Impact of Vertebral Fractures and Glucocorticoid Exposure on Height Deficits in Children During Treatment of Leukemia

Jinhui Ma,[1] Kerry Siminoski,[2] Nathalie Alos,[3] Jacqueline Halton,[4] Josephine Ho,[5] Elizabeth A. Cummings,[6] Nazih Shenouda,[4] Mary Ann Matzinger,[4] Brian Lentle,[7] Jacob L. Jaremko,[2] Beverly Wilson,[2] David Stephure,[5] Robert Stein,[8] Anne Marie Sbrocchi,[9] Celia Rodd,[10] Victor A. Lewis,[5] Caroline Laverdière,[3] Sara Israels,[10] Ronald M. Grant,[11] Conrad V. Fernandez,[6] David B. Dix,[7] Robert Couch,[2] Elizabeth Cairney,[8] Ronald Barr,[1] Stephanie Atkinson,[2] Sharon Abish,[9] David Moher,[12] Frank Rauch,[9] and Leanne M. Ward,[4] for the Canadian STOPP Consortium*

[1]McMaster University, Hamilton, Ontario L8S 4L8, Canada; [2]University of Alberta, Edmonton, Alberta T6G 2B7, Canada; [3]Université de Montréal, Montreal, Quebec H3T 1C5, Canada; [4]University of Ottawa, Ottawa, Ontario K1H 8L1, Canada; [5]University of Calgary, Calgary, Alberta T3B 6A8, Canada; [6]Dalhousie University, Halifax, Nova Scotia B3K 6R8, Canada; [7]University of British Columbia, Vancouver, British Columbia V6H 3V4, Canada; [8]University of Western Ontario, London, Ontario N6A 5W9, Canada; [9]McGill University, Montreal, Quebec H4A 3J1, Canada; [10]University of Manitoba, Winnipeg, Manitoba R3A 1S1, Canada; [11]University of Toronto, Toronto, Ontario M5G 1X8, Canada; and [12]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario M5G 1X8, Canada

ORCiD numbers: 0000-0003-1557-9185 (L. M. Ward).

Objective: To assess the effect of vertebral fractures (VF) and glucocorticoid (GC) exposure on height deficits in children during treatment of acute lymphoblastic leukemia (ALL).

Methods: Children with ALL treated without cranial radiation therapy (n = 160; median age, 5.1 years; 58.1% male) were followed prospectively for 6 years. Spinal deformity index (SDI) was used to quantify VF status.

Results: Baseline height *z* score ± SD was 0.3 ± 1.2. It fell by 0.5 ± 0.4 in the first 6 months for boys and by 0.4 ± 0.4 in the first 12 months for girls ($P < 0.01$ for both) and then subsequently recovered. The prevalence of VF peaked at 1 year (17.6%). Among those with VF, median SDI rose from 2 [interquartile range (IQR): 1, 7] at baseline to 8 (IQR: 1, 8) at 1 year. A mixed model for repeated measures showed that height *z* score declined by 0.13 (95% CI: 0.02 to 0.24; $P = 0.02$) for each 5-unit increase in SDI during the previous 12 months. Every 10 mg/m^2 increase in average daily GC dose (prednisone equivalent) in the previous 12 months was associated with a height *z* score decrement of 0.26 (95% CI: 0.20 to 0.32; $P < 0.01$).

Conclusions: GC likely plays a major role in the observed height decline during therapy for ALL. Because only a minority of children had VF, fractures could not have contributed significantly to the height deficit in the entire cohort but may have been important among the subset with VF. (***J Clin Endocrinol Metab*** **104: 213–222, 2019)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA
Copyright © 2019 Endocrine Society
Received 22 May 2018. Accepted 17 September 2018.
First Published Online 20 September 2018

*The Canadian STOPP Consortium is a pan-Canadian, pediatric bone health working group.

Abbreviations: ALL, acute lymphoblastic leukemia; GC, glucocorticoid; IQR, interquartile range; LS BMD, lumbar spine bone mineral density; SDI, spinal deformity index; VF, vertebral fracture.

Downloaded from https://academic.oup.com/jcem/article/104/2/213/5103424 by guest on 11 April 2024

Children with acute lymphoblastic leukemia (ALL) experience height deficits during treatment, and these deficits may persist after therapy has ended (1–11). A number of factors have been associated with the observed height impairments, apart from the cancer itself, including the use of cranial radiation therapy, intensive chemotherapeutic regimens, malnutrition, episodes of infection, precocious puberty, GH-GF1 deficiency, younger age, taller stature at diagnosis, and female sex (1–11). Two other possible contributors to height deficits have not been explored in this population: the development of vertebral fractures (VF), and glucocorticoid (GC) exposure as part of the chemotherapy.

It is well documented in adults that VF lead to height loss (12, 13). Children with ALL experience VF at substantial rates, so it is possible that vertebral body compression could contribute to the observed height impairments (14, 15). In support of this hypothesis, one study reported that relatively greater deficits in spine height than in leg length contributed to net height deficits in these children (16). The adult marker of VF—absolute height loss—is not useful in children because normal childhood growth can lead to a net gain in height even when VF have occurred (17). Instead, a VF in a child would be expected to limit growth relative to children of the same age, expressed as a reduction in the height *z* score over the period during which the VF developed. A confounding issue in children is the possibility of vertebral body reshaping through bone growth, with consequent elimination of its contribution to a permanent height deficit (17, 18). Applying the adult approach of considering only new VF, without also evaluating the state of previously fractured vertebrae, could therefore lead to erroneous conclusions. This issue can be circumvented through use of the spinal deformity index (SDI), a measure of overall VF burden that incorporates both new fractures and the present condition of prior fractures into a single assessment of current overall spine fracture status (19).

Many authors have assumed there is a direct effect of ALL chemotherapeutic agents on growth, but the roles played by specific drugs used in the various regimens have not been analyzed (3, 8, 9). GC have been proposed as potential contributors to height deficits in ALL, given that they are part of every ALL treatment protocol at high and prolonged doses and given that they are well documented as affecting growth when used in a wide range of conditions (1, 3, 10, 20, 21). However, the role of GC in creating height deficits in ALL has not been explored or quantified.

The STeroid-induced Osteoporosis in the Pediatric Population (STOPP) research consortium prospectively studied a cohort of children with ALL for 6 years (14, 15, 22, 23). Research data encompassed anthropometric measurements, annual evaluation of VF status using standardized methodology, and details of drug treatment that included full GC dosing records. This data set therefore provides a unique opportunity to evaluate the contributions of VF and GC to height deficits in children during the treatment phase of ALL.

