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Glucocorticoids and insulin resistance in children with acute lymphoblastic leukemia

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Abstract

Background—Children treated for acute lymphoblastic leukemia (ALL) are more likely to become overweight. Prolonged exposure to high-dose glucocorticoids may cause insulin resistance and facilitate development of this phenotype.

Procedure—Body mass indices (BMI) and insulin resistance (HOMA-IR) were prospectively measured among on- (n=31) and off-therapy participants (n=29). On-therapy participants were assessed prior to and while on glucocorticoids (5 days of prednisone 40 mg/m^2 or dexamethasone 6 mg/m^2) given as part of routine maintenance chemotherapy, with a subset (n=10) receiving an intravenous glucose tolerance test (IVGTT) while on glucocorticoids.

Results—Baseline HOMA-IR values among on- and off-therapy participants were similar, but among on-therapy participants, HOMA-IR increased significantly with glucocorticoid exposure (median 3.39 vs. 1.26; $p<0.01$) with 45.2% of participants having values >4.39 (upper 2.5th percentile among normal weight adolescents). Although baseline HOMA-IR was significantly correlated with current BMI ($r=0.48$, $p<0.01$), change in HOMA-IR following steroid exposure was not correlated with any demographic or treatment characteristic including current BMI. Among those with IVGTT data, HOMA estimates in general correlated with values derived from a minimal model analysis ($r\sim0.7$).

Conclusions—High-dose glucocorticoids given as part of routine chemotherapy were associated with a significantly increased insulin resistant state. Given the amount and duration of glucocorticoids children with ALL experience, these physiologic changes could be an important contributor to the development of therapy-related obesity.

Keywords

acute lymphoblastic leukemia; glucocorticoid; insulin resistance; obesity; survivor

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INTRODUCTION

Overall survival for children diagnosed with acute lymphoblastic leukemia (ALL) now exceeds 85% (1). However, survivors are at increased risk of adverse long-term health related outcomes, including subsequent obesity and cardiovascular morbidity (2). Insulin resistance may be one of the mechanisms by which increased adiposity leads to cardiovascular disease (3). Exposure to even relatively low dose exogenous glucocorticoids can reduce insulin sensitivity and impair β-cell function in genetically-susceptible individuals (4). At the higher doses used in ALL therapy, such effects can be observed even in lean healthy controls without known risk factors for diabetes (5), and chronic supraphysiologic exposure has been shown to result in hyperglycemia and obesity in the non-cancer population (6).

Intermittent treatment with pulses of high-dose potent glucocorticoids, e.g. prednisone and dexamethasone, including a prolonged maintenance phase lasting 2-3 years is a backbone of many contemporary ALL therapeutic protocols (7;8). Some studies suggest that glucocorticoid exposure may be specifically associated with an increased risk of obesity in this population (9-11). By some estimates, over the past 20 years, cumulative glucocorticoid dosing has increased by more than 60% for some ALL treatment groups (7;8).

To further investigate the physiologic relationship between glucocorticoid exposure and insulin resistance among children treated for ALL, we performed a prospective study to 1) measure insulin resistance among children currently receiving glucocorticoid-based maintenance chemotherapy using homeostatic model assessment (HOMA); 2) compare such measurements of insulin resistance between on-therapy and similarly treated off-therapy survivors; and 3) determine if differences in insulin resistance are associated with changes in BMI during and after treatment. Additionally, in a subset of on-therapy participants currently receiving glucocorticoid therapy, we examined the correlation between HOMA estimates with those derived from a frequently-sampled intravenous glucose tolerance test (IVGTT), given that glucocorticoid exposure may represent a more dynamic rather than steady state condition (12;13). We chose to examine changes during the maintenance treatment phase as that is a period characterized by few acute therapy-related complications, and also when our participants receive half or more of their glucocorticoid exposure.

METHODS

Participants

Eligible participants were diagnosed with ALL at age<22 years, treated between 1990-2010 at Seattle Children's Hospital, and in first continuous complete remission. Two participant cohorts were recruited from July 2007 to December 2010: 1) on-therapy individuals who have received at least one month of glucocorticoid-based maintenance chemotherapy per current Children's Oncology Group (COG) protocols (typically 5 day glucocorticoid pulse, repeated every 28 days), currently ages 5-21 years; and 2) children who have completed therapy at least one year prior to enrollment and currently ages 8-21 years. Among 44 on-therapy and 49 off-therapy participants approached for this study, 37 (84.1%) and 31 (63.3%), respectively, were enrolled. Six enrolled on-therapy participants (5 of 6 being female) were subsequently excluded: 3 completed therapy prior to completion of study procedures; 2 experienced disease relapse while still on-therapy; 1 discontinued glucocorticoids because of musculoskeletal side effects. Two enrolled off-therapy participants were subsequently excluded due to incomplete insulin resistance data. Final data analysis included 31 on-therapy and 29 off-therapy children. Enrolled on-therapy participants who were age ≥7 years also were eligible to participate in a frequently-sampled IVGTT; of 21 eligible children, 10 underwent an IVGTT.

