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REVIEW

Bone health in childhood cancer: review of the literature and recommendations for the management of bone health in childhood cancer survivors

G. Marcucci[1], G. Beltrami[2], A. Tamburini[3], J. J. Body[4], C. B. Confavreux[5], P. Hadji[6], G. Holzer[7], D. Kendler[8], N. Napoli[9,10], D. D. Pierroz[11], R. Rizzoli[12] & M. L. Brandi[1*], on behalf of the International Osteoporosis Foundation Cancer and Bone Working Group

[1]Bone Metabolic Diseases Unit, Department of Biomedical, Experimental and Clinical Sciences, University of Florence; [2]Department of Pediatric Orthopaedic Oncology; [3]Hematology-Oncology Service, Department of Pediatrics, University Hospital AOU-Careggi, Florence, Italy; [4]Université Libre de Bruxelles, Brussels, Belgium; [5]University of Lyon - INSERM UMR 1033-Lyos — Expert Center for Bone Metastases and Secondary Bone Oncology (CEMOS), Rheumatology Department Hospices Civils de Lyon, Pierre Bénite, France; [6]Department of Bone Oncology, Endocrinology and Reproductive Medicine, Nord West Hospital, Frankfurt, Germany; [7]Department of Orthopedics and Traumatology, Medical University of Vienna, Vienna, Austria; [8]Division of Endocrinology, Department of Medicine, University of British Columbia, Vancouver, Canada; [9]Unit of Endocrinology and Diabetes, Department of Medicine, Università Campus Bio-Medico di Roma, Roma, Italy; [10]Division of Bone and Mineral Diseases, Washington University in St Louis, St Louis, USA; [11]International Osteoporosis Foundation (IOF), Nyon; [12]Division of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland

Correspondence to: Prof. Maria Luisa Brandi, Head Bone Metabolic Diseases Unit, Department of Biomedical, Experimental and Clinical Sciences, University of Florence, Largo Brambilla n.3, 50134 Florence, Italy. Tel: +39-055-7946304; Fax: +39-055-7946303; E-mail: marialuisa.brandi@unifi.it

In the past decades, new cancer treatment approaches for children and adolescents have led to a decrease in recurrence rates and an increase in long-term survival. Recent studies have focused on the evaluation of the late effects on bone of pediatric cancer-related treatments, such as chemotherapy, radiation and surgery. Treatment of childhood cancer can impair the attainment of peak bone mass, predisposing to premature onset of low bone mineral density, or causing other bone side-effects, such as bone quality impairment or avascular necrosis of bone. Lower bone mineral density and microarchitectural deterioration can persist during adulthood, thereby increasing fracture risk. Overall, long-term follow-up of childhood cancer survivors is essential to define specific groups at higher risk of long-term bone complications, identify unrecognized long-term adverse effects, and improve patient care. Children and adolescents with a cancer history should be carefully monitored, and patients should be informed of possible late complications of their previous medical treatment. The International Osteoporosis Foundation convened a working group to review the bone complications of pediatric cancer survivors, outlining recommendations for the management of bone health, in order to prevent and treat these complications.

Key words: childhood cancer, childhood cancer survivor, osteoporosis, osteonecrosis, chemotherapy, radiotherapy

Introduction

During the past 30 years, changes in the treatment of children and adolescents with cancer have led to substantial improvements in survival, with a 5-year survival rate of childhood cancer close to 80% [1]. This results in an increasing number of childhood cancer survivors (CCSs) who received cancer treatment during growth. On the other hand, CCSs are at substantial risk of late adverse effects of cancer treatment. The adverse events can systemically involve the whole organism, including the cardiac, gastrointestinal, genitourinary, musculoskeletal, neurological, and pulmonary systems, as well as the endocrine system, skeletal maturation and growth, sexual development, fertility, and reproduction. CCSs are also at an increased risk of secondary neoplasms, and cognitive and emotional impairments [2–8]. Although childhood cancers and their treatments have been shown to impact bone health, there are limited data on this topic

[9]. Endocrine, metabolic, and skeletal sequelae are among the most frequently described complications, affecting between 20% and 50% of subjects [10–14]. All cancer therapies can decrease bone mineral density (BMD) through long-term endocrine alterations, such as gonadal dysfunction, growth hormone (GH) deficiency, and altered body composition [15–19]. These therapies can also directly affect bone cells. Furthermore, modifiable factors, such as nutritional deficiency and less physical activity, can modify bone mass and quality.

The aim of this study is to review bone complications in CCSs and propose recommendations for the management of bone health in these patients.

Materials and methods

The International Osteoporosis Foundation convened a working group to review the literature regarding bone health in childhood cancer and propose recommendations for the management of bone health in CCSs. As in previous initiatives and publications, the International Osteoporosis Foundation (IOF) working group consists of clinical scientists and experts in the field of bone metabolism and oncology.

Randomized controlled studies, prospective–retrospective studies, case–control studies, cohort studies, systematic reviews, and meta-analyses published from 1992 to 2017 were searched on PubMed using the following search terms: (i) osteopenia, osteoporosis, fragility fracture, bone mineral density; (ii) acute lymphoblastic leukemia, Hodgkin and non-Hodgkin lymphomas, osteosarcoma, Ewing's sarcoma, chondrosarcoma, brain tumors, and neuroblastoma; (iii) hormonal deprivation, glucocorticoids, physical activity, immobilization and limb surgery, radiotherapy, chemotherapy, hematopoietic stem-cell transplantation (HSCT), and calcineurin inhibitors; (iv) guidelines, survivors of childhood cancers. Case reports and case series were also included due to the limited evidence available in the current literature. Only English-language papers were reviewed. Letters, comments, editorials, expert opinions, and personal communications were excluded. The selection of studies was based on relevance to the broad scope of this study. A list of the most important papers based on their review of the literature was made, followed by a set of preliminary recommendations graded according to the strength of underlying evidence, based on the available guidelines, literature reviews, and the expert opinions of the working group. Subsequently, the plan of the manuscript, the recommendations, and the conclusions were further discussed. All positions were graded on quality of evidence as High, Moderate, Low, or Very low [Grading of Recommendations Assessment, Development and Evaluation (GRADE); http://www.gradeworkinggroup.org] [20].

