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Title Page

Title: Bone mineral density corrected for size in childhood leukaemia survivors treated with haematopoietic stem cell transplantation and total body irradiation

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Short title: Bone mineral density in HSCT survivors

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Key words: bone mineral density, long term survivors, haematopoietic stem cell transplantation, leukaemia, total body irradiation

Abstract

Background: Childhood leukaemia survivors treated with haematopoietic stem cell transplantation and total body irradiation (HSCT-TBI) have multiple risk factors for reduced bone mineral density (BMD) and growth failure; hence BMD assessment must take body size into consideration. This study aimed to evaluate size-corrected BMD in leukaemia survivors treated with and without HSCT-TBI. **Methods:** Childhood leukaemia survivors treated with HSCT-TBI (n=35), aged 17.3(10.5-20.9) years were compared with those treated with chemotherapy-only (n=16) aged 18.5(16.1-20.9) years and population references. Outcomes measures included anthropometric measurements and BMD by Dual-energy X-ray absorptiometry. BMD was corrected for size as bone mineral apparent density (BMAD). Statistical analysis: 1 and 2-sample t-tests, and regression analysis (5% significance). **Results:** HSCT-TBI survivors were lighter, shorter with reduced spinal heights compared with chemotherapy-only subjects and population references. Compared with population references, HSCT-TBI survivors showed lower BMD-SDS (p=0.008), but no difference in BMAD-SDS, and chemotherapy-only survivors showed no differences in neither BMD-SDS nor BMAD-SDS. All HSCT-TBI participants with BMD-SDS <-2 had BMAD SDS >-2. BMAD-SDS was negatively associated with age (r=-0.38, p=0.029) in HSCT-TBI survivors. **Conclusions:** Size-corrected BMD are normal in HSCT-TBI survivors in young adulthood, but may reduce overtime. BMD measurements should be corrected for size in these patients to be clinically meaningful.

(250/250 words)

Introduction

Childhood leukaemia with poor prognostic factors are treated with haematopoietic stem cell transplantation (HSCT) after conditioning which may include cytotoxic drugs, monoclonal antibodies and total body irradiation (TBI). Previous studies showed that HSCT survivors have a 71% 15-year cumulative incidence for developing any chronic health problems. [1] Endocrine late effects such as growth hormone deficiency (GHD), hypogonadism and hypothyroidism are common in childhood HSCT survivors especially those who received TBI. [2][3] Reduced bone mineral density (BMD) has also been reported. [4][5][6][7] HSCT-TBI survivors have multiple risk factors that may contribute to reduced BMD such as endocrine dysfunction, abnormal body composition including reduction in lean mass, nutritional compromise, steroid treatment and sedentary lifestyle.

Dual-energy X-ray absorptiometry (DXA) scanning is the current recommended method for the assessment of bone mineral content (BMC) and BMD in children and adolescents with increased fracture risk. The International Society for Clinical Densitometry (ISCD) guidelines recommend that in the absence of vertebral compression fracture, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and BMD Z-score ≤ -2 . [8] However, the BMD output from DXA scanning is given as an areal bone density, i.e. the ratio of BMC to projected bone area g/cm^2 (areal BMD). It does not account for the depth of the bone which is a three-dimensional structure (volumetric BMD). [9] Therefore, smaller bones of the same volumetric density will have an apparently lower areal BMD than larger ones, as such, individuals with short stature and smaller bones will be over-reported with reduced BMD. [10] In addition, the ISCD guidelines have not only emphasised the need for size-correction in children with short stature, but also adjustment for soft-tissue measurements in the presence of malnutrition and skeletal muscle deficits. [11] This is particularly relevant to children with chronic diseases, such as in the case of HSCT-TBI survivors, where short stature [12] and reduced lean muscle mass [13] are common as a result of GHD, hypogonadism, hypothyroidism, steroid therapy and/or poor nutrition.

National reference data for size-corrected BMD adjusted for age, gender and ethnicity have recently become available for children and young adults in the UK. [14] This study primarily aimed to compare size-adjusted volumetric BMD in childhood leukaemia survivors treated with and without HSCT-TBI with population references. The secondary aim is to investigate risk factors associated with size-adjusted BMD in leukaemia survivors treated with HSCT-TBI.

Method

Approval for this study was granted by the local Research Ethics Committee (reference number: 10/H0102/67, 06/Q2001/151, 06/Q2002/89). Participants and, where relevant, their parents gave informed written consent or assent prior to participation in the study.

