival analysis showed that pamidronate did not impair the efficacy of chemotherapy and might improve the durability of limb reconstruction.⁵⁵⁾ In a cohort of 19 pediatric cancer patients, zoledronate was administered safely and appeared to result in improved bone strength and pain control.⁵⁶⁾ Limited data are available on the use of BPs in children after HSCT. In 19 children with chronic graft-versus-host disease after HSCT, BPs improved BMD.⁵⁷⁾

Conclusion

Low BMD is prevalent among CCS diagnosed with different types of cancer. Therapeutic modalities affecting BMD are essential for treating cancer. Thus, periodic evaluations of BMD in CCS should be performed. We need to pay more attention to CCS with many risk factors for reduced BMD, and proper management is needed during therapy as well as after cessation of treatment. Moreover, long-term follow-up is necessary to maintain bone health after cancer treatment. Further studies are required to analyze the efficacy and safety of medication.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Table 3. Bisphosphonates treatments in pediatric cancer patients

Study	Disease	No. of cases	Bisphosphonates	Changes of BMD z-score
Lim et al. ⁵¹⁾ (2016)	Osteosarcoma	9	Pamidronate	Lumbar spine +0.108±0.062
Barr et al. ⁵²⁾ (2002)	Acute lymphoblastic leukemia	10	Pamidronate	Total body +0.96, Lumbar spine +1.11
Goldbloom et al. ⁵³⁾ (2005)	Acute lymphoblastic leukemia	2	Pamidronate	Total body +0.7/+1.02 at 20 months
Lee et al. ⁵⁴⁾ (2013)	Acute lymphoblastic leukemia Non-Hodgkin lymphoma	24	Pamidronate	Lumbar spine +2.06
Meyers et al. ⁵⁵⁾ (2011)	Osteosarcoma	40	Pamidronate	NA
August et al. ⁵⁶⁾ (2011)	Neuroblastoma, osteosarcoma Ewing sarcoma Undifferentiated sarcoma DSRCT, Rhabdoid tumor Primitive neuroectodermal tumor Rhabdomyosarcoma	19	Zoledronate	NA
Carpenter et al. ⁵⁷⁾ (2007)	Who received HSCT	18	Various	+1.77
Lethaby et al. ⁶⁰⁾ (2007)	Acute lymphoblastic leukemia	15	Alendronate	Lumbar spine +0.64
Wiernikowski et al. ⁶¹⁾ (2005)	Acute lymphoblastic leukemia Non-Hodgkin lymphoma	10	Alendronate	Lumbar spine +0.51 Total body bone mineral content +0.49

BMD, bone mineral density; NA, not available; DSRCT, desmoplastic small round cell tumor; HSCT, hematopoietic stem cell transplantation

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