Subjects and Methods

Patients and study design

Children aged 1 month to 17 years with ALL were enrolled in the core STOPP study (N = 188) from 2005 to 2007; eligibility criteria have been described (22). The research ethics board of each participating institution approved the study, and informed consent/assent was obtained before enrollment. Because our goal was to understand the height trajectory and potential recovery in those without GH-IGF1 deficiency, patients who received cranial radiation therapy (n = 28) were excluded from the current study, leaving 160 study subjects for analysis. Patients were studied within 30 days of GC initiation and were followed up prospectively for 6 years. Data were censored at patients' last follow-up visit or when bisphosphonate therapy was initiated for osteoporotic fractures.

Clinical data

Clinical data were obtained at baseline, every 3 months in the first 4 years, and then annually during the last 2 years. Height was measured three times at each visit by a pediatric nurse or research associate using a regularly calibrated stadiometer, and the average was recorded. Measurements were made in the standing position when a child was able to stand; if not, the child was measured in the supine position. Weight was determined using either a digital or a mechanical scale. Height, weight, and body mass index (kg/m^2) were converted to age- and sex-matched *z* scores using the National Center for Health Statistics normative database of the US Centers for Disease Control and Prevention (24). Height velocity *z* scores were determined for each 6-month period using published normative data (25). Lumbar spine bone mineral density (LS BMD) by dual-energy x-ray absorptiometry was captured every 6 months for 4 years and then annually. LS BMD *z* scores were calculated using published normative data as previously described (22). Leukemia risk category and pubertal staging were also determined as previously reported (22). Dietary calcium and vitamin D intake was assessed using a food frequency questionnaire, and daily intake for each nutrient (diet plus supplement) was expressed as the percentage of the estimated average requirement based on the Institute of Medicine's dietary reference intakes (22, 26). Children were treated according to the Children's Oncology Group leukemia protocols except for one site that used the Dana-Farber Cancer Institute protocol. GC dosage was adjusted according to the leukemia protocols by the treating oncologist. GC doses were converted to prednisone equivalents (mg/m^2) and were expressed as the average daily dose over a specified time period (27–29).

Downloaded from https://academic.oup.com/jcem/article/104/2/213/5103424 by guest on 11 April 2024

VF

Lateral thoracolumbar spine radiographs were obtained at baseline and annually, with the presence of VF assessed independently by two pediatric radiologists according to the modified Genant semiquantitative method; a third radiologist adjudicated discrepancies (22, 30). Vertebral bodies were graded according to the extent of reduction in height ratios when the anterior vertebral height was compared with the posterior height, the middle height with the posterior height, and the posterior height with the posterior height of adjacent vertebral bodies. The following reductions in height ratios were defined: grade 0 (normal), 20% or less; grade 1, >20% to 25%; grade 2, >25% to 40%; grade 3, >40%. The SDI was calculated as the sum of Genant grades from T4 to L4 (19) and ranged from 0 to 39.

Statistical analysis

Data were summarized using frequency and percentage for categorical variables and mean and SD or median and interquartile range (IQR) for continuous variables. Box plots were generated to illustrate the trajectory of height, height velocity, and average daily GC intake over time. One-sample *t* test was used to compare children's height and height velocity *z* scores with those of the healthy population. Both univariate and multivariate linear mixed models for repeated measures with a first-order autoregressive covariance structure were constructed to relate clinical variables to declines in height *z* scores. By using a first-order autoregressive covariance structure, we assumed the correlation between outcomes assessed at adjacent time points was greater than that between outcomes assessed at nonadjacent time points. In the multivariate linear mixed model, sex was incorporated in the model because it has been proposed as a predictor in some published studies, though it was not significant in our univariate analysis. Akaike information criterion was used for assessing the model fit. Results were expressed as effect sizes with 95% CIs. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). Differences were considered significant when $P < 0.05$.

Results

Clinical characteristics of the cohort

The disposition of the 160 children included in this study and reasons for lack of available data at each time point are presented in Fig. 1. Clinical features at baseline are summarized in Table 1, with baseline anthropometric measurements carried out at a median of 21 days (IQR, 14 to 27 days) after diagnosis with ALL. Among the 160 children, three (two girls and one boy) experienced relapse of leukemia but survived, and five were treated with bisphosphonate therapy for osteoporotic fractures. None of the patients in this cohort had received spinal or testicular radiation therapy.

Height and height velocity

At baseline, boys were slightly taller than the healthy average (mean *z* score ± SD = 0.4 ± 1.1; $P < 0.01$) (Fig. 2a). The greatest decline in height *z* score for boys occurred from baseline to 6 months, when it fell by 0.5 ± 0.4 ($P = 0.01$) to −0.1 ± 1.1. The decrease in height *z* score was reflected in the height velocity *z* score of −2.8 ± 2.3 ($P < 0.01$) for the same time interval (Fig. 2b). In the second 6-month period, from 6 to 12 months, the height velocity *z* score rose markedly to 0.5 ± 2.4, which was not significantly different from the healthy average, and the height *z* score increased slightly to 0.1 ± 1.2 at 12 months. Both height velocity and height *z* scores subsequently remained at or slightly above the healthy means for the remainder of the study. The change in height *z* score from baseline to 6 years was −0.1 ± 0.6, which was not a significant difference.

The overall temporal profile was similar in girls with some subtle differences. At baseline, girls' height *z* scores were comparable to the healthy average. As with boys, the height velocity *z* score was low over the first 6 months (−2.7 ± 2.4; $P < 0.01$), which led to a decline in the height *z* score. Although the height *z* score nadir for boys occurred at 6 months, the lowest value for girls was slightly later at 12 months. It decreased by 0.4 ± 0.4 ($P = 0.01$) from baseline to 1 year, when it reached −0.3 ± 1.1 ($P < 0.05$). Height *z* scores in girls were not different from the healthy average at 2 years, and as for boys, both height velocity and height *z* scores subsequently remained at or slightly above the healthy means for the remainder of the study. The final height *z* score at 6 years was not different from baseline (difference of 0.00 ± 0.6).