The review contains four sections:

- Part I: Key points of peak bone mass and bone evaluation in children and teenagers
- Part II: Bone health in CCSs
- Part III: Contributing factors of bone mass impairment in CCSs
- Part IV: Recommendations for bone health in CCSs

Part I: Key points of peak bone mass and bone evaluation in children and teenagers

Attainment of peak bone mass and assessment of BMD

In young adults, BMD is dependent on peak bone mass (PBM) [21, 22]. Patients treated for childhood or adolescent cancer may not undergo optimal bone growth at puberty [22, 23]. An inadequate lean mass acquisition, weight-bearing physical activity, and diet might also impair the attainment of PBM [21–26].

The World Health Organization (WHO) operational definition of osteoporosis on the basis of *T*-score is not applicable in children and adolescents, in whom a *Z*-score, derived from age- and sex-matched BMDs in a healthy population, should be used [27]. Juvenile osteoporosis, referring to a BMD less than expected for age in children and adolescents, has been defined as a BMD >2 SD below the age- and sex-appropriate reference population (*Z*-score < -2 SD) [27]. In 2013, the International Society for Clinical Densitometry (IS-CD) proposed that the diagnosis of osteoporosis in children and adolescents should not be made on the basis of densitometric criteria alone, but that an overall assessment of bone health, such as the presence of fractures due to low trauma, should also be considered (http://www.iscd.org/official-positions/2013-iscd-official-positions-pediatric/)[28]. On the other hand, a BMD *Z*-score > -2.0 does not preclude the possibility of skeletal fragility and increased fracture risk (http://www.iscd.org/official-positions/2013-iscd-official-positions-pediatric/). Moreover, the Official Position stated that in children with short stature or growth delay, spine, and total body less head BMC and areal BMD (aBMD) results should be adjusted (for the spine, adjustment is recommended using either bone mineral apparent density or the height *Z*-score; for total body less head, adjusted using the height *Z*-score) [29, 30]. Finally, in children for whom other sites are not measurable, lateral distal femur scans by dual-energy X-ray absorptiometry (DEXA) are often feasible, and the recent availability of reference data for lateral distal femur for use in children is an important advance [31].

Quantitative computed tomography (QCT), evaluating volumetric BMD and trabecular and cortical bone compartments, requires much higher radiation doses than DEXA, and is therefore difficult to use in children. A more powerful tool is the high-resolution peripheral QCT, which evaluates, at the distal forearm and tibia, the cortical and trabecular microarchitecture and densities with a resolution up to 82 μm [32]. The radiation is lower, but the technique is complex, particularly for growing bones, and it therefore remains a research tool.

Role of sex hormones

Estrogen has a role for attaining PBM in both sexes, as demonstrated by the lower BMD in young females with late menarche, as well as in males with loss-of-function mutations in the estrogen receptor α gene and aromatase gene [33–37]. On the other hand, androgens enlarge the cross-sectional area of long bones that increase mechanical strength, may promote trabecular bone development and thickness in young adulthood, subsequently promote cortical consolidation in midlife, and maintain cortical thickness and trabecular bone volume in older men through the

stimulation of periosteal apposition and trabecular bone formation [37, 38].

Bone remodeling as assessed by bone turnover markers

Morning fast serum procollagen type I N propeptide (s-PINP) and serum C-terminal telopeptide of type I collagen (s-CTX) are recommended by the IOF and the International Federation of Clinical Chemistry (IFCC) for the evaluation of bone turnover [39]. Current findings in cancer-treated children show decreased bone formation and increased bone resorption [40]. However, the evaluation of biomarkers in these patients can be difficult because of the lack of reliable reference values and their large variations according to age, gender, or pubertal stage [40]. Bone biomarker data from longitudinal prospective studies on cancer-treated children and long-term survivors are lacking. Alterations in bone metabolism markers and growth deficits during therapy may display a trend to recovery in the long term. These findings are confirmed in adults treated for childhood cancer, who showed reduced BMD and even asymptomatic vertebral fractures, but no evident differences in bone turnover between patients and a control group [41, 42].

Part II: Bone health in CCSs

Osteopenia/osteoporosis in CCSs

The prevalence of osteopenia and osteoporosis in CCSs is not yet well documented. Moreover, the occurrence of fractures is still insufficiently characterized among CCSs [11, 43]. Supplementary Table S1, available at *Annals of Oncology* online, summarizes the main studies on CCSs and bone status. Some pediatric cancer treatments, listed below, are no longer used in current treatment protocols; however, it is important to report them for CCSs.

Acute lymphoblastic leukemia. Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood, and most data on low BMD in CCSs are focused on this type of cancer. The disease process *per se* and its treatments, such as high cumulative doses of steroids, methotrexate, HSCT, cranial and testicular radiation, are all potential risk factors for BMD deficits [14]. In summary, during treatment of pediatric forms of ALL, low BMD is commonly described, as well as reduced levels of bone formation markers, and this may lead to an increase of fracture incidence [44–47]. A prospective cohort study, conducted within the STeroid-associated Osteoporosis in the Pediatric Population (STOPP) research program, showed that children with ALL had a high incidence of vertebral fractures after 12 months of chemotherapy, and the presence of vertebral fractures and reductions in spine BMD *Z*-scores at baseline were highly associated clinical features [48]. The STOPP research program showed that vertebral compression was an under-recognized complication of newly diagnosed ALL, and whether the fractures will resolve through bone growth during or after leukemia chemotherapy remains to be determined [49].

Rayar et al. enrolled children and adolescents with ALL at the time of the first clinical remission. Twenty-three (18.5%) patients developed fractures, but the fracture sites were not reported. Older age and lower LS-BMD at diagnosis were predictors of lower LS-BMD during continuation therapy, and dexamethasone and lower LS-BMD were associated with fractures. The authors concluded that using these variables could be feasible to develop a predictor model to define the risk of bony morbidity in children receiving ALL therapy [50]. Mostoufi-Moab et al. [51] conducted a longitudinal assessment of BMD and bone structure in childhood survivors of ALL without cranial radiation. Their findings suggested that ALL treatment in childhood without cranial radiation may not result in long-term detrimental effects on bone development. However, given the lack of complete normalization of trabecular and cortical BMD, future studies are needed to confirm complete BMD recovery, and additional investigations would be useful to find a connection between changes in bone outcomes to short- and long-term fracture risk [51].

