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ORIGINAL ARTICLE

Bone mineral density is compromised in very long-term survivors of irradiated childhood brain tumor

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ABSTRACT

Introduction: The increase in the number of childhood brain tumor survivors warrants detailed research to increase our knowledge regarding the possible physical and psychosocial adverse outcomes of tumor and tumor therapy. The aim of this study was to evaluate the current bone health by measuring the bone mineral density (BMD) in irradiated, adult long-term survivors of childhood brain tumors.

Material and methods: We studied a national cohort of 74 adult survivors of childhood brain tumors treated with irradiation in Finland between 1970 and 2008. Dual X-ray absorptiometry (DXA) was performed for the femoral necks, total hips, and lumbar spine. Laboratory tests were conducted for evaluating the pituitary, thyroid, and gonadal functions. The participants were interviewed, examined clinically, and the disease and treatment related data were retrieved from the patient files.

Results: One fourth of the patients (23.6%) had sex- and age-normalized *z*-scores below the expected range for age (*z*-score ≤ -2.0). Mean BMD scores were decreased in all the DXA measurement sites. Male sex was associated with low BMD ($p < .05$), while body mass index (BMI) had a significant positive association with BMD ($p < .01$). Mode of irradiation (with or without spinal irradiation) or inclusion of chemotherapy in the treatment did not affect BMD significantly. However, patients with a ventriculoperitoneal shunt had lower BMD than those without a shunt ($p < .05$). Follicle stimulating hormone (FSH) and luteinizing hormone (LH) were negatively associated with BMD in women ($p < .05$). However, a higher cumulative dose of glucocorticoids during treatment was not associated with lower BMD, while low BMD was significantly associated with previous fractures in long bones.

Discussion: Low BMD should be taken in consideration in treatment of irradiated childhood brain tumor survivors especially in those with previous fractures in long bones.

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Introduction

Brain tumors are the second most common malignancy in childhood [1]. The advances in the diagnosis and treatment have resulted in improved survival; the overall 5-year survival in Finland reached 79.1% for all and 59.5% for malignant brain tumors in children diagnosed between 2001 and 2010 [2]. The increase in the number of childhood brain tumor survivors warrants detailed research to increase our knowledge regarding the possible physical and psychosocial adverse outcomes of tumor and tumor therapy.

Bones constantly undergo the processes of resorption and formation [3]. Most of the lumbar and femoral bone mineral density (BMD) is achieved by the age of 18.8–20.5 years in a healthy population [4]. The BMD during the stable period between the stage of bone mass accumulation during growth and the subsequent bone loss period is defined as peak bone mass [5]. It determines the risk of osteoporotic fractures in later life [4,6]. Diseases that reduce the accumulation of skeletal mass during childhood and adolescence may have an impact on the peak bone mass and future bone health [7].

Reduced BMD has been identified as a common consequence of many childhood cancers and cancer therapies [8–19]. The causes of BMD deficits in childhood cancer patients are multifactorial. Children with brain tumors are affected by several factors that may lead to low BMD, such as radiation therapy [8–10,13,14,16–18], chemotherapy [8,14,17,18], corticosteroids [8–10,13,16,17], antiepileptic drugs [15,16], hemiplegia [15], hormonal deficiencies [8–10,13,14,16–19], reduced physical activity [8,13,16–19] and malnutrition [8,9,17,18].

Previous studies on BMD in childhood brain tumor survivors have been conducted in smaller patient cohorts

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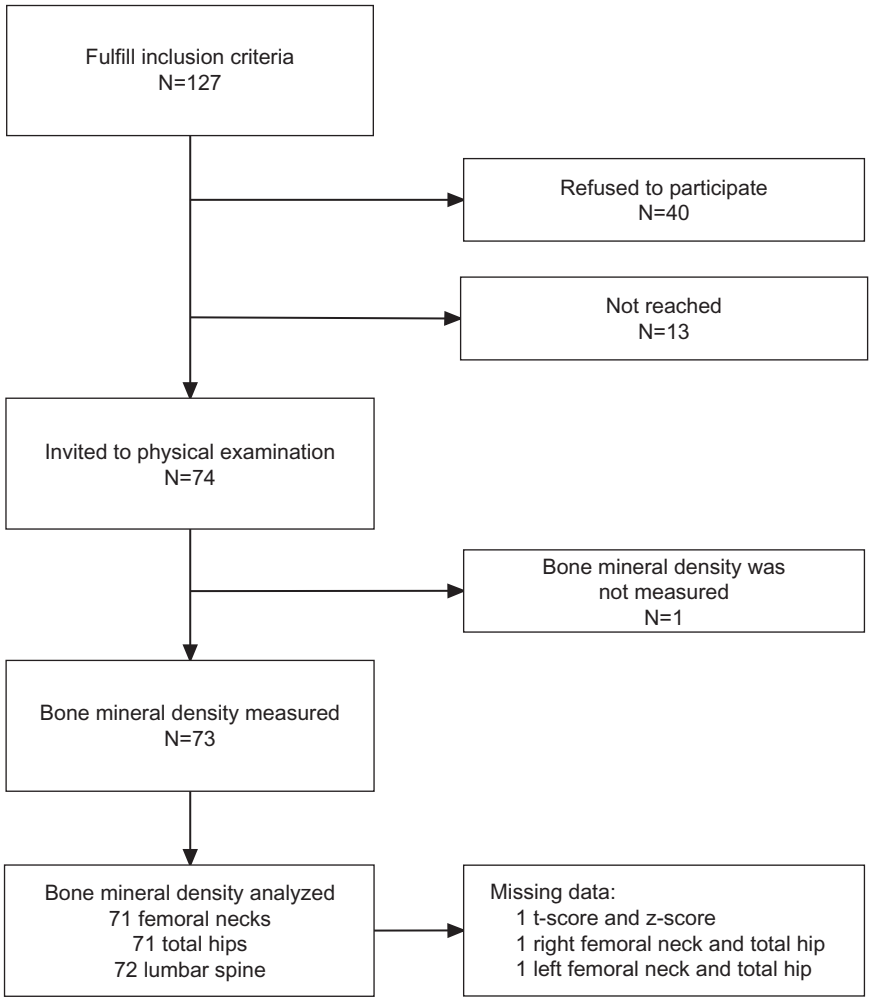