VF

Twenty-three children (14.4%) had VF present at baseline (Table 1). New fractures developed in 31 subjects (19.4%) over 6 years; 14 of these subjects (45.2%) had VF at baseline. In other words, 40 children had VF during the course of the study (including baseline). Most children who experienced new fractures did so in the first year (21 of 160; 13.1%) so that the proportion with fracture (17.6%) was highest at this time (Table 2). As a result, the median SDI among those with fractures rose from 2.0 (IQR: 1, 7) at baseline to 8.0 (1, 8) at 1 year (Table 2). Of 40 children with VF at any time during the study, six received osteoporosis therapy and were thereafter excluded from this analysis. Among the remaining 34 children with VF, 28 (82.4%) underwent complete vertebral body reshaping (*i.e.,* all vertebral bodies had a Genant grade of 0) by their last follow-up visit, whereas the others underwent partial reshaping (Genant grades improved, but not all children progressed to Genant grade 0 for all vertebral bodies). The mean ± SD residual spine deformity in these children (as expressed by the SDI) was 3.1 ± 3.3. The reshaping phenomenon together with the decreased rate of new fractures after the first year led to a marked decline in the SDI among

Downloaded from https://academic.oup.com/jcem/article/104/2/213/5103424 by guest on 11 April 2024

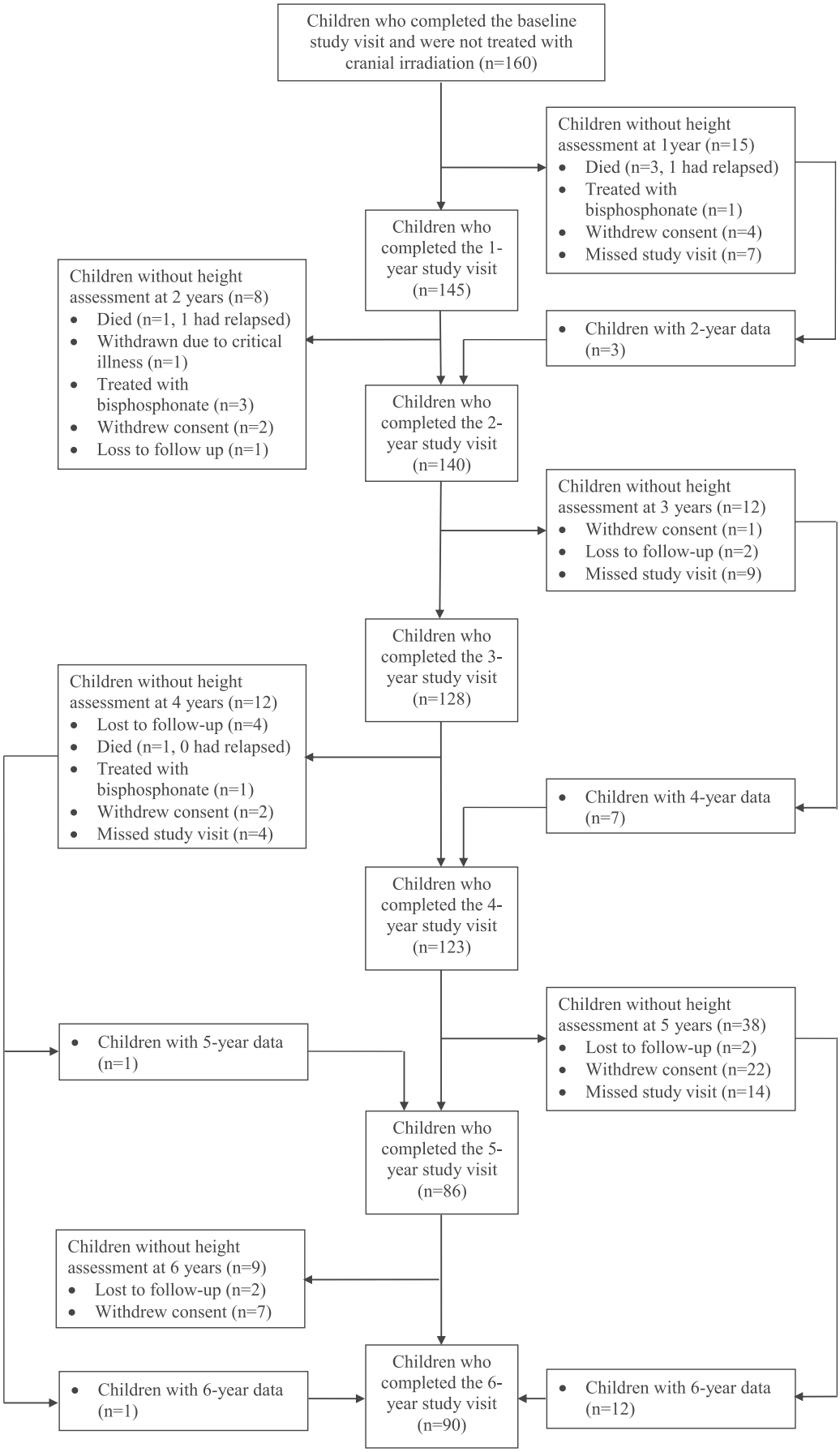

Figure 1. Disposition of patients from baseline to 6 y.

Downloaded from https://academic.oup.com/jcem/article/104/2/213/5103424 by guest on 11 April 2024

Table 1. Description of the Cohort at Baseline

Clinical Parameters	Results (n = 160)
Demographic data	
Age, y, median (IQR)	5.1 (3.3, 9.3)
Male, n (%)	93 (58.1%)
Ethnicity, n (%)	
White	119 (74.4%)
Aboriginal peoples of North American	10 (6.3%)
South Asian (*e.g.,* East Indian, Pakistani, Punjabi, Sri Lankan)	6 (3.7%)
Black	7 (4.4%)
Other	18 (11.2%)
Characteristics of the leukemia	
Leukemia risk category,[a] n (%)	
Standard risk	108 (68.8%)
High risk	49 (31.2%)
Leukemia diagnosis, n (%)	
Precursor B-cell acute lymphoblastic leukemia	153 (95.6%)
T-cell acute lymphoblastic leukemia	6 (3.8%)
Other	1 (0.6%)
White blood cell count at diagnosis,[a] n (%)	
$\geq 20 \times 10^9$/L	34 (21.9%)
$<20 \times 10^9$/L	121 (78.1%)
Treatment protocol, n (%)	
Children's Oncology Group protocol	133 (83.1%)
Dana Farber protocol	27 (16.9%)
Anthropometry	
Height *z* score, mean (SD)	0.3 (1.2)
Weight *z* score, mean (SD)	0.5 (1.2)
Body mass index *z* score, mean (SD)	0.6 (1.6)
Pubertal stage = Tanner 1, n (%)	139 (86.9%)
Nutritional intake[a]	
Average daily vitamin D ≥50% DRI, n (%)	64 (42.9%)
Average daily calcium ≥100% DRI, n (%)	135 (90.6%)
Radiological findings	
LS BMD *z* score, mean (SD)	−1.2 (1.3)
Bone age at baseline, y, median (IQR)	5.0 (3.0, 9.3)
Chronological age to bone age difference, y, median (IQR)	0.03 (−0.3, 0.4)
VF status	
Children with VF (grade 1 or higher)	23 (14.4%)

Abbreviation: DRI, dietary reference intake.