Finally, regarding the long-term effects of allogeneic BMT (bone marrow transplant) on bone, the whole-body bone mass tends to be only marginally lower in BMT patients than in ALL survivors treated without BMT, and the size-adjusted bone mass (BMC for bone area) remains normal [52].

Hodgkin and non-Hodgkin lymphomas. Regarding bone health in childhood Hodgkin and non-Hodgkin lymphomas, most studies were conducted long after completion of therapy [24]. Most patients treated for childhood malignant lymphomas had no apparent deficits in bone mass and tended to maintain their normal BMD during follow-up [24]. Therefore, childhood lymphoma survivors appear to be only at negligible risk for lower BMD [52].

Osteosarcoma. Osteosarcoma is the most common primary malignant bone tumor in children and adolescents. The introduction of neoadjuvant chemotherapy has improved the survival and limb-salvage rate by decreasing the tumor burden before surgery [53]. The long-term survivors of osteosarcoma usually have lower PBM, with premature osteopenia/osteoporosis, and higher fracture risk [54–56]. Moreover, most young patients with osteosarcoma could fail to achieve optimal lean mass, because of chemotherapy, nutritional deficits, and reduced physical activity levels during and after treatment [42, 54–56].

Ewing's sarcoma. Ewing's sarcoma is another common primary skeletal malignancy in childhood, usually treated with chemotherapy, surgery, and local radiation therapy [57]. Treatment regimens have led to survival rates approaching 70% of patients with no metastases at diagnosis. Low BMD and risk of fractures can occur due to chemotherapy and limited mobility. The risk of fractures could be associated with bone microarchitectural changes, but further studies should be conducted [56].

Chondrosarcoma. Chondrosarcoma is a malignant bone tumor but is uncommon in children. The standard treatment consists of a wide resection or aggressive curettage, only for selected low-grade extremity chondrosarcomas, and is usually not followed by conventional adjuvant treatment [58]. Very little data exist on effects on bone health.

Other childhood tumors: brain tumors and neuroblastoma. BMD has been reported to be reduced in up to one-third of survivors of childhood brain tumors [59]. Children with brain tumors are subject to several risk factors, such as decreased physical activity, glucocorticoid treatment, GH deficiency, hypogonadotropic hypogonadism due to cranial–spinal irradiation. The latter is probably the most important risk factor [59, 60]; however, further studies are necessary.

Finally, some data are also available on bone complications (short stature and osteopenia) in neuroblastoma, an embryonic malignancy of early childhood treated with high-dose therapy and HSCT [61].

Part III: Contributing factors of bone mass impairment in CCSs

Figure 1 summarizes the main contributing factors of bone mass impairment in CCSs, which are described below.

Hormonal deprivation

In both sexes, the degree of gonadal impairment due to cancer treatment is related to the age, dose, and fractionation schedule for radiation therapy and chemotherapy, and it can negatively affect PBM and bone mass [10, 11, 28, 34, 35, 62, 63]. Moreover, in young females, GnRH agonists can be used for short-term use in patients with estrogen-dependent tumors. Overall, standard GnRH agonist treatment regimens of 6 months cause significant bone loss in both the trabecular and cortical bones [64]. After treatment discontinuation, bone loss recovers slowly, but may not be completely recovered in all women [64]. Specific future investigations on CCSs and the usefulness of treatment to prevent bone loss could be valuable.

Moreover, GH deficiency (GHD) is a major side-effect of radiotherapy and has a negative effect on BMD. GHD can lead to decreased bone turnover, delayed growth in children, low PBM, and increased fracture risk in adults [10, 65, 66].

Glucocorticoids

Glucocorticoids have a central role in the treatment of most childhood tumors. Their effects on bone metabolism have been widely studied, both in adults and in children [13, 67, 68] (Figure 2). In the cancer setting, the use of steroids is rarely continuous with chemotherapy programs, but a relatively high dose is common, either to prevent side-effects such as nausea and allergy or to potentiate anticancer drugs. Thus, the attributable part of bone quantity/quality reduction due to steroids is less easy to evaluate, and probably depends on the dose itself, but also time of exposure, cumulative dose, or compounds used [10, 67].

Physical activity, immobilization, and limb surgery

Decreased physical activity or the immobilization in subjects with childhood cancer and CCSs increases bone resorption and negatively affects BMD [23, 24, 28, 54]. However, skeletal responses to disuse can be highly variable [23].

Depending on the sites where the surgery is carried out, its effects will, of course, be different [70]. Limb reconstructions in children usually have a long functional recovery. Patients must be