Figure 1. Outline of the flowchart of subjects studied.

involving younger patients or with a shorter follow-up time [8–10,13,14,16–19]. To our knowledge, this is the first national, population-based study conducted on very long-term survivors of irradiated childhood brain tumors to evaluate their current bone health.

Material and methods

Patients

In Finland, all childhood brain tumors are treated in the University hospitals of Oulu, Kuopio, Turku, Tampere, or Helsinki. The patients were identified from the patient registries of these hospitals.

All patients who fulfilled the following criteria were included in the study: (i) brain tumor diagnosis before the age of 16 years, (ii) irradiation as part of the treatment, (iii) follow-up of $\geq$5 years since the cessation of therapy, (iv) age $\geq$16 years at the time of the present study, and (v) no known progressive disease at the time of the present study. In addition to irradiation, patients may have undergone surgery, shunt operation(s), or chemotherapy. The chemotherapy protocols varied according to the histology, and time period. The most commonly used protocols were the 'eight-in-one' [20,21] protocol and a three-drug protocol involving cisplatin, vincristine, and lomustine for medulloblastoma [22,23].

A total of 127 irradiated childhood brain tumor survivors diagnosed and treated in Finland were initially identified to be eligible; however, 53 (41.7%) were unwilling to participate ($n = 40$) or could not be contacted ($n = 13$) (Figure 1). The participants and non-participants of the study were comparable with respect to sex, age at diagnosis or at the time of this study, and time since treatment (Table 1).

Data collection

All participants visited a doctor; data were collected, and a thorough physical examination was conducted. Information regarding current medication, physical activity level, and previous fractures was recorded using a questionnaire. Tumor treatment, hormonal treatments, and corticosteroid treatments were studied from the patient files. Body mass index (BMI) was calculated. The radiation physicist reevaluated the irradiation dosage charts and estimated the irradiation dose in Grays administered to the thalamic area.

Dual X-ray absorptiometry. A total of 73 patients were examined using dual X-ray absorptiometry (DXA). One male subject could not undergo the DXA because of severe

Table 1. Background characteristics of participants and non-participants.

Characteristic	Participants ($n = 74$)	Non-participants ($n = 53$)	p
Sex (male/female), *n* (%)	47 (63.5)/27 (36.5)	27 (50.9)/26 (49.1)	.202[a]
Age at diagnosis in years, mean (SD)	8.3 (4.3)	7.8 (4.5)	.538[b]
Follow-up duration (years) since cessation of tumor therapy, mean (SD)	18.9 (6.1)	20.8 (8.7)	.191[b]
Age at follow-up visit in years, mean (SD)	28.4 (6.8)	29.5 (8.2)	.399[b]
Location of the tumor			.571[a]
Posterior fossa, *n* (%)	34 (46.0)	25 (47.1)	
Middle brain, *n* (%)	22 (29.7)	16 (30.2)	
Hemispheric, *n* (%)	12 (16.2)	10 (18.9)	
Intraventricular, *n* (%)	2 (2.7)	2 (3.8)	
Pons, *n* (%)	4 (5.4)	0 (0.0)	
Dose of irradiation (Gy), mean (SD)	51.3 (5.2)	49.7 (11.1)[c]	.341[b]
Irradiation			.074[a]
Local irradiation, *n* (%)	39 (52.7)	17 (34.7)	
Craniospinal with local boost to the tumor bed, *n* (%)	30 (40.5)	27 (55.1)	
Cranial with local boost to the tumor bed, *n* (%)	3 (4.1)	5 (10.2)	
Stereotactic, *n* (%)	2 (2.7)	0 (0.0)	
Chemotherapy			.569[a]
Yes, *n* (%)	47 (63.5)	36 (69.2)	
No, *n* (%)	27 (36.5)	16 (30.8)	
Operation			.818[a]
Partial resection, *n* (%)	32 (43.2)	26 (49.1)	
Total resection, *n* (%)	29 (39.2)	19 (35.8)	
Biopsy, *n* (%)	10 (13.5)	5 (9.4)	
No operation, *n* (%)	3 (4.1)	3 (5.7)	
Reoperation			.680[a]
Yes, *n* (%)	19 (26.8)	12 (23.1)	
No, *n* (%)	52 (73.2)	40 (76.9)	
Ventriculoperitoneal shunt			.578[a]
Yes, *n* (%)	44 (59.5)	34 (65.4)	
No, *n* (%)	30 (40.5)	18 (34.6)	

[a]Exact chi-squared test.
[b]Student's *t*-test.
[c]$n = 50$, total dose not found in the patient files of three patients.

obesity, one male subject had left-sided hip prosthesis, and in one male subject, only left hip and lumbar spine were analyzed due to researcher error. For one female subject, only the BMD values could be obtained (Figure 1).