Participants' medical records were abstracted for prior chemotherapy and radiotherapy doses. Dosages (mg/m^2) of prednisone and dexamethasone (multiplied by 6.67 to approximate prednisone equivalence) were summed to determine cumulative glucocorticoid dose. Medical histories were updated for any participant not seen within the past year. The hospital's institutional review board approved the study, and all participants/guardians provided written informed consent and/or assent before participation.

Measurements

Primary outcomes of interest were current BMI and insulin resistance as measured by HOMA, and in a subset by IVGTT. Height, weight, and pubertal status were determined at time of study enrollment. Prior heights and weights from time of leukemia diagnosis, end of induction chemotherapy (one month after diagnosis), beginning of maintenance chemotherapy (approximately six months after diagnosis), and end of therapy (if applicable; typically 2-3 years after diagnosis) were abstracted from the medical record. BMI z-scores were then derived based on pediatric normative data, with overweight defined as z-score 1.036-1.644 (85-94th percentile for age and sex) and obese defined as z-score ≥1.645 (≥95th percentile for age and sex) (14). Individuals also were classified as overweight or obese if their absolute BMI was 25-29 kg/m^2 or ≥30 kg/m^2, respectively.

At the baseline research visit, following an overnight fast, blood was obtained for glucose and insulin. Given that HOMA assumes a steady-state condition, for on-therapy participants, this occurred at the beginning of a participant's 28 day maintenance course, prior to starting glucocorticoids and approximately 22 to 23 days from their last 5 day glucocorticoid pulse. For these participants, repeat fasting glucose and insulin were obtained between days 3 to 5 of their 5 day glucocorticoid pulse (either prednisone 40 mg/m^2/day or dexamethasone 6 mg/m^2/day depending on the treatment protocol).

For on-therapy children who participated in the frequently sampled IVGTT, after fasting overnight, participants returned once between days 3-5 of their glucocorticoid pulse. At 0900 h, baseline fasting glucose, insulin, and C-peptide were collected 5-10 minutes before glucose (0.5 g/kg, maximum 35 g; in a 25% solution) was administered intravenously over 3 minutes. Blood samples for the 3 analytes were then collected at 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 60, 80, 100, 120, 140, 160, 180, 200, and 220 min (13). Glucose was measured using an automated hexokinase method (Roche Diagnostics, Indianapolis, IN) while insulin and C-peptide were measured using automated immuno-enzymometeric assays (Tosoh Bioscience, San Francisco, CA).

Insulin resistance (HOMA-IR) was calculated from glucose and insulin values based on the updated model (HOMA2) given our desire to compare values with an IVGTT (15). This model also estimates insulin sensitivity (HOMA-%S = 100*(1/HOMA-IR)) and pancreatic β-cell function (HOMA-%B). In sensitivity analysis, the more widely used original HOMA-IR estimates (formula: (glucose (mmol/L) x insulin (mU/L)) / 22.5) also were examined (16). Although HOMA-IR is not used clinically, we chose to examine the proportion of individuals with values greater than 3.29 and 4.39, the upper quartile and upper 2.5th percentile identified in a large US population-based sample of adolescents, respectively (17). The minimal model was applied to the IVGTT data to derive estimates of insulin sensitivity (Si) and β-cell function, both the acute insulin response to glucose (AIR) and the disposition index (DI = Si x AIR), using the MINMOD Millennium program (18;19).

Statistical analyses

Continuous parameters with skewed distributions (e.g. HOMA-IR) were transformed when necessary. Differences in continuous parameters were compared using ANOVA and t-test.

Differences in proportions were assessed by Fisher's (unpaired) or McNemar's (paired) exact test. Pearson's coefficient described the correlation (r) between values. All tests were two-sided. We created multivariate linear regression models to examine demographic and treatment factors associated with log-transformed baseline HOMA-IR, as well as change in HOMA-IR following steroid exposure, reported as β-coefficients (β-coeff) with corresponding 95% confidence intervals (CI). Final models adjusted for sex, current pubertal status, and current BMI z-scores as well as BMI z-scores at time of diagnosis. Sensitivity analyses examined estimates based on the original HOMA model in place of HOMA2. Overall, correlation between HOMA-IR values derived using the HOMA2 vs. original HOMA model exceeded 0.99 ($p<0.001$), while correlation between HOMA-%B estimates was 0.81 ($p<0.001$). All analyses were performed using STATA, version 11 (Stata Corporation, College Station, TX)

RESULTS

The on-therapy group was more likely to be male compared with the off-therapy group (83.9% vs. 37.9%), while the median age at study assessment, as expected, was younger among on-therapy compared with off-therapy participants (9.4 vs. 15.8 years; Table I). Two off-therapy participants were diagnosed with growth hormone deficiency after completing ALL therapy; both were receiving growth hormone supplementation at the time of study assessment. No participant was diagnosed with diabetes or was on insulin or other diabetes medications at the time of study assessment. Two participants had a history of asparaginase-related pancreatitis, since resolved.