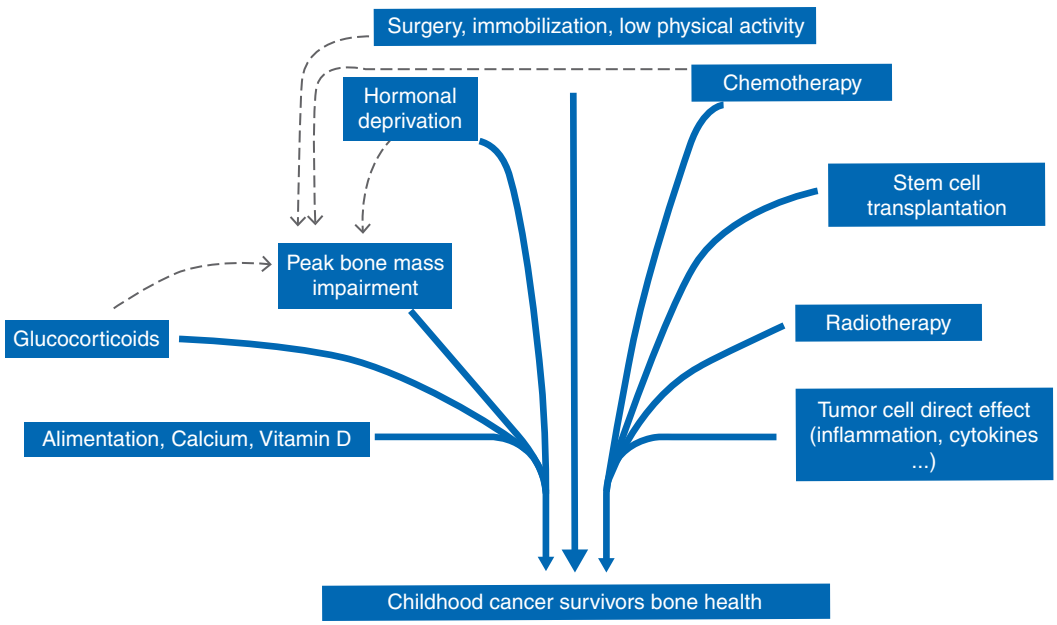

Figure 1. The main contributing factors of bone mass impairment in childhood cancer survivors. The following factors can negatively affect the bone health status of childhood cancer survivors: an inadequate diet, especially characterized by calcium and vitamin D deficiency, prolonged treatments with glucocorticoids, failure to achieve sufficient bone mass peak, hormone alterations involving growth hormone and/or gonadal hormones, reduced or absent physical activity, cancer treatments including chemotherapy, radiotherapy, stem-cell transplantation, and last, the inflammation and altered secretion of cytokines due to cancer cells. Furthermore, the achievement of the peak bone mass, a fundamental factor for bone mass in adulthood, can be negatively influenced by prolonged use of corticosteroids, hormonal deficits implicated in skeletal growth, and limitations of motor function.

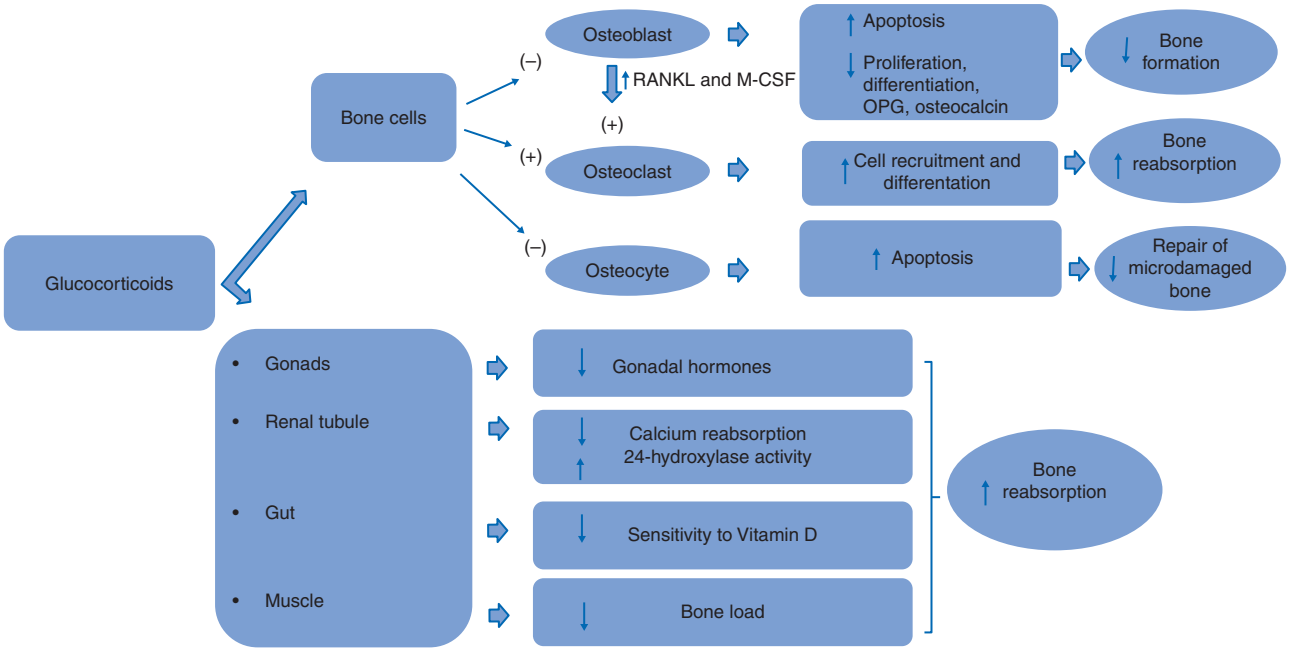

Figure 2. The effects of glucocorticoids on bone. The figure shows the effects of glucocorticoids on bone cells and other organs/systems. Bone cells: Glucocorticoids have mostly inhibitory effects on osteoblasts and osteocytes, inhibiting bone formation and decreasing the repair of microdamaged bone. Moreover, glucocorticoids have stimulatory effects on osteoclasts, with consequent increase of cell recruitment and differentiation, followed by bone reabsorption. However, the effects by glucocorticoids on osteoclasts are less evident compared with effects by osteoblasts on osteoclasts mediated by RANKL and M-CSF. Other organs: The increase of bone reabsorption due to glucocorticoids is also mediated by the effects of glucocorticoids on other organs, described below. In fact, glucocorticoids have catabolic effects on muscle, with the consequent reduction of bone load (in addition to an increased fracture risk due to muscle weakness); in the intestinal tract they reduce the absorption of vitamin D; in the renal tubule they decrease calcium reabsorption and increase 24-hydroxylase activity; and last, gonadotropin secretion can be reduced, leading to a loss of sex steroids. RANKL, receptor activator of nuclear factor kappa-B ligand; M-CSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; ↑, increase; ↓, decrease; (−), inhibitory effect; (+), stimulatory effect [68, 69].

immobilized with consequent disuse osteoporosis. This is a feared consequence that could cause implant failures and fractures. Moreover, as a consequence of immobilization, the stiffness of soft tissues and the poor compliance of sick children trigger a vicious circle that delays the healing of weight-bearing bones [13]. Care should be taken to ensure rapid healing of orthopedic reconstruction in an interdisciplinary fashion, even if the literature remains quite limited in this field.