[a]Sample size was 160 except for nutritional intake (n = 149), leukemia risk category (n = 157), and white blood cell count at diagnosis (n = 155).

those with fractures, which fell to a median value of 2.0 (IQR: 2, 4) at 3 years and remained low until the end of the study, when it was 1.5 (IQR: 1, 2.5).

GC Exposure

In the first 30 days after diagnosis, 105 of 160 children (65.6%) were treated with dexamethasone, whereas 55 received other GC preparations as part of their chemotherapeutic regimen. Of total GC exposure, 35% occurred in the first 6 months of treatment, with an average ± SD daily dose of 13.8 ± 5.1 mg/m^2 for boys and 12.3 ± 3.6 mg/m^2 for girls (Fig. 2c). The dose then decreased to 7.7 ± 4.3 mg/m^2 for boys and 7.3 ± 3.1 mg/m^2 for girls in the second 6 months of treatment (*i.e.*, from 6 to 12 months) and remained stable until 24 months before falling further. By 30 months, 64 of the 67 girls (96%) had stopped GC treatment, and by 42 months, all boys (100%) had discontinued GC therapy.

Clinical predictors of declines in height *z* scores

Children with VF had lower height and height velocity *z* scores than those without VF at baseline and at 90% of the follow-up time points, although the differences did not reach statistical significance (Table 3). We also compared characteristics between children with and without VF over 6 years and found that children who had a VF at baseline or follow-up had significantly lower LS BMD *z* scores than those without a fracture history both at baseline (mean ± SD = −1.8 ± 1.5 vs −1.0 ± 1.2; $P = 0.001$) and 72 months (mean ± SD = −1.2 ± 1.1 vs −0.2 ± 1.3; $P = 0.001$). (Table 4). Children treated with dexamethasone in the first 30 days had less GC exposure overall between baseline and 12 months (mean ± SD = 3.6 ± 0.7 g/m^2 vs 4.5 ± 2.2; $P = 0.01$), with less of a decline in height *z* scores from baseline to 12 months than those who received other GC in the first 30 days (mean ± SD = −0.32 ± 0.46 vs −0.52 ± 0.41; $P = 0.01$).

Univariate analysis was carried out to assess relationships between clinical factors and declines in height *z* scores (Table 5). The two parameters of primary interest in this study were average daily GC dose (over the prior 12 months) and change in SDI (over the prior 12 months), and both were significantly associated with height *z*-score declines. Age was also a significant predictor. Multivariate analysis showed that height *z* scores declined by 0.13 (95% CI: 0.02 to 0.23; $P = 0.02$) for each 5-unit increase in the SDI during the previous 12 months (Table 6). Every 1 SD decrease in LS BMD *z* score was associated with a height *z* score decrement of 0.11 (95% CI: 0.04, 0.18; $P < 0.01$), every 10 mg/m^2 increase in average daily GC dose in the previous 12 months was associated with a height *z*-score decrement of 0.26 (95% CI: 0.20 to 0.32; $P < 0.01$), and each 10-year increase in age related to a height decrement of 0.08 (95% CI: 0.01 to 0.16; $P = 0.01$). Confirming the univariate result, sex was not a significant determinant of declining height.

Discussion

Growth rates fell markedly during the first 6 months of therapy for our subjects with childhood ALL, which led to a significant decline in the height *z* score from baseline

Downloaded from https://academic.oup.com/jcem/article/104/2/213/5103424 by guest on 11 April 2024

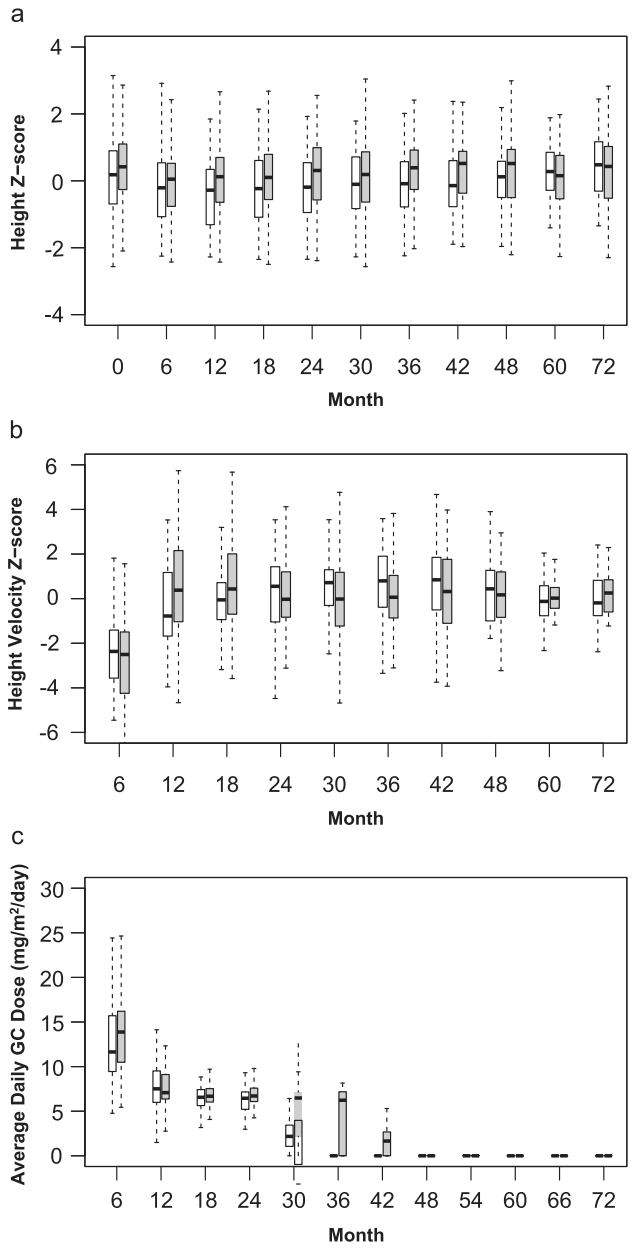

Figure 2. Trajectories for (a) height *z* scores at baseline and every 6 mos, (b) height velocity *z* scores, and (c) average GC daily dose. For height velocity and average GC daily dose, the 6 on the horizontal axis indicates the time interval from baseline to 6 mos, the 12 indicates the time interval from 6 to 12 mos, and so on. Girls are shown in white bars and boys in gray bars. Minimum, first quartile, median, third quartile, and maximum values are shown in the boxplot. The horizontal solid black lines within the box indicate the median.

