Mini Review

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Skeletal Morbidity in Children and Adolescents during and following Cancer Therapy

Sogol Mostoufi-Moab[a] Leanne M. Ward[b]

[a]Department of Pediatrics, The Children's Hospital of Philadelphia, The University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; [b]Department of Pediatrics, The Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada

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Abstract
Skeletal abnormalities are common in children and adolescents diagnosed and treated for a malignancy. The spectrum ranges from mild pain to debilitating osteonecrosis and fractures. In this review, we summarize the impact of cancer therapy on the developing skeleton, provide an update on therapeutic strategies for prevention and treatment, and discuss the most recent advances in musculoskeletal research. Early recognition of skeletal abnormalities and strategies to optimize bone health are essential to prevent long-term skeletal sequelae and diminished quality of life in childhood cancer survivors.

Introduction

Risk-directed therapy has substantially improved treatment outcomes for pediatric cancer, and almost 85% of children diagnosed with a malignancy will become long-term survivors [1]. This success relies on treatments with significant potential for long-term toxicities. High-risk cancer survivors for skeletal morbidity include survivors of pediatric acute lymphoblastic leukemia (ALL), brain tumors, and allogeneic hematopoietic stem cell transplantation (HSCT), and any malignancy with significant glucocorticoid (GC) exposure [2–5]. Importantly, given extended survivor follow-up, improved understanding of cancer biology, and availability of alternative treatment strategies, prompt recognition of treatment-associated complications in developing organs, such as the musculoskeletal system, becomes increasingly relevant for providers addressing the management and prevention of bone toxicity in childhood cancer survivors (CCS).

The skeleton is a 3-dimensional organ that consists of cortical geometry and density components, each with relative contributions to bone strength. Imaging techniques such as peripheral quantitative computed tomography (QCT) and magnetic resonance imaging (MRI) can assess bone cross-sections and provide insight as to the relative contributions of bone cross-sectional geometry and density to bone strength [6]. Skeletal development in childhood is characterized by sex-, maturation-, and race-specific increases in trabecular and cortical bone mineral density (BMD) and cortical dimensions [7]. These rapid

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E-Mail karger@karger.com
www.karger.com/hrp

Sogol Mostoufi-Moab, MD, MSCE
The Children's Hospital of Philadelphia
2716 South Street, 14th Floor
Philadelphia, PA 19146 (USA)
E-Mail moab@email.chop.edu

accumulations of bone mass and changes in bone shape (modeling) are dependent on the coordinated actions of growth hormone (GH) and sex steroids in the setting of adequate biomechanical loading and nutrition [8]. Biomechanical loading by the muscle, also known as the functional "muscle-bone unit," plays a critical role in the expansion of cortical dimensions during this period. Thus, the growing skeleton is particularly vulnerable to the effects of childhood cancer therapies (such as chemotherapy and radiation) and complications that interfere with skeletal metabolism, and this may result in muscle deficits or poor muscle function.

Musculoskeletal abnormalities can be recognized at the time of cancer diagnosis (particularly in children diagnosed with ALL), during treatment, and/or persist as long-term sequelae after treatment. For example, the radiological abnormalities attributed to the leukemia process can occur in up to 70% of children at the time of ALL diagnosis [9]. Osteotoxic chemotherapy, prolonged treatment with GC, poor nutrition, vitamin D insufficiency, and poor muscle mass are recognized risk factors that contribute to bone pathology during and subsequent to cancer therapy, resulting in negative skeletal outcomes such as osteoporosis, long bone and vertebral fractures, and osteonecrosis (ON). In children after HSCT and/or cranial radiation, evolving endocrine disorders further impact skeletal morbidity and compound survivor quality of life due to pain and compromised mobility. Despite recognized musculoskeletal abnormalities in cancer survivors, there are limited consensus guidelines for the assessment and treatment of skeletal morbidity after cancer therapy. This limitation is further impacted by a lack of long-term follow-up studies dedicated to evaluating and addressing bone sequelae of childhood cancer therapy. In this review article, we will focus on substantial advancement over the past few decades in the knowledge of bone pathogenesis and skeletal morbidity in childhood leukemia patients and other pediatric cancer survivors.

Osteoporosis, Fracture Risk, and Recovery in ALL

Based on the International Society of Clinical Densitometry (ISCD), in the absence of vertebral compression fractures, the diagnosis of osteoporosis in pediatrics is indicated by the presence of both a clinically significant fracture history and BMD Z score ≤–2.0. The ISCD defines a clinically significant fracture history as (1) two or more long bone fractures by the age of 10 years and (2) three or more long bone fractures at any age up to 19 years [10]. Dual energy X-ray absorptiometry (DXA) is a 2-dimensional technique by which bone is presented as the combined sum of cortical and trabecular bone within the projected bone area. As bone depth is not factored into DXA results, reliance on BMD systematically underestimates bone density in shorter individuals. This limitation is of paramount importance in children and adolescents with chronic disorders complicated by poor growth [11]. For example, in children treated with GC, one could falsely attribute the decreased areal BMD (aBMD) as evidence for osteopenia, rather than GC-associated reductions in linear growth. The greatest challenge in interpreting pediatric DXA measurements includes the selection of an optimal method to adjust for the influence of bone size as both bone mineral content (BMC) and aBMD are highly influenced by skeletal dimensions. Zemel et al. [11] demonstrated that spine whole body BMC/aBMD Z scores adjusted for height-for-age Z scores (HAZ) were least biased compared with height age or chronological age. Thus, adjustment for height-for-age Z scores is an effective way of adjusting for the effect of height on DXA BMC/aBMD measurements. The current standard for reporting DXA results is the aBMD Z score, which provides an estimate of the standard deviation(s) away from the mean for chronological age and sex [12, 13]. However, other mathematical models of estimating volumetric BMD have been proposed to circumvent the confounding effects of bone size on DXA measurements of bone mass. One of the most commonly used methods is bone mineral apparent density, which assumes that a vertebral body is shaped like a cube [14].