The bone mineral content and BMD of the lumbar spine and four femoral sites (femoral necks and total hips) were measured using DXA with Lunar Prodigy DXA bone densitometry in Oulu, Lunar Prodigy Advance DXA bone densitometry in Kuopio, Lunar iDXA DXA densitometry in Tampere (Lunar Corporation, General Electric Madison, WI, USA), Hologic Discovery A DXA in Helsinki, and Hologic QDR 4500C DXA densitometry in Turku (Hologic Inc., Bedford, MA, USA). The results are expressed as age- and sex-normalized *z*-scores provided by the manufacturers.

As per the World Health Organization (WHO), osteoporosis is defined by a BMD T-score ≤ -2.5 SD at any site; and osteopenia by a BMD T-score between -1.0 and -2.5 SD [5,15,24,25]. The score represents the degree of bone loss since the achievement of peak bone mass [16]. However, the International Society for Clinical Densitometry recommends to report BMD in pre-menopausal women and in men <50 years of age in *z*-scores (BMDZ). A *z*-score ≤ -2.0 indicates 'below the expected range for age and sex' [26].

Hormonal analyses. Hormonal functions were evaluated from the blood samples collected after overnight fasting. The samples were analyzed in Nordlab, Oulu University Hospital. Serum luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone in male subjects, estradiol (E2) in female subjects, thyroid-stimulating hormone (TSH), free thyroxine (fT4), insulin-like growth factor (IGF1), and insulin-like growth factor binding protein 3 (IGFBP3) were measured. To minimize the impact of the circadian rhythm, the samples were collected between 7:30 AM and 10:00 AM. The samples were analyzed using chemiluminescence (LH, FSH, E2, TSH, and fT4) (Advia Centaur XP, Siemens Healthare, Munich, Germany), liquid chromatography-mass spectrometry (testosterone) (Agilent 6410 Triple Quad LC/MS, Agilent Technologies, Santa Clara, CA, USA), and immunoassay (IGF1 and IGFBP3) (Immulite 1000 Immunoassay, Siemens Healthcare, Munich, Germany) methods. The blood samples could not be collected for one subject. Two hormonal samples could not be analyzed due to errors in transporting the samples or problems related to the laboratory (fT4, $n = 1$; E2, $n = 2$).

Statistics

Differences in the mean values of the two groups were tested using Student's *t*-test. Exact chi-squared test was used for comparing the distributions of categorical data. The association between BMD and continuous variables were evaluated using linear regression analyzes, and results are presented as β-coefficients (β) and their 95% confidence intervals (95% CIs). Multivariate linear regression model with forward-stepwise variable selection procedure was used to identify the variables that best predicted BMDZs. A logistic regression model was used to estimate the influence of 1 SD decrease in the BMDZ on the fractures. The results are

Table 2. Comparison of the BMD *z*-scores at the follow-up visit, BMI, age at diagnosis, follow-up time, and age at the follow-up visit between the male and female subjects.

	Total, mean (SD), $n = 73$	Males, mean (SD), $n = 46$	Females, mean (SD), $n = 27$	Mean difference	p[a] (95% CI)
Right femoral neck	−0.91 (0.93)[b]	−1.09 (0.84)[c]	−0.59 (1.01)[d]	0.50 (0.06–0.95)	.028[e]
Left femoral neck	−0.82 (1.03)[b]	−1.02 (1.01)[c]	−0.48 (1.00)[d]	0.54 (0.04–1.03)	.033[e]
Right total hip	−0.77 (1.08)[b]	−0.98 (0.87)[c]	−0.41 (1.32)[d]	0.57 (−0.02 to 1.16)	.056
Left total hip	−0.69 (1.16)[b]	−0.91 (1.01)[c]	−0.31 (1.31)[d]	0.60 (−0.005 to 1.19)	.052
Lumbar spine	−0.83 (1.15)[f]	−1.03 (1.08)	−0.47 (1.20)[d]	0.57 (0.01–1.12)	.044[e]
BMI (kg/m^2)	25.2 (6.2)	24.0 (5.1)	27.2 (7.4)	3.2 (−0.1 to 6.5)	.055
Age at diagnosis (years)	8.3 (4.3)	8.0 (4.3)	8.7 (4.3)	0.6 (−1.4 to 2.7)	.549
Follow-up time (years)[g]	19.1 (6.1)	18.5 (6.0)	20.1 (6.4)	1.6 (−1.4 to 4.6)	.285
Age at follow-up visit (years)	28.4 (6.8)	27.5 (6.3)	29.9 (7.3)	2.4 (−0.8 to 5.7)	.141

[a]Student's *t*-test.
[b]$n = 71$.
[c]$n = 45$.
[d]$n = 26$.
[e]Significance level: 0.05.
[f]$n = 72$.
[g]Follow-up duration since the cessation of tumor therapy.

presented as odds ratios (ORs). Statistical analyzes were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA).