to 6 months in boys and from baseline to 1 year in girls. These height deficits are similar in magnitude to those reported in the literature for the treatment phase of ALL (8). Consistent with our hypothesis that the occurrence of VF and exposure to GC might contribute to height deficits, we observed that the highest rate of VF occurred in the first year, which was aligned with the period of greatest GC exposure (*i.e.*, in the first 6 months of the study). In addition, after the first year, as SDI improved (because of fewer new fractures and reshaping of prior fractures) and GC dose declined, the height velocities returned to normal (or were even transiently above normal in some periods) and height *z* scores returned to the healthy normal mean. We found that every 5-unit increase in the SDI (per prior 12-month period) was associated with a height *z* score deficit of 0.13. The rate of VF was highest at 1 year after GC initiation when it was 17.6%; therefore, VF cannot have contributed significantly to the height deficit in the entire cohort. On the other hand, VF appear to have played a role in height loss among the individual fracture subjects. Increases in SDI from 2 at baseline to 8 at 1 year were of sufficient magnitude that VF could have affected growth within this subgroup.

In contrast, the effect size for GC was clinically relevant for the entire cohort. The model found that every 10-mg/m^2 increase in average daily GC dose (during the previous 12 months) was associated with a height *z* score decrement of 0.26. This effect size is pertinent to the group's GC exposure, which peaked in the first 6 months (an average daily dose of 13.8 mg/m^2 for boys and 12.3 mg/m^2 for girls). Bone growth occurs at the growth plate as chondrocytes proliferate, differentiate, produce cartilage matrix, and are then supplanted by osteoblasts that replace the newly formed cartilage with bone (20). Pharmacologic levels of GC influence each of these processes through both indirect and direct mechanisms (20, 21). Indirect actions occur primarily via inhibition of various facets of the GH-IGF1 axis, which is a principal regulator of longitudinal growth (21). Direct mechanisms involve changing gene expression within chondrocytes and bone cells, modulating a large number of proteins and metabolic pathways (21, 31, 32). Together, these GC pharmacologic effects lead to a variety of growth-impeding changes, such as apoptosis of osteoblasts and growth plate chondrocytes and stimulation of osteoclasts (21, 31, 32).

Our multivariate model also evaluated the roles of sex and age as predictors of growth impairment. We found no effect of sex and a very small, although statistically significant, positive relationship of height loss to increasing age. These findings differ from those of several studies reporting that age <4 years was associated with a greater final height deficit (8, 10) and that this effect of age was more pronounced in girls (16). These differences in results compared with findings in our study may relate to dissimilar patient populations or treatment regimens. It is worth noting, however, that most descriptions of augmented height deficits in young girls occur in the context of cranial radiotherapy, perhaps a consequence of increased vulnerability of the hypothalamic-pituitary

Downloaded from https://academic.oup.com/jcem/article/104/2/213/5103424 by guest on 11 April 2024

Table 2. VF Time Course Among Children With Fractures

Time (y)	N[a]	Children With VF, n (%)	Number of VF per Child [Mean (SD)]	SDI [Median (IQR)]
0	158	23 (14.6)	2.5 (2.4)	2.0 (1, 7)
1	131	23 (17.6)	3.4 (3.5)	8.0 (1, 8)
2	125	16 (12.8)	3.7 (3.0)	3.5 (2, 5.5)
3	119	13 (10.9)	3.1 (3.2)	2.0 (2, 4)
4	116	8 (6.9)	2.1 (2.8)	2.0 (1.5, 2.5)
5	79	8 (10.1)	2.0 (2.1)	1.5 (1, 4)
6	90	4 (4.4)	1.0 (0)	1.5 (1, 2.5)

[a]Number of children with a valid VF assessment.

axis to cranial radiation in younger female patients (4, 7). A number of studies on subjects not treated with radiation therapy reported results similar to ours (9, 33).

Outcomes in children treated without cranial radiation, such as in our cohort, have been variable, with some studies showing an effect on final height (3, 4, 8–10, 34) but others without (5, 7). It has been pointed out that the studies showing no effect on final height used older protocols with less intensive chemotherapy and were also limited in study size, which would have restricted the power to detect height changes (9). More recent studies that do describe a height effect showed final adult height deficits in the range of 0.5 SD (9). A decline in height of 0.5 SD is presumably more relevant to an individual with an expected final adult height at the fifth percentile as opposed to the 50th percentile, but even in the latter case, such a deficit would lower the final height from the 50th percentile to the 30th percentile. It is well documented that height differences of this magnitude are associated with lower school grades, lower incomes, increased health risks, decreased longevity, and other negative outcomes, so they should not be discounted (35–37).

Our study was not designed to assess final adult height, but only determinants of height deficits during ALL therapy. Although we have demonstrated that height *z* scores in this cohort returned to healthy mean values by the end of our 6-year study, it remains unknown whether these children will go on to attain a normal adult height. Reevaluation of this cohort after skeletal maturation would be of interest.

A limitation of this study is that blood testing was not performed, so we were unable to evaluate serum biomarkers that might be indicators of proposed contributors to height deficits, such as GH-IGF1 deficiency, sex hormone status, and malnutrition. On the other hand, we did not anticipate GH deficiency in this cohort because

Table 3. Comparison of Height and Height Velocity *z* Scores Between Children With and Without VF

	Children With VF		Children Without VF		
	n	Mean (SD)	n	Mean (SD)	*P*
Time			**Height *z* Score**		
Baseline	23	0.2 (1.2)	137	0.3 (1.2)	0.65
6 months	23	−0.2 (1.2)	137	−0.1 (1.1)	0.81
12 months	23	−0.3 (1.1)	122	−0.1 (1.2)	0.44
24 months	16	−0.4 (1.1)	124	0.1 (1.2)	0.13
36 months	13	0.0 (0.9)	115	0.1 (1.3)	0.64
48 months	8	0.1 (1.5)	115	0.1 (1.2)	0.97
60 months	8	−0.5 (1.2)	78	0.1 (1.1)	0.19
72 months	4	0.0 (0.76)	86	0.2 (1.2)	0.75
			Height Velocity *z* Score		
Baseline–6 months	23	−2.9 (2.5)	137	−2.7 (2.3)	0.76
6–12 months	23	0.0 (2.4)	137	0.1 (2.4)	0.83
12–18 months	23	0.2 (1.5)	122	0.6 (2.1)	0.48
18–24 months	23	0.0 (2.0)	122	0.2 (2.6)	0.78
24–30 months	16	−0.3 (2.6)	124	−0.1 (2.2)	0.74
30–36 months	16	0.7 (2.0)	124	0.3 (1.9)	0.45
36–42 months	13	−1.4 (4.9)	115	0.6 (2.5)	0.04
42–48 months	13	0.3 (1.0)	115	0.4 (2.5)	0.90
48–60 months	8	−0.1 (0.6)	78	0.0 (1.1)	0.75
60–72 months	8	−0.1 (0.6)	78	0.4 (2.0)	0.58