Bone morbidity in childhood ALL falls into two broad categories: systemic bone disease (osteoporosis, defined as low-trauma fractures with reductions in BMD parameters) and focal bone morbidity (namely ON, discussed in a subsequent section). This section will focus on osteoporosis, which manifests as vertebral and nonvertebral low-trauma fractures.

Our understanding of the frequency, timing, and predictors of fragility fractures, along with the potential for spontaneous (i.e., medication-unassisted) recovery from osteoporosis has largely stemmed from a Canadian multicenter observational cohort study of children with ALL followed for 6 years from diagnosis through the STeroid-induced Osteoporosis in the Pediatric Population (STOPP) research program. By studying STOPP's representative cohort of more than 180 children with ALL over 6 years from diagnosis, a number of striking findings were apparent [5, 15–17]. First, vertebral fractures were a more common manifestation of osteoporosis than nonverte-

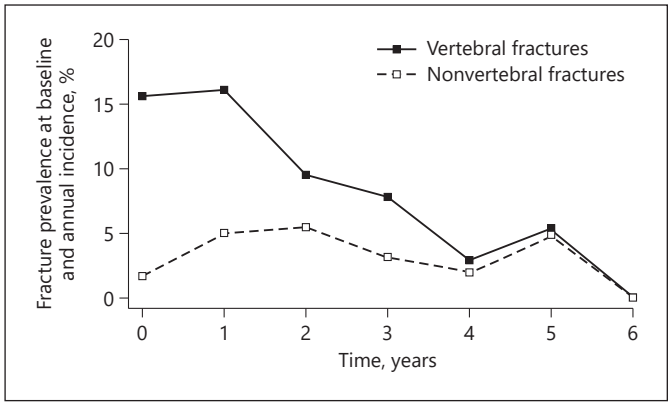

Fig. 1. The baseline prevalence and annual incidence proportions of vertebral and nonvertebral fractures in the 6 years following leukemia diagnosis. Reproduced with permission [11]. Copyright © 2018 *Journal of Bone and Mineral Research*.

bral fractures, occurring in 16% of children at or within a month of diagnosis. The annual incidence of new vertebral fractures peaked at 12 months (with a 16% incidence at this time point), followed by a progressive decline in the frequency of new spine fractures. Low-trauma nonvertebral fractures (radius, hands and feet, and tibia fractures being the most common) were most frequent in the first 2 years following diagnosis. Overall, 36% of children had at least one vertebral or nonvertebral fracture over the observation period, and nearly three quarters of the fractures occurred in the first 2 years. One of the seminal observations arising from this longitudinal study was that vertebral fractures were frequently asymptomatic (up to 45% of children with spine fractures at baseline did not have back pain), yet both symptomatic and asymptomatic vertebral fractures at baseline were highly predictive of future fractures, a phenomenon known in adults as "the vertebral fracture cascade" [18].

Between 4 and 5 years following diagnosis (at which time the vast majority of children were off chemotherapy), there was a slight rise in the incidence of vertebral and nonvertebral fractures, followed by a complete absence of fractures between 5 and 6 years (Fig. 1). A study by the current review's first author has recently shed light on a possible explanation for this natural history observation [3]. Using peripheral QCT at the tibia, initial increases in cortical dimensions following chemotherapy cessation were associated with declines in cortical BMD in pediatric ALL. Twelve months later, cortical dimensions had stabilized and increases in cortical BMD were then observed. These findings suggest that the lag between increases in cortical dimensions and increases in cortical BMD likely reflected the recovery time needed to mineralize newly formed bone arising from the growth process and may explain the period of relative bone fragility observed following chemotherapy cessation.

With these natural history observations in hand, the STOPP Consortium then sought to determine the predictors of incident vertebral and long bone fractures and the factors that influence recovery from osteoporosis. The most robust predictor of both incident vertebral and nonvertebral fractures was the presence of vertebral fractures at baseline (eightfold increased risk of a subsequent new vertebral fracture and a fourfold increased risk of a subsequent new nonvertebral fracture, if vertebral fractures were present around the time of diagnosis). Greater average daily GC exposure was also a potent risk factor. Spine BMD Z score at baseline was a risk factor but less strongly so, with only 55 and 85% increased risks of incident vertebral and nonvertebral fractures, respectively, for every 1 SD reduction in spine BMD Z score. These observations speak to the importance of understanding the skeletal phenotype around the time of leukemia diagnosis, in order to predict which children will go on to sustain fragility fractures during and following chemotherapy.

As a final step, in order to understand which children should be targeted for future osteoporosis prevention and intervention trials (which are currently lacking in pediatric ALL), the STOPP Consortium studied the potential for recovery from osteoporotic fractures. Reshaping to achieve normal vertebral dimensions following vertebral fractures is a uniquely growth-dependent phenomenon (called bone modeling), one that is not possible following epiphyseal fusion. Therefore, the "growing years" provide a unique window of opportunity to not only reclaim bone mass and density, but also restore normal vertebral morphometry. By 6 years following diagnosis, 77% of children with prior vertebral fractures had partial or absent vertebral body reshaping [17]. As shown in Figure 2, those without complete reshaping were older and had severer vertebral collapse at the time of diagnosis (as measured by the Spinal Deformity Index, which is the sum of the number and severity of vertebral fractures as determined by the Genant semiquantitative method) [19]. On the other hand, there was no difference in spine BMD Z scores between those with and without complete vertebral body reshaping. These epidemiological observations were indeed logical, since vertebral body reshaping is a process that takes place over years; it follows then that those with severer collapse and those who were older