Ethics

Written, informed consent was obtained from all the enrolled subjects and/or their legal guardians. The study was approved by the institutional Review Boards of Oulu, Kuopio, Turku, Tampere and Helsinki University Hospitals, Finland. The research was conducted according to the principles of the Declaration of Helsinki.

Results

Patient characteristics

A total of 74 (47 males) subjects participated in the study. The mean age at diagnosis was 8.3 years. The study subjects' mean age at the follow-up visit was 28.4 years, and the mean follow-up duration from the time of cessation of therapy was 18.9 years. More than half (52.7%) of the subjects had received local irradiation for the brain tumor, 40.5% craniospinal irradiation with the local boost, 4.1% cranial irradiation with local boost, and 2.7% stereotactic irradiation. Chemotherapy was a part of the treatment for 63.5% patients, and almost all patients had undergone surgery for the tumor (95.9%). Ventriculoperitoneal shunt had been placed in 59.5% subjects. No significant differences in tumor characteristics were noted between the participants and non-participants of the study (Table 1).

Bone mineral density

The overall mean BMDZs of the study population were −0.91 SD in the right and −0.82 SD in the left femoral neck, −0.77 SD in the right and −0.69 SD in the left total hip, and −0.83 SD in the lumbar spine (Table 2). One-third (31.4%) of the subjects had a difference of >0.5 in the BMDZs of the femoral necks. Male subjects had significantly lower BMDZs of the femoral necks and lumbar spine than female subjects (Table 2).

BMI had a strong positive association with BMDZ in all the measured areas ($p \leq .001$) (Table 3). Male subjects had lower BMI than female subjects; however, the difference was only borderline significant ($p = .055$). Age at diagnosis had a significant positive association with the BMDZ of the femoral necks [$\beta = 0.05$; 95% CI (0.002–0.10); $p = .044$ in the right and $\beta = 0.06$; 95% CI (0.001–0.11); $p = .045$ in the left femoral neck]. Age at the follow-up visit [$\beta = 0.06$; 95% CI (0.02–0.10); $p = .002$] and follow-up time [$\beta = 0.05$; 95% CI (0.004–0.09); $p = .031$] were associated positively with the BMDZs in the lumbar spine.

Effect of tumor location and treatments on BMD

More than half (52.8%) of the subjects had an infratentorial tumor and had significantly lower BMDZs in the left femoral neck and total hips than subjects with supratentorial tumors (Table 4). Tumors located in the pituitary or hypothalamus ($n = 7$) regions did not affect the BMDZs (Table 4).

Patients who had been treated with craniospinal irradiation had lower BMDZs in the total hips and the lumbar spine than patients treated without spinal irradiation. However, the difference was statistically significant only for the left total hip ($p = .017$) (Table 4). The patients treated using chemotherapy had lower BMDZs in all the measured areas compared with those not treated using chemotherapy. However, the differences were not significant (Table 4). Patients with a ventriculoperitoneal shunt (59.7%) had significantly lower BMDZs in the femoral necks and the total hips (Table 4). The cumulative dose of corticosteroids used for brain tumor treatment did not decrease the BMDZs in later life (Table 4).

In multivariate regression analyses with forward-stepwise variable selection (using ventriculoperitoneal shunt, cranial irradiation with or without spinal irradiation, chemotherapy and supratentorial or infratentorial tumor, BMI, dose of irradiation to the thalamic area, and total dose of corticosteroids during the tumor treatment as candidate variables), ventriculoperitoneal shunt and BMI were found to significantly

Table 3. Analysis of the BMD *z*-scores and hormones (FSH; LH; estradiol, E2 in female subjects and testosterone in male subjects, TSH; fT4; IGF1; IGFBP3), BMI, and patients with and without current hydrocortisone replacement therapy.