Downloaded from https://academic.oup.com/jcem/article/104/2/213/5103424 by guest on 11 April 2024

Table 4. Comparison of Characteristics Between Those With and Without VF Over 6 Years

Clinical Parameter	Children With ≥1 VF at Baseline or Follow-Up (n = 40)	Children Without VF (n = 120)	*P*
Age at baseline, y, mean (SD)	6.3 (3.8)	6.4 (4.1)	0.94
Male, n (%)	23 (57.5%)	70 (58.3)	0.93
Pubertal stage = Tanner 1, n (%)	34 (85%)	105 (87.5%)	0.89
Height *z* score at baseline, mean (SD)	0.1 (1.2)	0.4 (1.2)	0.30
Height *z* score at 72 mos, mean (SD)	0.2 (1.1)	0.3 (1.2)	0.81
Weight *z* score at baseline, mean (SD)	0.4 (1.5)	0.5 (1.1)	0.54
Weight *z* score at 72 mos, mean (SD)	0.3 (1.1)	0.8 (1.2)	0.08
BMI *z* score at baseline, mean (SD)	0.6 (2.1)	0.6 (1.4)	0.96
BMI *z* score at 72 mos, mean (SD)	0.3 (1.1)	0.9 (1.1)	0.05
LS BMD *z* score at baseline, mean (SD)	−1.8 (1.5)	−1.0 (1.2)	0.001
LS BMD *z* score at 72 mos, mean (SD)	−1.2 (1.1)	−0.2 (1.3)	0.001
Average daily GC dose over the first y since GC initiation, mg/m^2, mean (SD)	11.2 (5.0)	10.3 (3.0)	0.21
Average daily GC dose over the second y since GC initiation, mg/m^2, mean (SD)	7.0 (2.4)	6.8 (1.9)	0.52

Abbreviation: BMI, body mass index.

patients with cranial irradiation were excluded from the study. Another limitation is the inability to evaluate different chemotherapeutic regimens because the majority of our patients were treated under the same chemotherapy backbone (22). Furthermore, our study is limited by the lack of sitting height or arm span data to assess the effect of VF on upper to lower body proportions. Finally, our study was designed to monitor patients for a 6-year period, so we could not evaluate final adult height status in all patients.

Table 5. Univariate Model for Repeated-Measures Analysis of Clinical Predictors in Height *z*-Score Declines

Risk Factor	Effect Size (95% CI)	*P*
Age at baseline (10 y)	0.11 (0.04, 0.18)	<0.01
Sex (female vs male)	−0.02 (−0.08, 0.03)	0.45
Average daily GC dose in the past y (10 mg/m^2)	0.29 (0.23, 0.35)	<0.01
Change in SDI in the past y (5 units)	0.17 (0.06, 0.29)	<0.01
Decline in LS BMD *z* score in the past y	0.13 (0.06, 0.21)	<0.01
Leukemia risk category (high vs standard risk)	0.05 (−0.02, 0.11)	0.14
Change in BMI *z* score in the past y	0.01 (−0.02, 0.03)	0.69
Pubertal stage (stages 2–5 vs stage 1)[a]	0.01(−0.05, 0.08)	0.75
Average vitamin D intake in the past y	0.01(−0.03, 0.04)	0.75
Average calcium intake in the past y	0.00 (−0.07, 0.07)	0.98

Abbreviation: BMI, body mass index.

[a]Effect size for pubertal stage (late vs early puberty, *i.e.,* stages 3–5 vs stage 1 or 2 for females and stage 4 or 5 vs stages 1–3 for males) was −0.02; 95% CI: −0.09, 0.06; *P* = 0.67.

The findings in this study underscore the importance of viewing risks for height deficits individually for each child with ALL. Some factors, such as GC, likely affect all patients, although the magnitude of the effect may vary between individuals depending on the specific GC drug, the particular dose received, or differences in GC sensitivity. Other factors influence only specific subsets of children; for example, VF obviously have the potential to cause a height deficit only among those who sustain such fractures. For a child with multiple VF, however, this could be the principal determinant of his or her height deficit. Further studies may develop ways of applying known contributing factors to identify each child's risk for developing a height deficit during treatment of ALL.

What are the overall clinical implications of these findings? By showing that declining height *z* scores are directly related to the number and severity of incident VF, we have underscored the importance of timely VF identification. We have also demonstrated that although most children will go on to restore normal vertebral dimensions after VF-induced deformity, thereby obviating the

Table 6. Mixed Model for Repeated-Measures Analysis of Clinical Predictors in Height *z*-Score Declines

Risk Factor	Effect Size (95% CI)	*P*
Change in SDI in the previous 12 mos (5 units)	0.13 (0.02, 0.23)	0.02
Decline in LS BMD *z* score in the previous 12 mos	0.11 (0.04, 0.18)	<0.01
Average daily GC dose in the previous 12 mos (10 mg/m^2)	0.26 (0.20, 0.32)	<0.01
Age at baseline (10 y)	0.08 (0.01, 0.16)	0.03
Sex (female vs male)	0.00 (−0.05, 0.06)	0.94

Downloaded from https://academic.oup.com/jcem/article/104/2/213/5103424 by guest on 11 April 2024

need for bone-targeted intervention, a subset of children who are older or who have more severe vertebral collapse in the first 2 years of chemotherapy are at risk for persistent deformity (23). These are the children who should be targeted in future fracture prevention studies, with the goal of preserving vertebral body integrity and thereby maintaining overall stature. Together, these observations highlight the importance of understanding the spine phenotype in the first few weeks after ALL diagnosis. To this end, analyses are currently under way to assess the combination of risk factors that most accurately predict which children are most likely to develop VF.

Acknowledgments

This study was supported by the Canadian Institutes for Health Research (FRN 64285), the Children's Hospital of Eastern Ontario Research Institute, and the University of Alberta Women and Children's Health Research Institute. We are indebted to the efforts of the patients and families who have contributed to the STOPP study over many years. The Canadian STOPP Consortium thanks the following research staff: the research associates who managed the study at the coordinating center (the Children's Hospital of Eastern Ontario, Ottawa): Elizabeth Sykes (STOPP project manager), Maya Scharke and Catherine Bordeleau (database managers and analysts), Victor Konji (STOPP publications and presentations liaise, vertebral fracture workflow), Kathryn Zhang (literature searches), and the research associates who recruited patients and managed the study at the various sites across Canada.