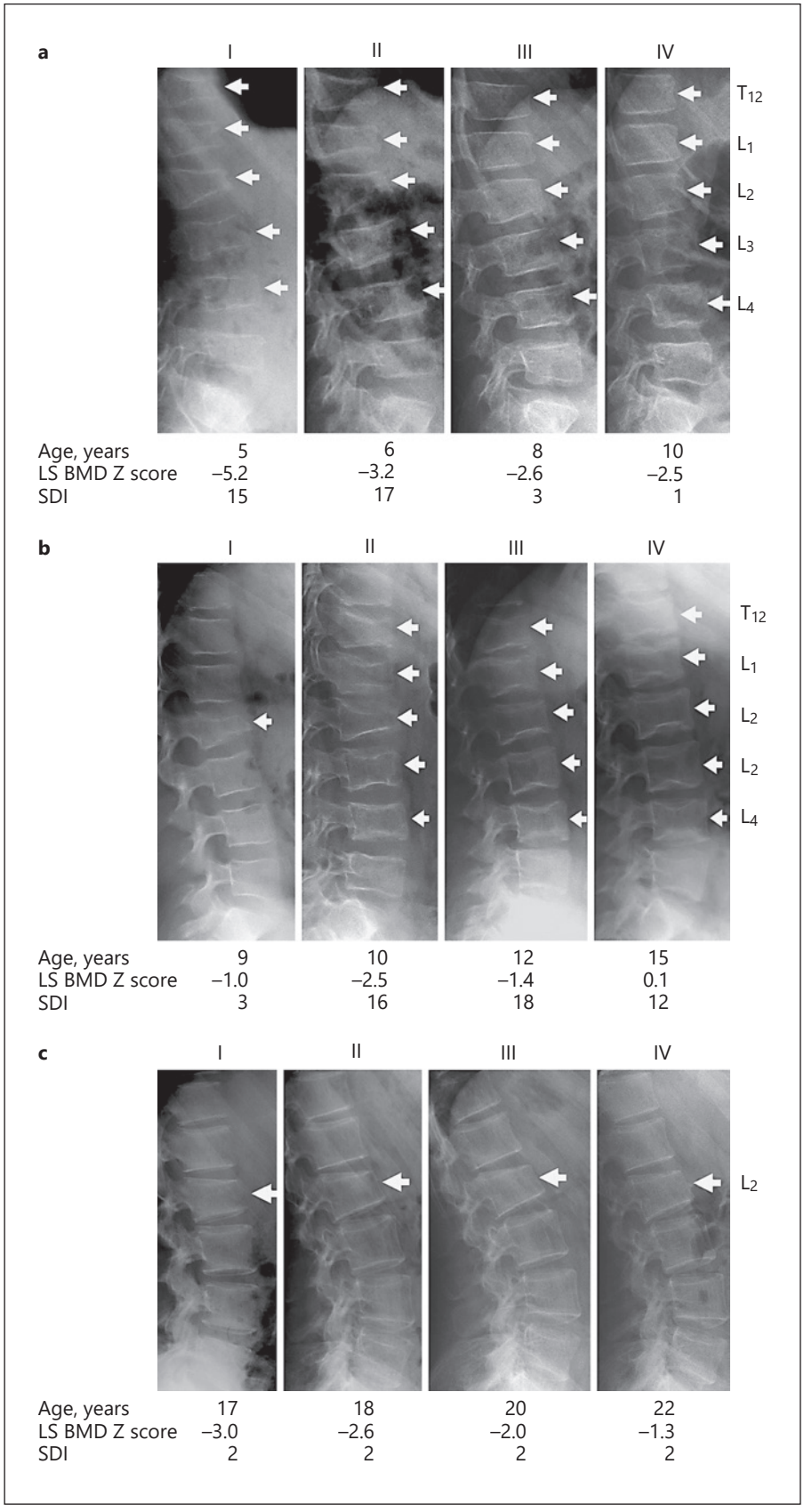

Fig. 2. Lateral spine radiographs from children with ALL and vertebral fractures. While clinically significant increases in spine BMD Z scores were observed in all 3 patients, vertebral body reshaping was incomplete or absent in 2 of the 3 patients, as follows. **a** Complete vertebral body reshaping: lateral lumbar spine radiographs from a 5-year-old boy with pre-B cell ALL who presented at diagnosis with multiple vertebral fractures (I). Subsequent films showed progressive vertebral body reshaping (II, III), with complete reshaping at 5 years after diagnosis (IV). **b** Incomplete vertebral body reshaping: lateral lumbar spine radiographs from a 9-year-old girl with pre-B cell ALL who presented with a severe vertebral fracture at L_2 at baseline (I), incident vertebral fractures at 12 months at T_{12}–L_4 (II), and incomplete vertebral body reshaping despite improvements in BMD Z scores at 12 and 15 years of age (III and IV). **c** Absent vertebral body reshaping: lateral lumbar spine radiographs from a 17-year-old boy with pre-B cell ALL who presented with a moderate vertebral fracture at L_2 at baseline (I) and absent vertebral body reshaping at subsequent time points (II–IV). LS BMD, lumbar spine bone mineral density; SDI, spinal deformity index from T_4 to L_4. Reproduced with permission [11]. Copyright © 2018 *Journal of Bone and Mineral Research*.

would have less potential for recovery from fractures due to insufficient residual growth potential.

What are the clinical implications of these findings? Most importantly, these findings indicate that to understand a child's risk of future fractures, regardless of skeletal site, the most important diagnostic test is a spine radiograph around the time of diagnosis. Among the children with early evidence for spine fragility, those who are older (peripubertal) and have more vertebral collapse are less likely to reshape vertebral bodies – these are the children who should be prioritized in much-needed osteoporosis prevention and intervention trials. Future trials in childhood, with the goal to prevent permanent vertebral deformity later in life, are motivated by studies showing that adults with residual vertebral deformity following fracture have chronic back pain and functional limitation [20, 21].