Radiotherapy

Radiotherapy is an integral therapy to the treatment of several childhood cancers, including leukemia, lymphoma, brain tumors, sarcomas, neuroblastoma, and nephroblastoma (Wilms tumor) [70, 71]. The risk of late effects from radiation treatments depends on the radiation source, field, cumulative dose, volume, and fractionation, as well as sex and age at the time of treatment [2, 70]. It is mainly cranial, orbital, infratemporal, and nasopharyngeal irradiation that can cause radiation-induced hypothalamic-pituitary injury, leading to GHD and central hypogonadism [72]. Alone or in combination with alkylating agent chemotherapy, it can also cause peripheral hypogonadism in case of pelvic, whole-abdomen, and lumbar/sacral spine radiation [73]. These endocrine alterations can affect bone growth, bone mass acquisition, and low BMD [74]. Local radiation doses of $\geq$40 Gy have been associated with hyperthyroidism [75], which can induce bone loss by activation of osteoclast activity [13]. Finally, some studies suggest that local and total body irradiation may affect BMD directly by damaging the bone marrow stroma, but others show conflicting findings [76–78].

In addition, other systemic dysfunctions involve cardiovascular, cerebrovascular, gastrointestinal, hepatic, pulmonary, reproductive, and urinary systems. Neurocognitive, neurosensory, and neurological deficits can occur [70]. The most common sites at risk of subsequent neoplasm include bone [70, 79], in addition to skin, breast, thyroid, and central nervous system [70].

Chemotherapy

The most commonly used chemotherapeutic agents in childhood cancer include alkylating agents, antibiotics, and antimetabolites [70, 80]. The risk for late effects depends on the cumulative dose, route of administration, treatment schedule, and the sex and age of the patient [70].

BMD is usually low in children treated with different chemotherapeutic regimens [45, 81]. Methotrexate has been consistently associated with reduced BMD in children treated for childhood cancer [82]. Through a cytotoxic effect on osteoblasts, this drug has been associated with reduced bone volume and impaired bone formation. It is unclear whether there is a synergistic effect

of methotrexate and steroids, as they are given together in the treatment of ALL [83]. In children treated for ALL, low doses of methotrexate suppress osteoblast activity and stimulate osteoclast recruitment [84]. Higher cumulative doses of methotrexate have been associated with a greater incidence of osteopenia [84]. *In vitro* studies with doxorubicin have described that it also has a toxic effect on osteoblasts [85]. Several chemotherapy regimens, such as methotrexate and cisplatin, are also nephrotoxic and may cause skeletal abnormalities [86]. Moreover, ifosfamide can damage renal tubular function and induce a Fanconi syndrome [87–89]. In long-term survivors of ALL, ifosfamide has been found to negatively affect BMD [73].

In addition to musculoskeletal abnormalities, it is known that chemotherapy exposure has been associated with gonadal, urinary tract, hepatic, cardiovascular, and neurocognitive and neurosensory deficits, as well as pulmonary fibrosis. Finally, secondary myelodysplasia and acute myeloid leukemia are also potential late complications of chemotherapy [62, 70].

Hematopoietic stem-cell transplantation

Patients undergoing HSCT often receive multiple treatments (i.e. methotrexate, steroids, total body irradiation, and high dose of alkylating agents) and can display low BMD levels. It is unclear whether there is additional risk from the transplant itself [52, 76, 90]. Moreover, as patients who have had an HSCT tend to have more severe acute and chronic therapy-related complications, they usually have additional risk factors, including poor nutrition, decreased physical activity, and less exposure to sunshine. In adulthood, transplant studies have shown 2%–10% loss of BMD, with high risk of fracture [90].

Part IV: Recommendations for bone health in CCSs

In 2018, the Children's Oncology Group (COG) published an update of long-term follow-up (LTFU) guidelines for survivors of childhood, adolescent, and young adult cancer surveillance and counseling recommendations (http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf) [91–95]. The COG is the world's largest organization devoted to clinical trials and research of childhood and adolescent cancer [91]. In Europe, there are three LTFU guidelines (in the UK, Scotland, and Germany) [70].

Recommendations

Based on the literature review, the available guidelines, and our experience, we propose the following evidence-based recommendations for clinical practice regarding bone health in CCSs.

Figure 3 shows a summary of the diagnostic-therapeutic algorithm of bone fragility for CCSs, which are explained and discussed in detail in the following paragraphs.

- The baseline assessment at entry into LTFU, which usually occurs 2 years after the end of cancer therapy, potentially damaging for bone health, should include a BMD evaluation (grade of evidence: moderate), followed by laboratory exams, in order to assess bone metabolism, renal function, and factors inducing secondary osteoporosis (grade of evidence: low). In case of young patients, BMD evaluation should be carried out at specialized centers capable of interpreting pediatric scans. Baseline anthropometric evaluations are useful to check for growth disorders, bone deformations, or BMI alterations that may have influenced bone health (grade of evidence: low).
- Recommendations regarding adequate calcium (or diet intake) and vitamin D supplementations, in case of deficit, in addition to adequate physical activity, to avoid negative lifestyles, should always be given, irrespective of BMD, as recommended in the general population (quality of evidence: low). Further studies are needed to establish the exact levels of vitamin D and precise physical activity programs for this specific population that may have an influence on skeletal growth and maintenance of bone mass in adulthood.
- When low BMD (juvenile osteoporosis) is reported, *Z*-score <-2 or *T*-score <-2.5 (based on age, pubertal development, and growth process), and/or fragility fractures, and/or chronic use of glucocorticoids, antiresorptive treatments (bisphosphonate) should be taken into consideration (grade of evidence in childhood/adolescent/young adult age: low; grade of evidence in adulthood: moderate). Also, if necessary, correction of endocrine alterations or other modifiable risk factors of impaired bone quantity/quality should be evaluated (grade of evidence: low). As, in most studies, BMDs in survivors improve with increasing time-off therapy, and if hormonal deficiencies are corrected, repeat measurements in case of normal results (BMD *Z*-score > -1) should not be necessary (grade of evidence: low).