	Femoral neck ($n = 71$)		Total hips ($n = 71$)		
	Right	Left	Right	Left	Lumbar spine ($n = 72$)
FSH (U/L) in female subjects ($n = 25$)					
B	−0.09	−0.11	−0.11	−0.13	−0.09
95% CI	(−0.17 to −0.003)	(−0.18 to −0.04)	(−0.21 to 0.003)	(−0.23 to −0.03)	(−0.19 to 0.01)
p[a]	.042[b]	.006[b]	.057	.015[b]	.070
FSH (U/L) in male subjects ($n = 45$)					
β	−0.03	−0.03	−0.03	−0.03	−0.001[c]
95% CI	(−0.06 to 0.01)	(−0.07 to 0.01)	(−0.06 to 0.01)	(−0.08 to 0.01)	(−0.05 to 0.04)
p[a]	.117	.131	.161	.098	.967
LH (U/L) in female subjects ($n = 25$)					
β	−0.05	−0.05	−0.07	−0.07	−0.07
95% CI	(−0.11 to 0.01)	(−0.11 to 0.01)	(−0.15 to 0.01)	(−0.15 to 0.01)	(−0.14 to −0.001)
p[a]	.121	.104	.098	.082	.046[b]
LH (U/L) in male subjects ($n = 45$)					
β	−0.05	−0.04	−0.03	−0.03	0.05[c]
95% CI	(−0.13 to 0.04)	(−0.14 to 0.07)	(−0.12 to 0.05)	(−0.13 to 0.07)	(−0.06 to 0.16)
p[a]	.255	.485	.447	.537	.376
E2 (nmol/L) in female subjects ($n = 23$)					
β	−0.96	−0.78	−0.68	−0.77	−0.99
95% CI	(−3.07 to 1.15)	(−2.81 to 1.25)	(−3.42 to 2.06)	(−3.43 to 1.90)	(−3.18 to 1.20)
p[a]	.357	.434	.611	.557	.357
Testosterone (nmol/L) in male subjects ($n = 45$)					
β	0.01	0.03	0.02	0.03	−0.01[c]
95% CI	(−0.03 to 0.05)	(−0.02 to 0.07)	(−0.02 to 0.06)	(−0.02 to 0.07)	(−0.05 to 0.03)
p[a]	.625	.227	.345	.222	.640
TSH (mU/L) ($n = 70$)					
β	−0.02	−0.05	−0.05	−0.08	−0.06[d]
95% CI	(−0.13 to 0.08)	(−0.17 to 0.06)	(−0.17 to 0.07)	(−0.20 to 0.05)	(−0.18 to 0.07)
P[a]	.672	.361	.441	.230	.369
fT4 (pmol/L) ($n = 69$)					
β	−0.06	−0.08	−0.09	−0.10	−0.10[e]
95% CI	(−0.13 to 0.01)	(−0.15 to −0.001)	(−0.16 to −0.01)	(−0.19 to −0.02)	(−0.18 to −0.02)
P[a]	.071	.048[b]	.033[b]	.015[b]	.014[b]
IGF1 (nmol/L) ($n = 70$)					
β	−0.002	0.002	−0.01	−0.01	−0.01[d]
95% CI	(−0.02 to 0.02)	(−0.02 to 0.02)	(−0.03 to 0.02)	(−0.03 to 0.02)	(−0.03 to 0.02)
p[a]	.839	.851	.593	.592	.531
IGFBP3 (mg/L) ($n = 70$)					
β	−0.04	−0.06	−0.02	−0.03	0.15[d]
95% CI	(−0.25 to 0.17)	(−0.29 to 0.16)	(−0.26 to 0.22)	(−0.28 to 0.23)	(−0.10 to 0.40)
p[a]	.698	.577	.888	.847	.228
Hydrocortisone replacement therapy, mean (SD)					
Yes ($n = 8$)	−0.35 (1.25)	−0.06 (1.38)	−0.19 (1.50)	−0.04 (1.67)	−0.71 (1.45)
No ($n = 64$)	−0.98 (0.87)[f]	−0.92 (0.95)[f]	−0.85 (1.01)[f]	−0.77 (1.06)[f]	−0.84 (1.12)
Mean diff.	0.63	0.86	0.66	0.73	0.13
95% CI of diff.	(−0.05 to 1.32	(0.10–1.61)	(−0.14 to 1.46)	(−0.12 to 1.59)	(−0.74 to 0.99)
p[g]	.071	.026[b]	.105	.091	.769
BMI (kg/m^2) ($n = 71$)					
β	0.06	0.07	0.09	0.10	0.07[h]
95% CI	(0.02–0.09)	(0.04–0.11)	(0.05–0.13)	(0.06–0.14)	(0.03–0.11)
p[a]	.001[b]	<.001[b]	<.001[b]	<.001[b]	.001[b]

[a]Univariate linear regression analysis.
[b]Significance level: 0.05.
[c]$n = 46$.
[d]$n = 71$.
[e]$n = 70$.
[f]$n = 63$.
[g]Student's *t*-test.
[h]$n = 72$.

influence the BMDZs of the femoral necks and the total hips. In the lumbar spine, only BMI had a significant positive association with the BMDZ (Table 5).

Hormonal status and BMD

In females, there was a negative association between FSH and the BMDZ of the femoral necks and the left total hip and between LH and the BMDZ of the lumbar spine (Table 3). In males, the levels of FSH and LH were not associated with the BMDZ. Further, no association was found between the measured E2 in females or the testosterone in males and the BMDZ (Table 3). It is noteworthy that fT4 was associated negatively with the BMDZ in the left femoral neck, total hips, and lumbar spine, while no association was found between TSH and the BMDZ (Table 3). The levels of IGF1 and IGFBP3 were not associated with the BMDZ (Table 3). The ongoing hydrocortisone replacement therapy did not

Table 4. Associations between the BMD *z*-scores and the location of the tumor and the tumor treatments (irradiation, chemotherapy, ventriculoperitoneal shunting, total dose of glucocorticoids administered during brain tumor treatment).