As vertebral compression fractures are often asymptomatic, early detection of vertebral fractures in ALL patients remains essential for timely clinical management. To date, early detection of vertebral fractures has relied largely on spinal radiographic assessment, resulting in high radiation exposures (150–300 μSv). Vertebral fracture assessment by DXA is a proven clinical tool for diagnosing vertebral deformities and fractures [22]. Since DXA vertebral fracture assessment can be performed at substantially lower radiation doses (10–40 μSv), this useful technology offers a practical and reliable method for the identification of clinically relevant vertebral fractures in children in lieu of conventional radiography of the spine [23].

What can be done in the meantime? There are no controlled trials of osteoporosis-specific drugs to prevent or treat osteoporosis in pediatric ALL. A controlled study addressing nutrition was undertaken by Kaste et al. [24], who showed no added benefit from calcium and vitamin D supplementation over routine nutritional counseling to BMD development in pediatric ALL. A class of agents which holds promise includes bisphosphonates, potent antiresorptive agents that have been used in the adult cancer patient setting, as well as in pediatric leukemia to treat advanced vertebral compression and ON on compassionate grounds [25–27]. In the absence of controlled trials addressing the risks and benefits of bone-targeted therapy such as bisphosphonates, the current standard of care is to encourage weight-bearing within the limits of the illness, identify and treat endocrinopathies in a timely manner, and reserve bisphosphonates for children with ALL who have significant, persistent quality-of-life-limiting back or bone pain.

Long-Term Skeletal Impact of Hematopoietic Stem Cell Transplantation

Prevalence, or total number of cases in a given population, measures burden of disease irrespective of time or exposure to identified risk factors for disease of interest. The true prevalence of fractures after childhood HSCT is not known, and only a few studies to date have actually examined the prevalence of fracture rates in long-term pediatric HSCT recipients [3, 28]. While an increased prevalence of fractures compared to normative age in the pediatric population is not reported in long-term survivors of childhood HSCT, most studies to date are limited by cross-sectional design and the use of self-report for identifying fractures. Therefore, the true prevalence or incidence (the number of new fractures over a defined time period) of clinically asymptomatic fractures remains poorly delineated in this increasing population at significant risk for inadequate bone accrual and metabolism.

The pathogenesis of skeletal abnormalities in pediatric allogeneic HSCT recipients is multifactorial. HSCT myeloablative treatment regimens result in direct damage of osteoprogenitor cells within the recipient's bone marrow, negatively affecting bone formation [29]. Additional risk factors contributing to poor bone acquisition and accelerations in bone resorption in HSCT survivors include malnutrition [30], reduced muscle strength [31], chemotherapy [32], total body irradiation (TBI), immune suppressive therapies with GC, and treatment-related endocrinopathies (e.g. GH deficiency, hypogonadism) [33]. Graft-versus-host disease and dysregulation of the immune system serve as additional threats to bone health, due to osteoclast activation and reduced osteoblast number and function [3, 34].

DXA-based studies in children and adults immediately following allogeneic HSCT reveal substantial bone deficits, in conjunction with elevated markers of bone resorption and low markers of bone formation [35–37]; however, the majority of DXA studies assessing bone outcomes in long-term survivors of pediatric allogeneic HSCT demonstrate variable findings ranging from normal to low BMD. These variable findings reflect differences in study design, Z scores arising from different normative databases and DXA machines, as well as DXA's limitation of confounding by short stature. DXA is a 2-dimensional technique that combines trabecular and cortical bone mass within a projected bone area. While clinically accessible, DXA lacks discrete measures of trabecular and cortical volumetric BMD or cortical dimensions. Consequently, assessing bone deficits in long-term survi-

vors of pediatric allogeneic HSCT by DXA is limited by variability in methodology and underestimation in DXA-related methodological errors of confounding by short stature due to lack of BMD Z score adjustment for HAZ as recommended by Zemmel et al. [11, 38, 39].

Significant deficits, on the other hand, are noted in long-term allogeneic HSCT survivors using 3-dimensional imaging techniques such as quantitative CT that distinguishes between cortical and trabecular bone [2, 40]. Kaste et al. [40] reported significant deficits in QCT measures of spine trabecular volumetric BMD in allogeneic HSCT survivors (median Z score –0.88; range –4.06 to 3.05) at a median of 5 years after HSCT. These deficits were not associated with gender, age at HSCT, interval since HSCT, conditioning regimen, or endocrine dysfunction in survivors [40]. Similarly, Mostoufi-Moab et al. [2] reported substantial growth failure (median height Z score –1.21), low tibia trabecular volumetric BMD (median Z score –1.05; range –1.33 to –0.78), smaller cortical dimensions (even after adjustment for shorter tibia length), and reduced muscle cross-sectional area measured by peripheral QCT in long-term survivors of allogeneic HSCT (range 3–16 years since HSCT) compared to a large healthy reference population. The magnitude of these deficits exceeded those observed in children with active Crohn's disease [41], juvenile rheumatoid arthritis [42], and chronic kidney disease [43], highlighting the lasting impact of allogeneic HSCT and its therapies. Importantly, the vast majority of the HSCT recipients in this study had not been treated with GC or immune suppressive medications for many years. This study also delineated discrete associations between TBI, GH deficiency, and tibia trabecular and cortical deficits despite appropriate hormone replacement in subjects with a diagnosis of endocrinopathy. Allogeneic HSCT survivors also demonstrate significant pubertal delay as expected from treatment-related toxic gonadal effects. Thus, treatment-associated GH deficiency and hypogonadism further contribute to compromised skeletal acquisition in pediatric allogeneic HSCT survivors. Future longitudinal studies are necessary to determine whether these deficits progress or recover over time and to identify associations with fracture.