In the following paragraphs, the recommendations are further discussed, subdividing them into 'Assessment and Monitoring' and 'Prevention and Treatment'.

Assessment and monitoring

Bone mineral density. The frequency and severity of bone mineral deficits reported for CCSs suggest that specific diagnostic and treatment interventions during childhood and adulthood should be undertaken.

Although reduced BMD after childhood cancer treatment might recover spontaneously following cessation of therapy, adults treated for childhood cancer frequently have reduced BMD and an increased risk of fractures [9, 11, 15]. COG LTFU guidelines recommend an initial evaluation of BMD by DEXA or QCT at entry into LTFU and 2 years after completion of cancer therapy for children treated with agents and or modalities predisposing to BMD decrease (i.e. methotrexate, corticosteroids, or HSCT), or in case of survivors with GHD, hypogonadism, delayed puberty, or hyperthyroidism.

We recommend the use of DEXA at the spine and femur, based on age, to diagnose and monitor BMD changes in these patients. The number of aBMD revaluations depends on the magnitude of the ongoing risk of fracture, the magnitude of low aBMD, and periods when significant clinical changes are expected [30]. Results from the baseline evaluation and possible treatment intervention should then determine the frequency of subsequent follow-ups (grade of evidence: moderate).

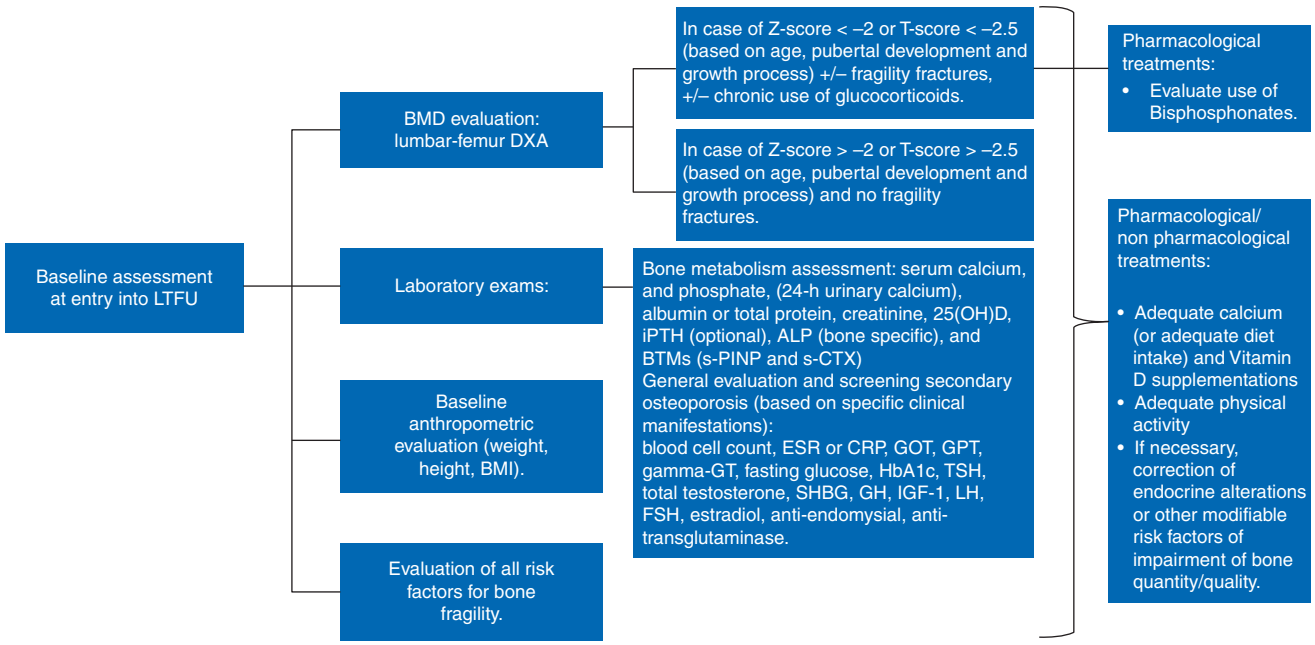

Figure 3. The diagnostic–therapeutic algorithm of bone fragility for childhood cancer survivors. LTFU, long-term follow-up; BMD, bone mass density; DEXA, dual-energy X-ray absorptiometry; 25(OH)D, 25-hydroxyvitamin D; iPTH, intact parathyroid hormone; ALP, alkaline phosphatase; BTMs, bone turnover markers; s-PINP, serum-procollagen type I N propeptide; s-CTX, serum C-terminal telopeptide of type I collagen; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; GOT, glutamic oxaloacetic transaminase; GPT, alanine aminotransferase; gamma-GT, gamma glutamyl transferase; Hba1C, hemoglobin A1c; TSH, thyroid-stimulating hormone; SHBG, sex hormone-binding globulin; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; FSH, follicle-stimulating hormone; BMI, body mass index.

The use of QCT should be avoided because of the higher radiation dose applied (grade of quality: very low).

In the future, imaging methods based on magnetic resonance imaging or bone densitometer using ultrasound, such as the recent radiofrequency echography multi-spectrometry technique, may be considered, especially in the pediatric population, to closely monitor quantity and quality of the trabecular and cortical bone tissue. However, such techniques must still be validated and standardized in the pediatric population (grade of quality: very low).

Bone turnover markers. The interest of bone turnover marker (BTM) levels, such as s-PINP and s-CTX, during LTFU in survivors, should be further evaluated, and levels should be considered in relation to age, skeletal growth, or recent fractures [39, 40]. Evaluation and monitoring of BTM concentrations can show the bone turnover and effects of treatments on bone metabolism, but the prediction of fracture risk independently from BMD still needs stronger evidence on which to base practice (grade of quality: very low). Data demonstrating a predictive role of BTMs for fracture risk in secondary osteoporosis are lacking [28, 40]. Moreover, BTM levels are influenced by several factors, such as vitamin D, IGF-1, physical activity, and nutrition, which should be taken into consideration [40].