	Femoral neck ($n = 71$)		Total hip ($n = 71$)		
	Right	Left	Right	Left	Lumbar spine ($n = 72$)
Location of the tumors, mean (SD)					
Infratentorial ($n = 38$)	−1.09 (0.84)[a]	−1.12 (0.84)	−1.08 (0.85)[a]	−1.01 (0.96)	−0.88 (1.15)
Supratentorial ($n = 34$)	−0.72 (1.00)	−0.48 (1.14)[b]	−0.44 (1.22)	−0.32 (1.26)[b]	−0.76 (1.16)
Mean difference (95% CI)	−0.37	−0.63	−0.64	−0.69	−0.12
95% CI of the difference	(−0.80 to 0.07)	(−1.10 to −0.16)	(−1.15 to −0.14)	(−1.22 to −0.16)	(−0.66 to 0.43)
p[c]	.096	.009[d]	.013[d]	.011[d]	.670
Pituitary or hypothalamus					
Tumor ($n = 7$)	−0.80 (1.29)	−0.28 (1.58)[e]	−0.73 (1.39)	−0.43 (1.70)[e]	−1.14 (1.47)
Other ($n = 65$)	−0.92 (0.90)[f]	−0.87 (0.97)	−0.78 (1.06)[f]	−0.71 (1.11)	−0.79 (1.12)
Mean difference	0.12	0.59	0.05	0.28	−0.35
95% CI of the difference	(−0.62 to 0.87)	(−0.29 to 1.46)	(−0.82 to 0.92)	(−0.71 to 1.27)	(−1.27 to 0.56)
p[c]	.745	.183	.910	.576	.447
Irradiation, mean (SD)					
Local, cranial or stereotactic irradiation ($n = 43$)	−0.84 (1.02)[g]	−0.71 (1.06)[g]	−0.61 (1.20)[g]	−0.42 (1.18)[g]	−0.65 (1.17)
Craniospinal irradiation ($n = 29$)	−1.02 (0.80)	−0.98 (0.99)	−1.01 (0.86)	−1.08 (1.02)	−1.08 (1.09)
Mean difference	0.18	0.27	0.41	0.66	0.43
95% CI of the difference	(−0.27 to 0.63)	(−0.23 to 0.76)	(−0.11 to 0.92)	(0.12 to 1.20)	(−0.12 to 0.97)
p[c]	.423	.291	.121	.017[d]	.121
Chemotherapy, mean (SD)					
Yes ($n = 45$)	−0.98 (0.87)[h]	−0.95 (0.95)	−0.88 (1.01)[h]	−0.85 (1.10)	−0.97 (1.02)
No ($n = 26$)	−0.78 (1.04)	−0.60 (1.16)[i]	−0.58 (1.20)	−0.39 (1.21)[i]	−0.58 (1.33)
Mean difference	−0.20	−0.35	−0.30	−0.46	−0.38
95% CI of the difference	(−0.66 to 0.25)	(−0.86 to 0.16)	(−0.84 to 0.23)	(−1.03 to 0.10)	(−0.99 to 0.22)
p[c]	.378	.175	.258	.107	.209
Ventriculoperitoneal shunt, mean (SD)					
Yes ($n = 43$)	−1.15 (0.91)[g]	−1.05 (0.98)[g]	−1.05 (1.04)[g]	−0.91 (1.15)[g]	−1.02 (1.16)
No ($n = 29$)	−0.57 (0.86)	−0.50 (1.04)	−0.37 (1.03)	−0.36 (1.10)	−0.54 (1.09)
Mean difference	−0.58	−0.55	−0.68	−0.55	−0.48
95% CI of the difference	(−1.01 to −0.15)	(−1.03 to −0.07)	(−1.18 to −0.18)	(−1.10 to −0.01)	(−1.03 to 0.06)
p[c]	.009[d]	.026[d]	.009[d]	.047[d]	.080
Total dose of glucocorticoids in prednisolone during the Brain tumor treatment (g/m^2) ($n = 72$)					
B	−0.03[j]	−0.03[j]	−0.04[j]	−0.04[j]	−0.05
95% CI	(−0.07 to 0.02)	(−0.07 to 0.02)	(−0.08 to 0.01)	(−0.09 to 0.01)	(−0.10 to 0.01)
p[k]	.222	.273	.125	.133	.078

[a] $n = 37$.
[b] $n = 33$.
[c] Student's *t*-test.
[d] Significance level: 0.05.
[e] $n = 6$.
[f] $n = 64$.
[g] $n = 42$.
[h] $n = 46$.
[i] $n = 24$.
[j] $n = 71$.
[k] Linear regression analysis.

Table 5. Multivariate regression analyses of the BMD *z*-scores with forward-stepwise variable selection procedure (with ventriculoperitoneal shunt, cranial irradiation with or without spinal irradiation, chemotherapy and supratentorial or infratentorial tumor, BMI, dose of radiation to the thalamic area, and total dose of corticosteroids during the tumor treatment as candidate variables).

	β (95 % CI); p	
	Ventriculoperitoneal shunt	BMI
Right femoral neck	0.73 (0.31–1.14); $p = .001$	0.07 (0.04–0.11); $p < .001$
Left femoral neck	0.60 (0.12–1.07); $p = .015$	0.08 (0.04–0.12); $p < .001$
Right total hip	0.70 (0.24–1.14); $p = .003$	0.09 (0.05–0.13); $p < .001$
Left total hip	0.62 (0.12–1.11); $p = .015$	0.10 (0.06–0.15); $p < .001$
Lumbar spine	NS	0.07 (0.02–0.11) p=.006

Forward-stepwise multivariate regression analysis of peripheral hormones (IGF1; IGFBP3; fT4, and testosterone) and BMI

	β (95% CI); p	
	BMI	Testosterone
Left Femoral Neck	0.09 (0.03–0.15); $p = .005$	0.05 (0.007–0.09); $p = .025$
Right Total Hip	0.08 (0.03–0.14); $p = .003$	0.05 (0.009–0.09); $p = .018$
Left Total Hip	0.11 (0.05–0.17); $p \leq .001$	0.06 (0.02–0.10); $p = .007$

NS: non-significant association.