The Canadian STOPP Consortium (a pan-Canadian, pediatric bone health working group): Principal Investigator: Leanne M. Ward (Children's Hospital of Eastern Ontario, Ottawa); Alberta Children's Hospital: Josephine Ho, Reinhard Kloiber, Victor Lewis, Julian Midgley, Paivi Miettunen, David Stephure; British Columbia Women's Hospital and Health Sciences, Vancouver: Brian C. Lentle; British Columbia Children's Hospital, Vancouver: Tom Blydt-Hansen, David Cabral, David B. Dix, Kristin Houghton, Helen R. Nadel; Brock University, St. Catharines: John Hay; Children's Hospital of Eastern Ontario, Ottawa: Janusz Feber, Jacqueline Halton, Roman Jurencak, Jinhui Ma, MaryAnn Matzinger, Johannes Roth, Nazih Shenouda, Karen Watanabe-Duffy; Children's Hospital, London Health Sciences Centre, University of Western Ontario, London: Elizabeth Cairney, Cheril Clarson, Guido Filler, Joanne Grimmer, Scott McKillop, Keith Sparrow, Robert Stein; IWK Health Center, Halifax: Elizabeth Cummings, Conrad V Fernandez, Adam M. Huber, Bianca Lang, Kathy O'Brien; McMaster Children's Hospital, Hamilton: Steve Arora, Stephanie Atkinson, Ronald Barr, Craig Coblentz, Peter B. Dent, Maggie Larche; Montréal Children's Hospital, Montréal: Sharon Abish, Lorraine Bell, Claire LeBlanc, Anne Marie Sbrocchi, Rosie Scuccimarri; Ottawa Hospital Research Institute, Ottawa: David Moher; Shriners Hospital for Children, Montreal: Frank Rauch; Ste. Justine Hospital, Montreal: Nathalie Alos, Josee Dubois, Caroline Laverdière, Veronique Phan, Claire Saint-Cyr; Stollery Children's Hospital, Edmonton: Robert Couch, Janet Ellsworth, Jacob Jaremko, Kerry Siminoski, Beverly Wilson; Toronto Hospital for Sick Children, Toronto: Ronald Grant, Martin Charron, Diane Hebert; Université de Sherbrooke, Sherbrooke: Isabelle Gaboury; Winnipeg Children's Hospital, Winnipeg, Manitoba: Celia Rodd, Sara Israels, Kiem Oen, Maury Pinsk, Martin Reed, Shayne Taback.

Financial Support: Primary funding source was Canadian Institutes of Health Research, CIHR FRN 64285 (to L.M.W.). Additional funding sources were the University of Alberta Women and Children's Research Institute, Canadian Child Health Clinician Scientist Career Enhancement Award (to L.M.W.), University of Ottawa Research Chair Award (to L.M.W.), Children's Hospital of Eastern Ontario (CHEO) Research Institute Capacity Building Award (to L.M.W.), and CHEO Departments of Pediatrics and Surgery.

Correspondence and Reprint Requests: Leanne M. Ward, MD, University of Ottawa, Room 250H, Research Institute, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario K1H 8L1, Canada. E-mail: Lward@cheo.on.ca.

Disclosure Summary: The authors have nothing to disclose.

References

1. Essig S, Li Q, Chen Y, Hitzler J, Leisenring W, Greenberg M, Sklar C, Hudson MM, Armstrong GT, Krull KR, Neglia JP, Oeffinger KC, Robison LL, Kuehni CE, Yasui Y, Nathan PC. Risk of late effects of treatment in children newly diagnosed with standard-risk acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol*. 2014;**15**(8):841–851.
2. Clayton PE, Shalet SM, Morris-Jones PH, Price DA. Growth in children treated for acute lymphoblastic leukaemia. *Lancet*. 1988;**331**(8583):460–462.
3. Moëll C, Garwicz S, Marky I, Mellander L, Karlberg J. Growth in children treated for acute lymphoblastic leukemia with and without prophylactic cranial irradiation. *Acta Paediatr Scand*. 1988;77(5):688–692.
4. Sklar C, Mertens A, Walter A, Mitchell D, Nesbit M, O'Leary M, Hutchinson R, Meadows A, Robison L. Final height after treatment for childhood acute lymphoblastic leukemia: comparison of no cranial irradiation with 1800 and 2400 centigrays of cranial irradiation. *J Pediatr*. 1993;**123**(1):59–64.
5. Katz JA, Pollock BH, Jacaruso D, Morad A. Final attained height in patients successfully treated for childhood acute lymphoblastic leukemia. *J Pediatr*. 1993;**123**(4):546–552.
6. Cicognani A, Cacciari E, Rosito P, Mancini AF, Carlă G, Mandini M, Paolucci G. Longitudinal growth and final height in long-term survivors of childhood leukaemia. *Eur J Pediatr*. 1994;**153**(10):726–730.
7. Bongers ME, Francken AB, Rouwé C, Kamps WA, Postma A. Reduction of adult height in childhood acute lymphoblastic leukemia survivors after prophylactic cranial irradiation. *Pediatr Blood Cancer*. 2005;**45**(2):139–143.
8. Vilela MI, Viana MB. Longitudinal growth and risk factors for growth deficiency in children treated for acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2007;**48**(1):86–92.
9. Viana MB, Vilela MI. Height deficit during and many years after treatment for acute lymphoblastic leukemia in children: a review. *Pediatr Blood Cancer*. 2008;**50**(2 Suppl)509–516, discussion 517.
10. Vilela MI, Serravite MO, Oliveira NB, de Brito PC, Ribeiro-Oliveira A Jr, Viana MB. Height deficit and impairment of the

Downloaded from https://academic.oup.com/jcem/article/104/2/213/5103424 by guest on 11 April 2024