Focal Bone Morbidity: Osteonecrosis

ON, bone death caused by inadequate blood supply, is a serious and debilitating complication of ALL and its treatment. Cumulative incidence of symptomatic ON at the end of leukemia therapy ranges from 0.9 [44] to 17.6% [45], while asymptomatic ON occurs in up to 53.9% [45]. In symptomatic children, the clinical course is often multiarticular and bilateral, with the hips and knees most commonly affected [46]. Studies using whole-body MRI demonstrate widespread multifocal skeletal lesions affecting upper and lower extremity joints (hips, knees, shoulders), long bones, as well as small bones of the hands and feet [47]. Pediatric HSCT recipients are similarly at high risk for developing ON, with prevalence as high as 44% in survivors screened by MRI [40]. However, the true prevalence of ON is unknown, as the majority of HSCT recipients do not undergo prospective screening assessment with MRI, which is a more sensitive method for detecting ON [48]. Other identified risk factors for ON include age >10 years [45, 46], female sex [44, 49], Caucasian race [46], and in some but not all studies, increased BMI [50, 51].

The etiology of developing ON is complex and attributed to the use of high-dose GC [52]. Other postulated pathophysiological mechanisms include altered bone and lipid metabolism and thrombophilia. In HSCT survivors, a higher incidence of ON is present in TBI-based conditioning regimens likely due to radiation-induced microvascular damage [53]. The risk of ON after HSCT further increases with graft-versus-host disease, due to graft-versus-host disease-related increased risks for microangiopathy [54]. The final common pathway in the development of ON is compromised blood flow resulting in infarction and necrosis of the bone [55]. ON results from direct suppression of osteoblasts, apoptosis of osteocytes, stimulation of intramedullary lipocyte proliferation and hypertrophy within the bone marrow (resulting in reduced blood flow), and stasis and ischemia (due to impact on vascular endothelial and smooth muscle cells) [54, 56].

The onset of ON in ALL is highly variable with several case reports of ON detected at diagnosis [57]; however, over 50% of children present within the first 2 years from leukemia diagnosis [45, 46, 58]. MRI is a sensitive tool for detecting ON at earlier stages and in asymptomatic locations [45]. This is important as visible ON on X-ray imaging indicates advanced stages. Research from St. Jude's Hospital using a prospective MRI surveillance of hips, shoulders and knees identified all patients with ON within the first year of ALL diagnosis. In this study, the cumulative incidence at 1 year was 14.6% for grade 2–4 ON and 35.4% for grade 1 ON. Importantly, the presence of ON at initial MRI screening performed within the first 6–8 months of ALL therapy was the most robust predictor of subsequent ON progression [45]. Patients with grade 1

ON at first MRI screening were more likely to develop symptomatic grade 2–4 ON (26%) compared to patients initially negative for ON (14%) [45]. This observation speaks to the importance of understanding the skeletal phenotype for ON early in the course of ALL, in order to identify which children are at risk for clinically significant progression. While the St. Jude's data support MRI of the most vulnerable joints (hips and knees) early in the course of ALL chemotherapy, the lack of proven therapy to prevent progression may diminish the enthusiasm for early recognition. At the very least, this approach forms the basis for a future intervention trial based on the early identification of ON lesions in high-risk children, followed by early treatment to prevent progression.

Candidate genes as potential predictive biomarkers for patients at genetic risk for developing ON include *PAI-1* (SERPINE 1) [59], *VDR* [60], CYP3A4, ACP1, and SH3YL1 (a locus on chromosome 2 that regulates lipid levels and osteoblast differentiation) [45, 59, 61]. Thrombophilia testing for factor V Leiden, prothrombin 20210G→A, and methylene tetrahydrofolate reductase (MTHFR, 677C–T) do not show an association with ON [62].

ON significantly contributes to short- and long-term disability in many survivors of pediatric hematological malignancies and HSCT [63]. Given the variable natural history of ON, treatment decisions are difficult with notable lack of established standardized regimens. Current treatment options for ON include analgesia [63], limited weight bearing, physical therapy, and surgical procedures including core decompression [64] and/or joint replacement [65]. Other newer surgical techniques include the use of vascularized bone grafts [66], and the combination of core decompression with the insertion of human bone morphogenetic protein [67]. While surgery is a conventional approach, the precise surgical intervention in a growing pediatric patient with open physes remains controversial [46, 68]. Alternative treatments have included vibration plates [69] or hyperbaric oxygen, all without clear benefits [70]. A number of medical therapies with inconsistent results include the use of calcium channel blockers (nifedipine), prostaglandin infusions, low molecular weight heparin, and statins [71, 72]. These pharmacological agents predominantly ameliorate the regulation of blood supply to target the local ischemia [73] or lipocyte proliferation [72]. Several small studies have reported the use of bisphosphonates for the treatment of ON [74–77]. The rationale for bisphosphonates stems from preventing osteoclast bone resorption during the revascularization and uncoupled bone remodeling phase in the ON bone, thus preserving bone shape [63, 78]; however, the data on the clinical and radiological outcomes of children with chemotherapy-associated ON treated with bisphosphonates remains limited [63, 79, 80]. While treatment with bisphosphonates contributes to pain improvement with a reduced requirement in oral analgesia, their use has failed to demonstrate the prevention, destruction, and subsequent collapse in most affected weight-bearing joints such as the hip joint [63]. The limited effectiveness of bisphosphonates in the treatment of ON is likely due to inadequate drug distribution to areas of necrotic bone [63]. The prophylactic administration of bisphosphonates, as future potential novel treatment approaches, may prove more effective in reducing the frequency and severity of ON during treatment for childhood hematological malignancies or HSCT [81]. Lastly, another potential use for bisphosphonates in CCS includes facilitation of vertebral body reshaping, given the demonstrated long-term skeletal effects in children with osteogenesis imperfecta [82].