Table 6. Analysis of the BMD *z*-scores of subjects who did and did not perform high-impact sports and subjects with and without previous fractures in the long bones.

	Femoral neck ($n = 71$)		Total hip ($n = 71$)		
	Right	Left	Right	Left	Lumbar spine ($n = 72$)
High-impact sports, mean (SD)[a]					
Yes ($n = 26$)	−0.88 (1.07)[b]	−0.76 (1.21)[b]	−0.83 (1.18)[b]	−0.67 (1.28)[b]	−1.17 (1.20)
No ($n = 46$)	−0.92 (0.86)	−0.86 (0.93)	−0.74 (1.04)	−0.70 (1.10)	−0.63 (1.09)
Mean diff.	0.04	0.10	−0.08	0.03	−0.53
95% CI of diff.	(−0.42 to 0.50)	(−0.41 to 0.62)	(−0.63 to 0.46)	(−0.55 to 0.60)	(−1.08 to 0.02)
p[c]	.864	.692	.756	.929	.059
Fractures in the long bones, mean (SD)[d]					
Yes ($n = 16$)	−1.34 (0.96)	−1.25 (1.23)[e]	−1.31 (0.99)	−1.28 (1.29)[e]	−1.38 (1.23)
No ($n = 56$)	−0.79 (0.89)[f]	−0.71 (0.95)	−0.62 (1.07)[f]	−0.53 (1.08)	−0.67 (1.09)
Mean diff.	−0.55	−0.54	−0.70	−0.75	−0.71
95% CI of diff.	(−1.07 to −0.04)	(−1.13 to 0.05)	(−1.29 to −0.10)	(−1.40 to −0.10)	(−1.35 to −0.08)
p[c]	.036[g]	.073	.023[g]	.025[g]	.028[g]

[a]Reported high-impact sports were ball games ($n = 14$), jogging ($n = 12$), group exercises ($n = 4$) and self-defense training or wrestling ($n = 2$).
[b]$n = 25$.
[c]Student's *t*-test.
[d]Reported fractures in the long bones were in the wrist ($n = 9$), humerus ($n = 1$), tibia ($n = 3$), femur ($n = 1$), femoral neck ($n = 1$), and elbow ($n = 2$).
[e]$n = 15$.
[f]$n = 55$.
[g]Significance level: 0.05.

significantly decrease the BMDZ. Replacement therapy for thyroid, growth hormone, or gonadal dysfunction did not increase the BMDZ.

In forward-stepwise multivariate regression analyses of the pituitary hormones (TSH, LH, and FSH as candidate variables), FSH showed a significant negative association with the BMDZs of the femoral necks and total hips (all $p < .05$). After BMI adjustment, the association disappeared, and FSH showed a significant negative association only with the BMDZ of the left femoral neck ($p = .049$). In forward-stepwise multivariate regression analyzes with peripheral hormones (IGF1, IGFBP3, fT4, as well as testosterone in male subjects and E2 in female subjects) and BMI as candidate variables, only BMI showed a strong positive association with BMDZ in all areas in the female subjects. In male subjects, both, BMI and testosterone were positively associated with the BMDZ in the left femoral neck and in both total hips ($p < .05$) (Table 5).

Physical activity, fracture rate, and BMD

A total 36.1% of the subjects performed high-impact sports activities. The reported high-impact sports are shown in Table 6. Participation in high-impact sports did not affect the BMDZs (Table 6).

Fractures were common in the study population; 39.7% of the subjects reported previous fractures, and 22.2% reported fractures in the long bones (Table 6). Patients with previous fractures in the long bones had significantly lower BMDZs in the right femoral neck, total hips, and lumbar spine (Table 6). A decrease of 1 SD in the BMDZ of the femoral necks increased the risk of fractures in the long bones [OR = 2.0; 95% CI (1.0–3.9); $p = .042$ in the right; OR = 1.7; 95% CI (0.9–3.0); $p = .079$ in the left]. Fracture risk increased with a reduction of 1 SD in the BMDZ of the total hips [OR = 1.9; 95% CI (1.1–3.5); $p = .029$ in the right; OR = 1.8; 95% CI (1.1–3.1); $p = .032$ in the left] and the lumbar spine [OR = 1.7; 95% CI (1.0–2.9); $p = .036$].

Discussion

Compromised BMD is common in irradiated childhood brain tumor survivors; 23.6% of the subjects had low sex- and age-normalized *z*-scores (*z*-scores $\leq$2.0). Compromised BMD was associated with an increased fracture risk. The association between low BMD and fracture risk is well established [24]. In the present study, the risk of fractures in the long bones was higher than previously reported [24]. Further, reduced BMD has been reported in smaller cohorts of childhood brain tumor survivors followed up for a shorter duration [8–10,13,14,17–19]. To our knowledge, only one previous study with a large cohort ($n = 163$) and short follow-up duration (6.8 years) has shown similar results [16].