GH/IGF-1 axis in patients treated for acute lymphoblastic leukemia during childhood. *Horm Res Paediatr*. 2013;**79**(1):9–16.
11. Halton JM, Atkinson SA, Barr RD. Growth and body composition in response to chemotherapy in children with acute lymphoblastic leukemia. *Int J Cancer Suppl*. 1998;**78**(S11):81–84.
12. Siminoski K, Jiang G, Adachi JD, Hanley DA, Cline G, Ioannidis G, Hodsman A, Josse RG, Kendler D, Olszynski WP, Ste Marie LG, Eastell R. Accuracy of height loss during prospective monitoring for detection of incident vertebral fractures. *Osteoporos Int*. 2005; **16**(4):403–410.
13. Siminoski K, Warshawski RS, Jen H, Lee K. The accuracy of historical height loss for the detection of vertebral fractures in postmenopausal women. *Osteoporos Int*. 2006;**17**(2):290–296.
14. Alos N, Grant RM, Ramsay T, Halton J, Cummings EA, Miettunen PM, Abish S, Atkinson S, Barr R, Cabral DA, Cairney E, Couch R, Dix DB, Fernandez CV, Hay J, Israels S, Laverdière C, Lentle B, Lewis V, Matzinger M, Rodd C, Shenouda N, Stein R, Stephure D, Taback S, Wilson B, Williams K, Rauch F, Siminoski K, Ward LM. High incidence of vertebral fractures in children with acute lymphoblastic leukemia 12 months after the initiation of therapy. *J Clin Oncol*. 2012;**30**(22):2760–2767.
15. Cummings EA, Ma J, Fernandez CV, Halton J, Alos N, Miettunen PM, Jaremko JL, Ho J, Shenouda N, Matzinger MA, Lentle B, Stephure D, Stein R, Sbrocchi AM, Rodd C, Lang B, Israels S, Grant RM, Couch R, Barr R, Hay J, Rauch F, Siminoski K, Ward LM; Canadian STOPP Consortium (National Pediatric Bone Health Working Group). Incident vertebral fractures in children with leukemia during the four years following diagnosis. *J Clin Endocrinol Metab*. 2015;**100**(9):3408–3417.
16. Davies HA, Didcock E, Didi M, Ogilvy-Stuart A, Wales JK, Shalet SM. Disproportionate short stature after cranial irradiation and combination chemotherapy for leukaemia. *Arch Dis Child*. 1994; **70**(6):472–475.
17. Dal Osto LC, Konji VN, Halton J, Matzinger MA, Bassal M, Rauch F, Ward LM. The spectrum of recovery from fracture-induced vertebral deformity in pediatric leukemia. *Pediatr Blood Cancer*. 2016;**63**(6):1107–1110.
18. Karlsson MK, Moller A, Hasserius R, Besjakov J, Karlsson C, Ohlin A. A modeling capacity of vertebral fractures exists during growth: an up-to-47-year follow-up [published correction appears in Spine. 2006;31(1):72]. *Spine*. 2003;**28**(18):2087–2092.
19. Kerkeni S, Kolta S, Fechtenbaum J, Roux C. Spinal deformity index (SDI) is a good predictor of incident vertebral fractures. *Osteoporos Int*. 2009;**20**(9):1547–1552.
20. Lui JC, Baron J. Effects of glucocorticoids on the growth plate. *Endocr Dev*. 2011;**20**:187–193.
21. Wood CL, Soucek O, Wong SC, Zaman F, Farquharson C, Savendahl L, Ahmed SF. Animal models to explore the effects of glucocorticoids on skeletal growth and structure. *J Endocrinol*. 2018;**236**(1):R69–R91.
22. Halton J, Gaboury I, Grant R, Alos N, Cummings EA, Matzinger M, Shenouda N, Lentle B, Abish S, Atkinson S, Cairney E, Dix D, Israels S, Stephure D, Wilson B, Hay J, Moher D, Rauch F, Siminoski K, Ward LM; Canadian STOPP Consortium. Advanced vertebral fracture among newly diagnosed children with acute lymphoblastic leukemia: results of the Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) research program. *J Bone Miner Res*. 2009;**24**(7):1326–1334.
23. Ward LM, Ma J, Lang B, Ho J, Alos N, Matzinger MA, Shenouda N, Lentle B, Jaremko JL, Wilson B, Stephure D, Stein R, Sbrocchi AM, Rodd C, Lewis V, Israels S, Grant RM, Fernandez CV, Dix DB, Cummings EA, Couch R, Cairney E, Barr R, Abish S, Atkinson SA, Hay J, Rauch F, Moher D, Siminoski K, Halton J; Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) Consortium. Bone morbidity and recovery in children with acute lymphoblastic leukemia: results of a six-year prospective cohort study. *J Bone Miner Res*. 2018;**33**(8):1435–1443.
24. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, Grummer-Strawn LM, Curtin LR, Roche AF, Johnson CL. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics*. 2002;**109**(1):45–60.
25. Baumgartner RN, Roche AF, Himes JH. Incremental growth tables: supplementary to previously published charts. *Am J Clin Nutr*. 1986;**43**(5):711–722.
26. Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press; 2011.
27. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int*. 2002;**13**(10):777–787.
28. Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, Kovac SH, Spettell CM, Saag KG. Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum*. 2006;**55**(3):420–426.
29. Dubner SE, Shults J, Baldassano RN, Zemel BS, Thayu M, Burnham JM, Herskovitz RM, Howard KM, Leonard MB. Longitudinal assessment of bone density and structure in an incident cohort of children with Crohn's disease. *Gastroenterology*. 2009; **136**(1):123–130.
30. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;**8**(9):1137–1148.
31. Ribeiro D, Zawadynski S, Pittet LF, Chevalley T, Girardin E, Parvex P. Effect of glucocorticoids on growth and bone mineral density in children with nephrotic syndrome. *Eur J Pediatr*. 2015; **174**(7):911–917.
32. Komori T. Glucocorticoid signaling and bone biology. *Horm Metab Res*. 2016;**48**(11):755–763.
33. Holm K, Nysom K, Hertz H, Müller J. Normal final height after treatment for acute lymphoblastic leukemia without irradiation. *Acta Paediatr*. 1994;**83**(12):1287–1290.
34. Vandecruys E, Dhooge C, Craen M, Benoit Y, De Schepper J. Longitudinal linear growth and final height is impaired in childhood acute lymphoblastic leukemia survivors after treatment without cranial irradiation. *J Pediatr*. 2013;**163**(1):268–273.
35. Özaltin E. Commentary: the long and short of why taller people are healthier and live longer. *Int J Epidemiol*. 2012;**41**(5):1434–1435.
36. Perkins JM, Subramanian SV, Davey Smith G, Özaltin E. Adult height, nutrition, and population health. *Nutr Rev*. 2016;**74**(3): 149–165.
37. Case A, Paxson C. Stature and status: height, ability, and labor market outcomes. *J Polit Econ*. 2008;**116**(3):499–532.

Downloaded from https://academic.oup.com/jcem/article/104/2/213/5103424 by guest on 11 April 2024