Subjects and recruitment

Survivors of childhood leukaemia treated with either chemotherapy alone or with HSCT-TBI under the paediatric or transition long term follow up clinics at the Bristol Royal Hospital for Children, United Kingdom (U.K.) from 2007-2012 who were 2 or more years after the completion of all oncological treatment and had undergone DXA scanning before the age of 21 years were identified from the patient databases. All HSCT-TBI survivors were under regular endocrine surveillance as per national standards. [15] Patients diagnosed with endocrine disorders such as growth, thyroid, sex hormone deficiencies were on appropriate replacement therapies. None were receiving glucocorticoid treatment. Exclusion criteria included active malignancy, untreated chronic diseases and pregnancy at the time of DXA scanning. Pregnancy in all females was ruled out by patient history and /or a urine pregnancy test if applicable on the day of the scan. Comparison was made against U.K. bone density reference data measured by DXA adjusted for age, sex and body size from 3598 male and female subjects aged between 4-21 years from 7 paediatric centres. [14]

Patient characteristics

Demographic data including age at the time of scanning, ethnicity, fracture history, family history of metabolic bone diseases, age at leukaemia diagnosis, and time elapse since completion of treatment. Treatment protocols, dosages and type of steroids, and duration of time from the last dose of steroids to DXA scanning were obtained from medical records and treatment summaries for all subjects. Different type of steroids taken were converted to equivalent strengths of hydrocortisone (Dexamethasone: Prednisolone: methylprednisolone: Hydrocortisone = 0.75:4:5:20) and summed to calculate the total dose.

In survivors who were also treated with HSCT-TBI, information was also collected on the age at HSCT-TBI, conditioning Chemotherapy, TBI dose and fractionation, additional radiotherapy such as cranial and/or testicular irradiation, history of graft versus host disease (GVHD) and other long term complications associated with HSCT-TBI.

Anthropometry and pubertal staging

All participants underwent clinical examination and anthropometric measurements at the time of scanning. Weight was measured to the nearest 0.1 kg on digital scales (Seca®, Hamburg, Germany) in light clothing without shoes, and height using a Harpenden® stadiometer (Holtain, Crymych, UK). Both outcomes were converted to Standard Deviation Scores (SDS) by Coles' method using the 1990 UK childhood growth reference data. [16] Pubertal assessment was scored according to Tanner stages by a paediatric endocrinologist.

DXA measurements

All participants underwent DXA scanning (Lunar Prodigy® narrow fan beam Scanner, GE Lunar, Madison, WI) supported by the software, "enENCORE" version 13.4 (GE Health Care). The DXA outputs needed for this study included bone mineral content (BMC), projected vertebral area of Lumbar vertebrae L1-L4, total fat mass and total lean body mass (LBM).

Bone mineral apparent density (BMAD) was calculated according to an adapted Carter methodology: [14][17]

$$\text{Lumbar spine BMAD (g/cm}^3\text{)} = (\text{BMC}_1 + \text{BMC}_2 + \text{BMC}_3 + \text{BMC}_4) / (\text{V}_1 + \text{V}_2 + \text{V}_3 + \text{V}_4)$$

where V_n is the volume of the n^{th} individual vertebra calculated as the posterior-anterior n^{th} vertebral area to the power of 1.5 and BMC_n is the bone mineral content of the n^{th} vertebrae.

SDS-scores for BMD and BMAD, were calculated according to Coles method, using UK sex, age and ethnic- specific reference data for bone mineral density by Crabtree *et al.* [14]

Lean body mass (LBM) SDS was calculated from population references as previously described. [18]

Statistical Analysis

Numeric data of patient characteristics were reported as median values (ranges) and SDS of each group were reported as mean values with 95% confidence intervals (CI). The SDS scores of BMD, BMAD and LBM of the HSCT-TBI and chemotherapy-only leukaemia survivors were compared with population reference using a 1-sample t-test as mean equals zero. A 2 sample t-test was used to compare the differences of the various parameters between the survivors treated with and without HSCT-TBI, and also between HSCT-TBI survivors with or without endocrinopathies. The associations between BMAD-SDS and potential risk factors including age of primary diagnosis and HSCT-TBI, time post HSCT-TBI, age of DXA scan, gender, presence of endocrinopathies, and lean mass were explored by univariate and multivariate regression analysis. A 5% level of significance

was used for all tests. All analyses were performed using statistical software, IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp 2015).