Observational and intervention studies should still be carried out to evaluate the application of these BTMs in these patients.

Prevention and treatment

Calcium and vitamin D supplementations and other recommendations. Vitamin D [25-hydroxyvitamin D (25(OH)D)] deficiency and insufficient calcium intake are common in pediatric patients affected by cancers, and in CCSs mean values for serum 25OHD result in the deficient or insufficient range in some, but not all studies [96–100]. They may benefit from adequate dietary intake/supplementation of calcium and vitamin D (grade of quality: low), although the role of sub-optimal vitamin D and calcium status in delayed recovery of bone mass after completion of cancer therapy requires further investigation [40, 101–107]. Regarding this, the dietary intake of calcium and vitamin D and the dosages of eventual calcium and vitamin D supplementation should be evaluated according to national guidelines. Indeed, the wise and balanced choice of the recommendations to follow depends on one's individual health outcome concerns, age, body weight, latitude of residence, dietary and cultural habits, making the regional or nationwide guidelines more applicable in clinical practice [108].

Long-term trials and intervention studies in these patients are needed to see whether supplementation of vitamin D and calcium can prevent increased morbidity from fractures not only in the period directly following treatment but also later in life.

Moreover, it is important to counsel survivors to avoid smoking, alcohol, cannabis, and excessive use of caffeine.

Physical activity. Physical activity, such as weight-bearing exercise, is an important factor for BMD growth in children and BMD maintenance in adults; therefore, it is recommended for CCSs to perform regular physical activity, always taking into consideration the patient's clinical situation (grade of evidence: low) [21, 104, 109]. Although physical activity and exercise have become a cornerstone in the prevention and treatment of chronic diseases such as osteoporosis, there are no data on the effects of

regular exercise from randomized controlled trials aiming to reduce cancer- and therapy-related sequelae in CCSs. Future prospective studies are necessary to elaborate adequate physical training programs in childhood and in subsequent periods for these patients [110].

Correction of endocrine alterations. Treatment of low BMD in CCSs can also imply the correction of underlying diseases that may exacerbate BMD deficits [10, 11].

In case of childhood cancer treatment that can alter the GH–IGF-I axis, GH replacement in CCSs may be considered [12, 32, 111]. However, in childhood, GH seems to be relatively weak as a bone-targeted anabolic treatment outside of the GHD setting. Therefore, considering the burden to children of multiple injections, the potential side-effects, and uncertainties about the longer-term safety, the benefits to prevent or treat osteoporosis outside of hormone replacement therapy for GHD do not justify its risks and costs [12, 112]. In adulthood, GHD may be associated with a decreased BMD, and BMC with an increased fracture risk. Recombinant human GH replacement induces a progressive increase in BMD for up to 5–7 years of treatment, but data on longer follow-ups are limited (grade of evidence: very low) [113].

In case of suspected testosterone deficiency in young age, it is advisable to seek specialist referral following no advancement in Tanner stage over a 6-month period in order to avoid delayed referral in a population of survivors at high risk of pubertal failure and consequent potential impairment of growth, metabolic health, bone mineral accretion, and quality of life as a result of testosterone deficiency [62]. The effect of testosterone replacement therapy on bone health in boys with delayed puberty has not been described. There are only a few studies conducted on adult male subjects that have shown the benefits of testosterone as replacement treatment [112]. Among male CCSs, limited data exist on the influence of androgen insufficiency on BMD (grade of evidence: very low) [11]. In case of testosterone deficiency, although testosterone replacement treatment may be appropriate in deficient patients following accepted endocrine guidelines, the potential benefits and risks of treatment need to be considered appropriately for each patient with cancer history [62, 114–119].

Among female survivors, estrogen replacement may prevent sex hormone deprivation-dependent risk of low BMD, but findings are not yet consistent across all studies (grade of evidence: very low) [11].

Overall, survivors treated with one or more potentially gonadotoxic treatments, and their providers, should be aware of the risk of premature ovarian insufficiency or testosterone deficiency and its implications for future fertility. Regarding this, we refer to the recommendations of 'International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) in collaboration with the PanCareSurFup Consortium' [62].

Treatments to decrease bone fragility: bisphosphonates and others. Bisphosphonates, inhibitors of bone resorption, are usually used in primary and secondary osteoporosis in adults, but in some cases are administered for low BMD in childhood, mostly in osteogenesis imperfecta [120]. Although bisphosphonates, such as alendronate and pamidronate, have not been evaluated in large groups of CCSs for safety and efficacy, several small studies, especially in children with ALL, have described that their use during and after the completion of chemotherapy can improve whole body BMD as well as BTMs (grade of quality: low) [121–125]. Supplementary Table S2, available at *Annals of Oncology* online, summarizes findings regarding the main published studies, based on expert opinion, on the use of bisphosphonates in pediatric cancer patients, the doses that have been used, and adverse events reported [121–125].

Overall, evidence is limited for recommending bone-specific drugs such as bisphosphonates in young adults with secondary osteoporosis [28]; the optimal duration of osteoporosis treatment is controversial and there are no specific dosages recommended for patients with pediatric cancers or CCSs. Regarding adult osteoporosis, the therapy should be reviewed after 3–5 years of treatment with bisphosphonates. Fracture risk should be reassessed after a new fracture, regardless of when it occurs. There is little evidence to guide decision making beyond 10 years of treatment, and management options in such patients should be considered on an individual basis [126, 127].

Regarding side-effects, bisphosphonates may cause an acute phase reaction after intravenous administration, and gastrointestinal side-effects can occur with all orally administered bisphosphonates [128]. In case of impaired renal function, an appropriate dose reduction should always be considered. Risk factors of bisphosphonate-related osteonecrosis of the jaw include duration of bisphosphonate treatment, intravenous administration, dental procedures (extraction/surgery), dental trauma/prosthesis, and an underlying diagnosis of cancer; however, this is rare and has not been described in the pediatric population to date [121, 129]. As the half-life of bisphosphonates in bone may be several years, concerns regarding the potential for long-term effects in children have been raised, such as the risk of impaired mineralization of bone, linear growth, and delayed bone healing after orthopedic procedures [11]. However, until now, few data exist supporting the risks of these adverse events in treated children. We are also reassured of the benign nature of bisphosphonates in the growing skeleton by patients with osteogenesis imperfecta who show normal bone growth but with slower remodeling of the metaphysis of long bones [121].