Skeletal Late Effects of Radiotherapy

The inhibitory effect of radiation on osteogenesis commonly results in hypoplasia and asymmetrical bone growth, particularly notable in flat bones due to growth by membranous ossification. Acute and long-term effects of radiation on the bone occur by direct damage to osteocytes and altered bone formation through arrest of chondrogenesis at the epiphyseal growth plate, failure to absorb calcified cartilage at the bone metaphysis, and altered diaphyseal periosteal activity [83–85]. Common musculoskeletal manifestations following radiation are many and include short stature due to physeal damage, scoliosis, kyphosis, angular deformities, vertebral fractures, avascular necrosis, slipped capital femoral epiphysis (SCFE), and the development of secondary benign or malignant tumors [86–88]. Additional radiation-associated late effects of the spine include changes of vertebral trabecular microarchitecture [89], as well as a disproportionately large reduction in sitting height relative to standing height [89–93]. The effect of radiation on the spine is multifactorial and due to direct effects of radiation on the growth plate, as well as endocrine complications of cranial radiation such as GH deficiency [94]. Scoliosis or kyphosis due to altered axial alignment is a common long-term effect of radiotherapy, with the prevalence of post-radiation scoliosis ranging from 10 to 80% and kyphosis from 2 to 48%, significantly higher than the

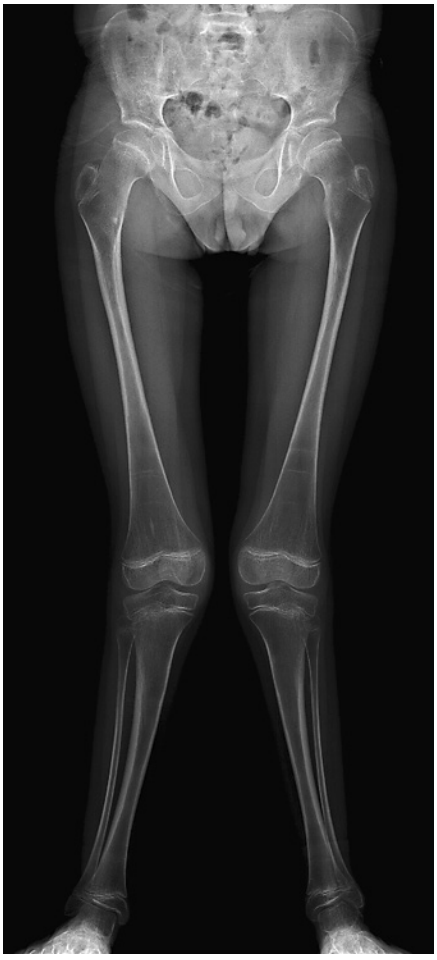

Fig. 3. Bilateral distal femoral and bilateral proximal tibial valgus deformities noted in this patient following total body irradiation for hematopoietic stem cell transplantation. Diffuse, bony demineralization is present due to chronic glucocorticoid treatment. The leg length discrepancy required correction with a bilateral distal femoral and bilateral proximal tibial medial epiphysiodesis.

prevalence of idiopathic scoliosis during adolescence [95, 96]. Identified risk factors include younger age, higher radiation doses, and asymmetric radiation. For example, the prevalence of scoliosis is higher among survivors of Wilms tumor (63%) and neuroblastoma (83%) given asymmetric radiation treatment compared to survivors of Hodgkin's lymphoma (39%) who receive symmetric radiation [97]. However, with refinement techniques in radiotherapy for most solid tumors, the higher rates of spinal deformity after radiation have gradually declined. In addition to asymmetry, vertebral endplate deformities are more common than previously appreciated. For example, in a cross-sectional study of 25 patients treated with allogeneic HSCT and TBI, vertebral deformities were present in the majority of patients, with 51 deformities identified in 14 (58%) patients [89].

TBI for HSCT has a multifactorial impact on the skeleton including reduced stature as a result of GH deficiency related to radiation damage of the pituitary somatotrophs along with diffuse physeal damage due to adverse effects of chemotherapy and radiation [98–101]. Other musculoskeletal effects of TBI include asymmetrical physeal disruption [102, 103], leading to metaphyseal changes and angular deformities, such as genu valgum (shown in Fig. 3) [102, 104, 105], requiring surgical intervention with hemiepiphysiodesis [105–107].

SCFE is a progressive displacement of the femoral head, through the physis, over the femoral neck [108]. It is another known complication related to the systemic effects of chemotherapy, TBI, and GH replacement in survivors [102, 109, 110]. In the largest retrospective review of GH replacement in CCS following radiation exposure compared to pediatric patients under GH treatment for idiopathic GH deficiency, survivors treated with TBI demonstrated a 211-fold increased risk for SCFE compared to pediatric patients with idiopathic GH deficiency, suggesting GH replacement itself may not directly contribute to the risk for SCFE in CCS [111]. Other identified key differences between SCFE following TBI compared to SCFE in the general population include younger age, lower BMI, prepubertal stage, and bilateral SCFE in CCS [109–111]. Approximately 50% of CCS cases demonstrate bilateral SCFE compared to 20–25% in the general population [109, 110] and were far more likely to present with an atypical valgus SCFE, which tends to be less severe and have a longer duration of symptoms [111, 112]. As shown in Figure 4, in a CCS with a suspected SCFE, lateral radiographs are critical to evaluate the hip, as the Klein line, an early sign of SCFE, will always be normal in a valgus SCFE [111–113]. Delays in diagnosing SCFE can result in proximal hip deformity, femoral acetabular impingement, and subsequent arthritis [108, 111, 114]. Detection of SCFE requires in situ fixation [115], with a greater need for prophylactic fixation of the contralateral hip (Fig. 4) given the higher propensity for bilateral hip involvement [109, 110].