Results

Demographics

A total of 49 childhood leukaemia survivors who have had one or more DXA scans before the age of 21 years were identified, which included 33 (18 Males) treated with HSCT-TBI and 16 (5 Males) with chemotherapy-only. Results of the first DXA scan was used in patients who had more than 1 scan. At the time of DXA scanning, HSCT-TBI survivors were of median age 17.3 (10.5-20.9) years and chemotherapy-only survivors 18.5 (16.1-20.9) years. In terms of pubertal staging, 22 (63%) in the HSCT-TBI and all (100%) in the chemotherapy-only groups were in Tanner stage 5 (table 1). All participants in both groups were White Caucasian.

The HSCT-TBI survivors included subjects with primary diagnosis of Acute lymphoblastic leukaemia (ALL) (n=28) and Acute myeloid leukaemia (AML) (n=5). All subjects in the chemotherapy-only group had ALL. The primary diagnosis of leukaemia was made at 3.8 (0.85-15.0) years and 5.6 (1.6-14.1) years of age in the HSCT-TBI survivors and chemotherapy-only survivors respectively. All subjects were treated according to contemporaneous UK national paediatric leukaemia at the time of their diagnosis including primary protocols UKALL11, UKALL 97/99, UKALL2003 for ALL, [19][20][21] AML10, AML12 for AML; [22][23] and relapse protocols R1, R2 and R3 for ALL. [24] [25] [26] Protocols for ALL consisted of complex regimens of high but variable doses of steroids with prednisolone and /or dexamethasone, [19][20][21][24][25][26]

In the HSCT-TBI group, HSCT-TBI took place at 7.6 (2.4-16.6) years of age, and the time post HSCT-TBI was 9.1 (2.3-16.6) years at the time of the study. All patients received TBI (total from 10-14.4 Gy, single fraction n=5, 6 fractions n=1, 8 fractions n=27) and 11 patients were also treated with additional cranial irradiation. The total dose of steroids given were lower in the HSCT-TBI than chemotherapy-only group (p=0.003). There was no statistical difference in the time from last steroid to DXA between the HSCT and chemotherapy only group (p=0.9).

Endocrine dysfunction

Endocrinopathies were present in the HSCT-TBI participants only: GHD (n=26, 78%), hypothyroidism (n=17, 52%), and hypogonadism (n=20, 61%, 9 Males). All patients were on appropriate hormone replacement at the time of the DEXA scan. GVHD had been previously diagnosed in 12 patients but no patients in either groups were on corticosteroids or immunosuppressant treatment at the time of DXA scanning. Second tumours had been reported in 2 HSCT-TBI survivors including 1 with meningioma and 1 with paraspinous rhabdoid tumour.

Fracture History

Bone-related history and fractures among the HSCT-TBI participants included 1 subject with vertebral fracture, 1 with avascular necrosis of the hip during primary treatment, 1 with incidental finding of aneurysmal bone cyst and 1 with osteoid osteoma. In the chemotherapy-only group, 1 patient had avascular necrosis of the hip at primary treatment and 2 subjects had histories of accidental long bone fractures due to trauma that occurred after completion of leukaemia treatment. There was no recorded family history of metabolic bone diseases in either groups. Any subjects with low vitamin D were on replacement.

Anthropometry and body composition outcomes

HSCT-TBI survivors were significantly shorter (p<0.001) and lighter (p=0.02) compared with the chemotherapy-only controls and population reference ranges (table 1). Sitting height was available in

28 HSCT-TBI and 16 chemotherapy-only patients. HSCT-TBI survivors had reduced sitting height compared with chemotherapy-only subjects ($p < 0.001$) and population references ($p < 0.001$). Chemotherapy-only subjects showed a trend towards reduced sitting height although not statistically significant ($p = 0.06$). HSCT-TBI survivors showed significant reduction in lean mass for height SDS compared with chemotherapy-only ($p < 0.001$) and population references ($p < 0.001$).