Thus, in the case of children affected by cancer, and in CCSs with low BMD or fragility fractures, the use of bisphosphonates can be envisaged, as proposed in COG LTFU guidelines (grade of evidence in childhood/adolescent/young adult age: low; grade of evidence in adulthood: moderate). However, long-term controlled studies with larger samples are needed to assess the risks and benefits of bisphosphonates in children with low BMD, as well as the long-term outcomes in adulthood.

Studies on the use of denosumab, a human monoclonal antibody that inhibits bone resorption by binding RANKL (receptor activator of nuclear factor kappa-B ligand), should also be carried out, in order to evaluate the effects on improvement of BMD and reduction of the risk of fragility fractures in these patients. Overall, pediatric data on safety and efficacy of denosumab are limited, unlike adult subjects with osteoporosis, bone metastases, or giant cell tumors. However, some evidence suggests that denosumab may also be beneficial in children in terms of increasing BMD, decreasing bone turnover, and preventing growth of certain skeletal neoplasms (grade of evidence: very low). As opposed to bisphosphonates, denosumab does not incorporate into bone matrix and bone turnover is not suppressed after its cessation.

After drug discontinuation, denosumab's effect on bone turnover is rapidly reversible, representing an important key difference from bisphosphonates. On the other hand, rebound increased bone turnover has led to severe hypercalcemia in several pediatric patients; therefore, further research is needed to clarify the use of denosumab in young patients [130]. Moreover, this turnover rebound appears to be associated with a marked increase in vertebral fracture risk [131]. Recently, the European Calcified Tissue Society formed a working group to perform a systematic review of existing literature on the effects of stopping denosumab [132]. In adulthood, a re-evaluation should be carried out after 5 years of denosumab treatment, and bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover. However, as the optimal bisphosphonate regimen post-denosumab is currently unknown, continuation of denosumab can also be considered until results from ongoing trials become available [132]. There are no data in pediatric populations, and further studies are needed in this regard.

Finally, teriparatide [parathyroid hormone (1–34)], an anabolic hormonal therapy approved for the treatment of severe osteoporosis in adults, does not represent a possible therapeutic option in cancer patients (grade of evidence: high). Moreover, it has a black box warning against its use in children, due to risk of osteosarcoma [112].

Avascular necrosis of bone in childhood cancer

Childhood cancer patients are also at increased risk of avascular osteonecrosis of bone (AVN), which can be a bone devastating complication in some cases [133]. It occurs more frequently after HSCT than after chemotherapy and/or radiotherapy [133–136]. Osteonecrosis is one of the most common therapy-related and debilitating side-effects of antileukemic treatment. An innovative approach to reduce osteonecrosis-associated morbidity might be systematic early screening for osteonecrosis by serial magnetic resonance images (grade of quality: very low) [137]. This is probably not realistic in routine daily practice. More research is needed to determine whether genetic testing for patients at high risk for developing AVN would reduce the morbidity associated with this complication. There is no evidence-based consensus on how osteonecrosis needs to be managed in pediatric ALL patients [138].

Osteonecrosis among long-term CCSs is rare. However, a retrospective cohort study described that CCSs had a significantly increased relative rate compared with the healthy population, especially those who were older at diagnosis and received dexamethasone or radiation therapy. Future investigations are needed to better delineate these results [139].

Discussion

Conclusions

CCSs have a multifactorial impact on bone fragility. Particular attention during cancer treatment should be paid to reduce the impact on future adult bone health. Once in remission or cured, patients should undergo prolonged follow-up for bone fragility to prevent fracture onset. More studies in large and homogenous patient groups are needed to better quantify the BMD loss, incidence of growth impairment, osteoporosis occurrence, fractures, relationship between DEXA parameters and fragility fractures, BTMs monitoring, and AVN in all childhood malignancies. A useful research axis would be to identity groups at higher risk of long-term bone complications, identify unrecognized long-term adverse effects, and improve patient care. Early detection of CCSs at high fracture risk should lead to adequate preventive or therapeutic measures, aiming to decrease morbidity and health costs, both at younger and older ages. For the multidisciplinary team taking care of CCSs, the overall target remains the reduction of cancer-related morbidity from treatment-induced bone loss in the increasing population of adolescents and young adults who have been adequately and successfully treated for childhood cancers.

In the development of these recommendations, several substantial knowledge gaps for clinical research were revealed. Until now, there have been no large observational or randomized trials capable of determining whether improving bone health in CCSs differs from the management of the general population with bone disorders. Future research should be approached in a systematic manner by large single-institution studies, or international multicenter collaborative projects to fill the highlighted gaps.

In response to USA recommendations to improve evidence-based follow-up care in these patients, a web-based support system for clinical decision making, called the Passport for Care (PFC), was recently developed [3]. The aim of the PFC is to foster clinician–survivor conversations and decision making, enhancing screening and long-term follow-up care, and ultimately to improve health outcomes, including bone health [3]. In some European centers, an electronic tool called 'Survivorship Passport (SurPass)' is used [140]. SurPass provides a summary of each survivor's clinical history, together with personalized follow-up and screening recommendations based on guidelines published by the IGHG and PanCareSurFup consortia [140, 141]. However, the 'bone toxicity' section of the IGHG is currently not available. Finally, optimal survivorship care should include an effective transition in care from pediatric to adult care; instead, transition to adulthood is currently suboptimal [142]. A well-coordinated transition of care is crucial for adherence to follow-up, because young adults are particularly at risk of loss for follow-ups, and adherence to late-effects screening decreases with age. Until now, despite the need to improve communication between pediatric oncology and primary care, only a few countries have existing national efforts to educate primary care physicians [142].

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