Osteochondroma is a benign bone tumor composed of bone and a cartilaginous cap, and it is the most common tumor secondary to radiation. The incidence of osteochondroma is approximately 10–12% after local radiation [116] and 5–24% after TBI [88, 117–119], with young age (3 years or younger) at the time of transplantation and conditioning with TBI as independent risk factors. Osteochondroma occurs due to disruption of the physis leading

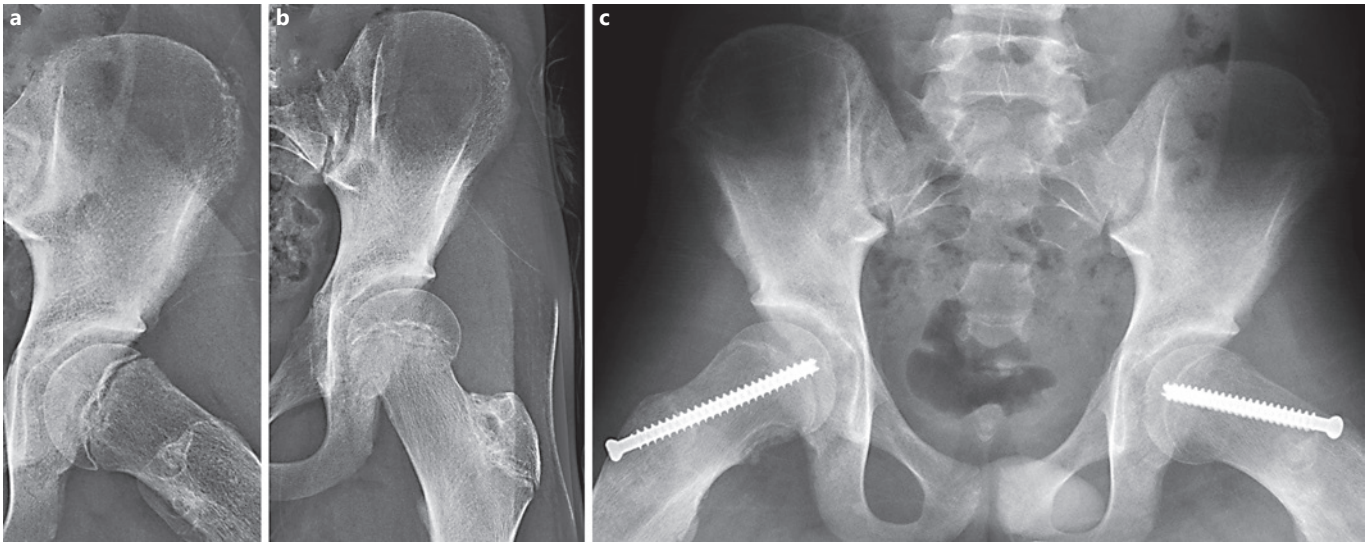

Fig. 4. a Frontal and frog leg lateral views of the hip demonstrate widening of the left proximal femoral physis. **b** The epiphysis is slipped laterally and posteriorly consistent with left valgus SCFE. **c** Bilateral hip pinning of proximal femurs as surgical correction for the SCFE. Hip joint spaces after surgical pinning are now symmetric with no evidence of avascular necrosis.

to abnormal endochondral ossification [102, 120]. Disruption of the physis following radiation and chemotherapy leads to longer duration of open growth plates, and thus increases the odds of developing an osteochondroma [116]. GH therapy may further increase growth of the exostosis and increase the likelihood of osteochondromas becoming symptomatic in patients during GH replacement (Fig. 5) [88, 118, 119]. Routine radiographic screening to detect osteochondromas is not recommended due to the unnecessary risk from radiation exposure and the lack of cost-effectiveness [88, 117], particularly as thorough histories and physical examinations are sufficient for the detection and clinical diagnosis of osteochondromas [88]. Yet, common indications for imaging include rapid increase in size, suspected malignant transformation, worsening or new pain, decreased functionality of the affected limb, or cosmetic considerations [106, 107, 121]. Long-term follow-up is strongly recommended given the possibility of secondary radiation-induced sarcomas [122, 123].

Fat and Bone: The Role of Cancer Therapy, Marrow Adiposity, and the Skeleton

The relationship between fat, bone, and systemic metabolism is a growing area of scientific interest. Marrow adipose tissue (MAT) is a well-recognized component of the bone marrow milieu and is metabolically distinct from current established subtypes of adipose tissue. Despite recent advances, the functional significance of marrow adipose tissue is still not clearly delineated. Bone and fat cells share a common mesenchymal stem cell within the bone marrow, and hormones and transcription factors such as GH, leptin, and peroxisomal proliferator-activated receptor γ influence mesenchymal stem cell differentiation into osteoblasts or adipocytes [124]. The mesenchymal stem cell osteogenic potential is more vulnerable than the adipogenic potential to radiation and chemotherapy, and this confers a risk for an abnormal fat-bone axis in survivors following cancer therapy and bone marrow transplantation. Long-term HSCT survivors treated with TBI demonstrate a twofold greater MAT volume when compared with age- and sex-matched controls [89]. The enhanced MAT is also associated with greater visceral adiposity and fat infiltration of muscle, reduced bone volume fraction, and abnormal bone microarchitecture. Similarly, adult patients receiving pelvic radiation therapy in combination with chemotherapy experience significant bone marrow cell depletion, bone loss with increased fracture risks, and enhanced MAT [125]. Future studies on the metabolic role of MAT may provide the critical insight necessary for selecting targeted therapeutic interventions to improve altered hematopoiesis and augment skeletal remodeling in cancer survivors.