BMD and BMAD

HSCT-TBI survivors demonstrated significantly lower BMD-SDS ($p = 0.008$), but no differences in BMAD-SDS ($p = 0.25$) in comparison to population references. The chemotherapy-only survivors were not different to population references in terms of BMD-SDS ($p = 0.7$) and BMAD-SDS ($p = 0.93$). (table 1, figure 1) There were no differences in BMD-SDS and BMAD-SDS between the HSCT-TBI and chemotherapy-only group. In the HSCT-TBI group, 2 patients with BMD-SDS of < -2 had BMAD-SDS > -2 (figure 2). Outcomes were unchanged when the analysis were repeated comparing all post-pubertal (Tanner stage 5) subjects only (table 1)

HSCT-TBI subjects with a primary diagnosis of ALL compared with AML showed no statistical differences in BMD-SDS $[-0.56 (-0.91, -0.22)$ vs $-0.29 (-2.55, 1.97)$, $p = 0.59$] or BMAD-SDS $[0.11 (-0.26, 0.47)$ vs $0.68 (-0.59, 1.97)$, $p = 0.22$]. Further analysis excluding AML subjects in the HSCT-TBI group showed the same findings with lower BMD-SDS but no statistical differences in BMAS-SDS compared with population references or the chemotherapy-only controls (table 1).

Factors associated with BMAD-SDS

Univariate regression analysis showed that BMAD-SDS was negatively associated with age at DXA scan ($r = -0.38$, $p = 0.029$) in the HSCT-TBI survivors (figure 3), whereas no significant relationship was shown in the chemotherapy-only subjects ($r = 0.4$, $p = 0.14$). No significance associations were demonstrated between BMAD-SDS with age at primary diagnosis or HSCT-TBI, time post HSCT-TBI, sitting height-SDS or lean mass-SDS. (table 2)

There was no difference in BMAD-SDS in HSCT-TBI survivors between genders, those who were treated with or without additional cranial irradiation, with history of GVHD post HSCT-TBI, and those with or without GHD, hypothyroidism or gonadal failure. (table 2). In addition, no associations were noted between BMD-SDS and the duration of time from last steroid or total dose in neither groups (table 2).

Multi-regression analysis did not show any differences in the relationship between BMAD-SDS and the above risk factors.

Discussion

This is the first study to report size-corrected BMD measurements from childhood leukaemia survivors treated with and without HSCT-TBI in the U.K. using the recently published national reference ranges which are size, gender and ethnically corrected. [14] Current international guidelines emphasise the importance of size correction in BMD measurements for the assessment of fracture risk in children and adolescents, especially in those with chronic health problems. [27] A number of previous studies have investigated BMD in childhood HSCT survivors, [4][5][6][7] but data on size-corrected BMD is limited.

Ruble et al investigated size-corrected BMD in childhood HSCT survivors by DXA and converted areal BMD to volumetric BMD according to Kroger et al which assumes the bone is shaped cylindrically. [28][29] In our study, BMAD was calculated as per Carter et al which assumes vertebral bodies have a cuboidal configuration [17] as this was the method used in the UK reference data. [14]

Both are validated methods for BMAD calculations, but neither account for the exact shape of lumbar vertebrae. [17][29] Alternative methods such as, quantitative Computed Tomography (QCT) enables measurement of true volumetric BMD and measures cortical and trabecular BMD separately. [7] Mostoufi-Moab et al reported a reduction in trabecular volumetric BMD of the left tibia on QCT in HSCT survivors compared with their population references. [30] Their outcomes, in contrast to our study, where HSCT survivors showed no differences in BMAD in comparison to reference population, may be due to discrepancies in patients' characteristics, anatomical site of measurement and techniques used. Our cohort compared with Mostoufi-Moab et al included a lower percentage of patients with a history of GVHD, and all our patients compared with 50% of their patients with GHD were on growth hormone treatment. Previous studies have shown that BMD outcomes between QCT and DXA are not equivalent in both children and adults. [31][32] Kruse et al reported discrepant results between QCT and DEXA in childhood cancer survivors particularly non-white patients, and did not show QCT to be more strongly associated with history of fractures than DEXA. [31] There is paucity of reference data for QCT in children and adolescents, and established international definitions for reduced BMD including osteoporosis may not be applicable in the interpretation of QCT outcomes.

The severity of low BMD can be over-reported when BMD is not corrected for size. In our study, all HSCT-TBI survivors with areal BMD-SDS <-2 had BMAD-SDS >-2 . Ruble et al reported 2% of their cohort with osteoporosis based on areal BMD, but none using volumetric BMD [28]. However, their study defined osteoporosis according to the WHO criteria which primarily refers to post-menopausal women and do not related to children and young persons with osteoporosis.