Male subjects had lower BMDZs of the femoral necks and the lumbar spine. Male sex has been reported as a risk factor for low BMD in childhood brain tumor survivors in two previous studies [14,17], while the risk is higher for women in the general population [24,27]. In the present study, BMI was lower in male subjects than in female subjects (although the difference was only borderline significant), which may partially explain the finding.

The nutrition particularly influences femoral mineralization [28]. The impact of malnutrition on BMD has been widely recognized in childhood brain tumor survivors [8,9,17,18]; however, few studies have evaluated the relationship between body composition and BMD with controversial results [10,13,17]. In healthy children, obesity increases the risk of low BMD and fractures [29–33]. Dissociation between weight and BMD gain during growth, imbalance between muscle mass and body size, and decrease in load-bearing exercise are suggested to decrease BMD in obese children [29–32]. Moreover, vitamin D deficiency is suggested to decrease BMD in obese children [34]. In adults, however, the impact of weight on BMD is found to be positive [35,36]. Increased mechanical loading [36], conversion of androgens to estrogen in the adipose tissue [36] and effects of adipose tissue on puberty [37] may explain the increased BMD.

Older age at diagnosis of childhood brain tumor has been reported as a risk factor for low BMD [18]; however, in the present study, patients with a younger age at diagnosis had lower BMDZs of the femoral necks. Nutrition, vitamin D, calcium, and weight-bearing physical activity mainly affect femoral mineralization [28]. Nutritional factors and weight-bearing physical activity have longer impact time on BMD during bone mineralization in patients with a younger age at diagnosis. Our study did not demonstrate a beneficial effect of high-impact sports on BMD, agreeing the results of Khrisnamoorthy [14].

Cranial irradiation has been suggested as a risk factor for low BMD in cancer patients [8,9,11,14,16–18]. Pietilä et al. [13] found lower BMD in patients treated with craniospinal irradiation ($n = 5$), but not with cranial irradiation ($n = 10$) in their study on 46 brain tumor survivors. Here, the difference between these treatment modalities was unclear because only the difference in their BMDZs for the left hip was statistically significant. Different chemotherapeutic agents, including cisplatin, ifosfamide, cyclophosphamide, and doxorubicin used by our study subjects are suggested to affect BMD by directly affecting the bones or indirectly affecting hormonal functions and blood mineral levels [25]. Limited data are available about the effect of chemotherapy on BMD in childhood brain tumor survivors [13,14,17,18]. In keeping with previous findings, chemotherapy was not significantly associated with lower BMD in this study [13,14,17,18]. We found that ventricular shunting and infratentorial tumor were associated with a lower BMD. The underlying mechanism is unclear; however, this may indicate greater hospitalization duration or overall disease severity.

Glucocorticoid treatment is a well-known risk factor for the development of osteoporosis [38]. Glucocorticoid treatment mainly affects the trabecular bone of the vertebrae [39]. Previous researchers have reported a high prevalence of asymptomatic vertebral fractures in children, adolescents, and adults treated with glucocorticoid treatment [39–42]. BMD may not be useful for identifying an individual's risk of developing vertebral fractures [39–42]. In the present study, the cumulative dose of glucocorticoids during tumor treatment was not associated with lower BMD.

Cranial irradiation also increases the risk for low BMD due to deficiencies of growth hormone or sex hormones; however, the results are controversial [8,10,13,16–19]. We did not find a significant association between the BMDZ and the measured IGF1 and IGFBP3 levels. This is because levels of IGF1 and IGFBP3 function poorly and may be normal in patients showing radiation-induced growth hormone dysfunction [43]. However, increasing FSH levels in female subjects negatively affected the BMDZ, which is consistent with that reported in a previous study on breast cancer survivors [44]. E2 levels were not associated with BMDZ in female subjects. The first marker of early ovarian dysfunction is an increase in the gonadotropin levels [44]. Serum estradiol levels may be unaffected [44]. In breast cancer survivors, FSH levels were above 21.2 U/L, suggesting menopause, and estrogen levels were above the postmenopausal range [44]. The FSH regulates spermatogenesis, and LH androgen synthesis in the testes [45]. In men, testosterone synthesis may be affected to a lesser degree because spinal irradiation does not cause testicular damage; however, this may adversely affect the ovaries in women [46]. Chemotherapeutic agents have a lesser adverse effect on androgen synthesis than on spermatogenesis [47,48]. A negative association was found between the fT4 level and BMD. Assessing the effect of the hormones on BMD is challenging because the subjects have co-existing central and peripheral hormonal dysfunctions and replacement therapy.

Limitations of this study include the lack of a control group and the use of different DXA techniques in different hospitals. However, the results of this study are presented in sex- and age-normalized *z*-scores given by the DXA manufacturers. We agree that the results obtained using different DXA techniques vary between scanners; however, this does not explain the overall low BMD observed in this study population.

We report significantly increased risks for BMD reduction and fractures in a national cohort of irradiated long-term survivors of childhood brain tumors. Osteoporosis is underdiagnosed in these survivors. Male subjects and subjects with low BMI are particularly at a risk of decrease in BMD. We observed an association between sex hormone dysfunction and low BMD. Good nutritional support and proper treatment of hormonal deficiencies are needed to prevent a decrease in BMD. Moreover, the results of this study highlight the need for a systematic follow-up of this patient group.

Disclosure statement

No potential conflict of interest was reported by the authors.

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