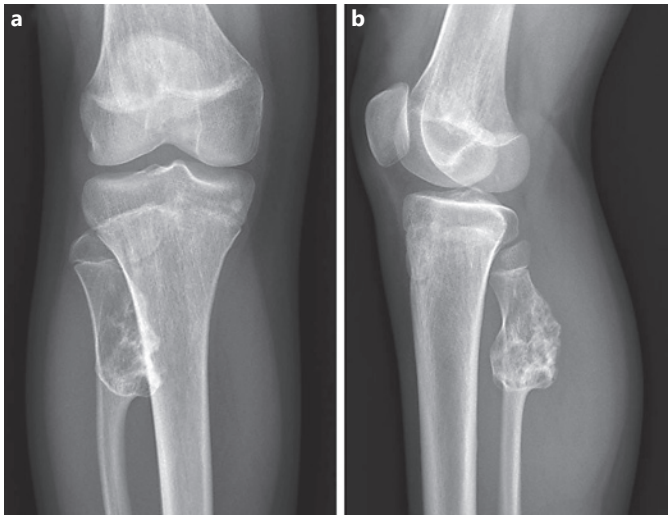

Fig. 5. a, **b** X-ray imaging demonstrates an osteochondroma of the proximal fibula, a 5 × 3.1 cm, sessile lesion arising from the proximal fibular metadiaphysis that is continuous with the underlying bone cortex. This osteochondroma presented with clinical symptoms of pain with strenuous physical activity in a 12-year-old female with a history of total body irradiation exposure for treatment of childhood leukemia and bone marrow transplantation. Notable growth of this lesion was appreciated at the patient's physical examination while under growth hormone therapy for underlying diagnosis of irradiation-induced growth hormone deficiency.

Developing Skeleton, Retinoids, and Cancer Precision Therapy

cis-Retinoic acid (*cis*-RA) and fenretinide [N-(4-hydroxypheny)retinamide] are retinoid derivatives with in vitro cytotoxicity against neuroblastoma cells [126]. *cis*-RA is a highly effective anticancer agent that induces cytodifferentiation and apoptosis as well as inhibition of angiogenesis and oncogene expression [127]. Retinoid derivatives are administered for the treatment of select pediatric cancers, including high-risk neuroblastoma, acute promyelocytic leukemia, and juvenile myelomonocytic leukemia. Guinea pig animal models treated with high doses of vitamin A demonstrate epiphyseal closure in the tibia and femur mediated by RA receptors, along with weight loss and poor growth [128]. Furthermore, these guinea pig animal models demonstrate epiphyseal closure by RA receptor-selective agonists that is inhibited by RA receptor-selective antagonists, suggesting that RA receptor agonist activity alone is sufficient for retinoid-induced epiphyseal closure [128]. CCS treated with retinoids are at marked risk for reduced longitudinal bone growth, abnormal osteoblast differentiation, and premature epiphyseal closure [129]. Furthermore, changes in bone markers of metabolism, poor growth, thyroid dysfunction, and hyperparathyroidism and bone pain have recently been described in pediatric patients treated with other newer targeted cancer therapies such as tyrosine kinase inhibitors (TKI) [130]. Thus, with future inclusion of retinoid derivatives and TKI in different pediatric cancer treatment regimens, a better understanding of its detrimental effects on the developing pediatric skeleton is paramount for timely interventions. Importantly, providers caring for CCS treated with retinoids and TKI should be aware of the adverse impact of these agents on the developing skeleton, and evaluate growth, bone pain as well as epiphyseal status. Future studies are needed to formally assess skeletal toxicity in pediatric patients treated with retinoid derivatives and TKI to address impaired bone growth and promote skeletal health in CCS.

Surveillance, Intervention, and Treatment Strategies

The most important components of the surveillance approach in CCS include assessment of bone pain, fractures, and functional mobility. Any of these identified problems should prompt relevant investigations and referrals to orthopedics, physical therapy, or rehabilitation medicine as appropriate. DXA is recommended for bone health assessment after childhood cancer therapy [131] and is clinically useful given low ionizing radiation exposure, ease, and availability, as well as accessibility for comparison with robust reference data [13]. Per the International Society of Clinical Densitometry recommendations, the posterior-anterior spine aBMD and total body less head bone mineral content are the preferred anatomical skeletal sites in pediatric DXA measurements [13]. However, as noted previously, limitations of DXA (variability of different normative databases resulting in different Z scores and underestimated BMD in shorter individuals) should be taken into consideration. Confounding by short stature is of paramount importance when interpreting BMD in CCS with poor growth and pubertal delay [11]. Importantly, a single DXA measurement is insufficient in dictating initiation of specific therapeutic interventions, and emphasis should be placed on fracture history, functional status (pain and mobility), and aBMD "trajectory" by serial DXA measurements [13]. Treatments for low BMD in CCS include prompt recognition and treatment of hormonal deficiencies, repletion of vitamin D insufficiency or deficiency, and supplementation

of poor calcium intake. Furthermore, CCS should be counseled to maintain regular physical activity and refrain from smoking and excessive alcohol consumption [132].

Summary and Future Directions

In summary, the growing skeleton is vulnerable to the cancer process and osteotoxic cancer therapy. Early recognition and intervention strategies to optimize bone health are essential to prevent long-term sequelae from fractures, spine and long bone deformities, and chronic pain in children and adolescents with malignancy. Landmark longitudinal studies in pediatric ALL assessing the timing and predictors of long bone and vertebral fractures as well as osteonecrotic lesions have shown that most of the bone morbidity occurs within the first 2 years, and that predictors of ON lesions and fractures are evident early in ALL treatment. These observations heighten the need for early identification of fractures and ON in those with limited potential for spontaneous recovery. Intervention trials are now needed to introduce bone protective therapeutics in those with early bone morbidity who are most likely to progress and least likely to recover (i.e., those with more advanced early bone morbidity and more limited potential for recovery due to limited residual growth potential). CCS require continued surveillance for skeletal morbidities into late adulthood with specific attention to bone health including optimization of nutrition, mobility, and exercise. Future studies are necessary to examine the impact of interventions such as bone-targeted therapy (i.e., antiresorptive agents, denosumab, or antisclerostin antibodies), exercise, and nutritional supplements both during and following cancer treatment [133].

Disclosure Statement

S.M.-M. has no potential conflicts of interest to disclose. L.M.W. has been a consultant to and participated in clinical trials with Novartis and Amgen.

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