The latest ISCD guidelines advised that the diagnosis of osteoporosis in children and adolescents should not be based on densitometric criteria alone. The finding of one or more vertebral compression fractures is indicative of osteoporosis. In the absence of vertebral compression fractures, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and BMD Z-score ≤ -2.0 . A clinically significant fracture history is one or more of the following: 1) two or more long bone fractures by age 10 years; 2) three or more long bone fractures at any age up to age 19 years. [8] Detailed fracture histories reported vertebral fracture in 1 patient in the HSCT-TBI group and 2 subjects from the chemotherapy group reported long bone fractures from trauma. Although individuals are likely to recall significant history of fractures, vertebral compression fractures are commonly asymptomatic and often under recognised during or after treatment in leukaemia patients. [33] Disproportionate loss of spinal height in HSCT especially those on growth hormone replacement are commonly assumed to result from poorer growth responses in the vertebral growth plates post irradiation. [33] Unrecognised vertebral compression fracture, which can lead to over 20% height loss, may also contribute to spinal height loss in some patients, but data in this aspect are lacking.

Meta-analyses have shown that lean body mass exerts a stronger effect than fat mass on BMD [34] secondary to mechanical loading and biochemical usage on bone development. It has been proposed that bone strength is influenced by mechanical muscle force and hormone factors, and the force that the muscles exert against bone is influenced by the amount of body mass the muscle and bones support, resulting in a positive relationship between muscle mass and bones. [35] The latest ISCD guidelines emphasised the need for adjustment in soft-tissue measurements in those with skeletal muscle deficits. [8] Loss of lean mass in HSCT-TBI survivors may be associated with treatment toxicity linked to TBI, chemotherapy and additional steroids for treatment of GVHD. We have demonstrated reduction in lean mass in HSCT-TBI survivors consistent with that previously reported,[13] but we have not found a relationship between lean mass and BMAD in our study. This may be due to the limited duration of follow up post HSCT-TBI and as reduction in lean mass continues with time, this may also have an effect on ongoing BMD reduction and should be further evaluated.

In terms of risk factors for reduced BMAD, our study demonstrated a positive association with increasing age consistent with previous study by Ruble et al. [28] There is increasing interest in the subject of frailty and premature aging in HSCT-TBI survivors that may have a direct and /or indirect

role in their bone health. It is not surprising that the presence of endocrine dysfunction was not associated with reduced BMAD in our study as all subjects with endocrinopathies were fully replaced. Similarly, it has been shown that BMAD was not decreased in children with thalassaemia after HSCT-TBI who were hormonally replete. [36] The lack of statistical associations between BMAD-SDS and steroid dosage does not exclude the impact of steroids on BMD, and the outcome may merely be due to the high doses which have exceeded the threshold to demonstrate a linear dose dependant effect. The total steroid doses in the chemotherapy-group were in fact higher than the HSCT-TBI group as a number of high risk patients received HSCT before completion of the primary leukaemia protocol.

The main strength of this study is the homogeneity of the cohort in terms of primary diagnosis. It is also the first study in the UK describing BMAD-SDS in HSCT-TBI survivors using multi-centred national reference data for our own population. However, the study was limited by the small numbers and cross-sectional design and fracture history may have been underestimated due to unrecognised vertebral collapse. The impact of the level and type of physical activity on bone density was not available in this study, but would be of great interest in future interventional studies. The treatment data of this study pre-dated the availability of electronic prescribing in our centre and there may be some imprecision in the dosages of total steroid exposure as additional doses given for other non-treatment purposes e.g. anti-emetics were not all available. Future studies should have longitudinal and multicentre designs supported electronic medical records

In conclusion, it is essential to correct BMD for size in patients with chronic disease affecting body composition and growth as in the case of HSCT-TBI survivors. Size corrected BMD is reassuring in long term survivors of childhood leukaemia treated with HSCT-TBI who are on appropriate hormone replacement during adolescents and young adulthood. However, BMAD-SDS may decline with age faster in HSCT-TBI survivors than in the general population. Longitudinal studies to investigate changes in size-corrected BMD over time and to screen systematically for asymptomatic fractures particularly vertebral collapse are needed. A consistent approach to surveillance for fracture risk is important for the long term follow up of HSCT-TBI survivors.

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Disclosure Statement

The authors have no conflicts of interest.

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Legends:

Table 1. Results of demographics, anthropometry, bone mineral density and body composition

Table 2. Impact of patient, disease and treatment characteristics influencing BMAD-SDS

Figure 1. Comparison of BMD-SDS and BMAD-SDS in HSCT and chemotherapy-only leukaemia survivors

Figure 2. Graph showing BMD-SDS against BMAD-SDS illustrated that BMD-SDS without size-correction over reported the number of patients with reduced BMD

Figure 3. Relationship between age at DXA scanning and BMAD-SDS