Both off- and on-therapy groups experienced significant increases in BMI z-scores during cancer therapy (Table I). The proportion of children overweight or obese at initial cancer diagnosis was the same in both groups (19%) with 45% of on-therapy participants overweight or obese at study enrollment compared with 28% among off-therapy participants (50% overweight/obesity rate at end of therapy). These BMI z-scores were similar to those observed in a larger cohort of ALL patients treated at our institution (n=165) over a similar time period, where we observed z-scores of 0.24±1.24, 0.65±1.33, and 0.76±0.94, at diagnosis, end of first month's induction chemotherapy, and at last follow-up (median 5.2 years after diagnosis), respectively (11).

Although on-therapy participants had significantly higher baseline fasting glucose levels compared with off-therapy participants (median 87 vs. 82 mg/dL, $p<0.01$; Table II), HOMA-IR was not significantly different (median 1.26 vs. 0.93, $p=0.38$). In both groups, HOMA-IR increased with higher BMI category ($p<0.05$; Figure 1), concurrent with decreased insulin sensitivity and increased β-cell function. When on-therapy participants were exposed to treatment glucocorticoid doses, HOMA-IR increased significantly compared with baseline values (median 3.39 vs. 1.26, $p<0.01$), including the proportion (45.2% vs. 9.7%, $p<0.01$) who now had values >4.39, the upper 2.5^{th} percentile identified in a large US population-based sample of normal weight adolescents (17). This occurred despite a significant increase in β-cell function (median 235% vs. 115%, $p<0.01$). The 2 patients with a history of asparaginase-related pancreatitis both had HOMA-IR and estimates of β-cell function within the normal range: ~1.3 and >100%, respectively. Overall results were similar if the analysis excluded pubertal children (Tanner stages 2-4) or children who received cranial radiotherapy (data not shown). Finally, although on-therapy patients treated with dexamethasone (n=18) experienced a greater increase in HOMA-IR following steroid exposure compared with those treated with prednisone (n=13), the difference was not statistically significant (mean 3.67 vs. 2.42; $p=0.28$).

Among all participants, baseline HOMA-IR was significantly correlated with current BMI ($r=0.48$, $p<0.01$) and less strongly with BMI at diagnosis ($r=0.27$, $p=0.04$), but not with any other demographic or treatment characteristic. Relationships were similar if the analysis was restricted to on-therapy participants. No significant correlations were seen between changes in HOMA-IR following steroid exposure with any demographic or treatment characteristics including current BMI. After adjustment for sex and pubertal status, current HOMA-IR remained associated with current BMI (β-coeff 0.40, 95% CI 0.18, 0.61; $p=0.001$), but not BMI at diagnosis (β-coeff 0.00; $p=0.98$). No demographic or treatment factors, including BMI, were predictive of change in HOMA-IR following steroid exposure in multivariate analyses.

Ten on-therapy participants provided IVGTT-based minimal model estimates of insulin sensitivity (Si=1.50 L/mU x 1/min, range (0.08-5.91)) and β-cell function (AIR=1975 mU/L x min, range (358-7492); DI=2387, range (620-3887)) while receiving glucocorticoid pulse chemotherapy (Figure 2). Overall correlation between minimal model and HOMA estimates ranged from 0.6-0.7 for most parameters, although in our limited sample, HOMA2 estimates appeared to be more sensitive to the effects of outliers compared with estimates derived using the original HOMA model (Table III). Of note, the participant with the greatest insulin sensitivity (Si=5.91 L/mU x 1/min) had the lowest estimated β-cell function (AIR=358 mU/L x min) and developed overt diabetes without evidence of autoantibodies approximately one year later, despite maintaining a normal BMI throughout treatment, suggesting inadequate β-cell function. In contrast, the participant with the lowest insulin sensitivity (Si=0.08 L/mU x 1/min) had the greatest β-cell function (AIR=7492 mU/L x min), and had a clinical course characterized by significant weight gain (BMI z-score 1.8 at diagnosis and 2.6 at study).

DISCUSSION

A variety of studies have found that the overall prevalence of insulin resistance appears to be increased among off-therapy leukemia survivors, even decades after therapy completion (2;20-23). However, none to our knowledge have examined the degree of insulin resistance present during glucocorticoid-based maintenance chemotherapy. In most contemporary pediatric ALL protocols, children receive half or more of their glucocorticoids during a 2-3 year maintenance phase, which often coincides with an important period for normal growth and development. In this study high-dose glucocorticoid therapy was associated with a significantly increased insulin resistant state, and for select patients this may be an important contributing factor to therapy-related obesity given both the dose and duration of exposure that patients experience. However, since obesity itself is also associated increased insulin resistance, the exact etiologic relationship between the 2 remains unclear (3).

Furthermore, although our IVGTT sample was small and therefore more to outliers, our preliminary results suggest that the correlation between minimal model and HOMA-based estimates are not dissimilar to those observed in the literature with larger samples (12). Therefore, HOMA-based estimates during glucocorticoid therapy may provide a valid estimate of changes in insulin resistance under such conditions in future studies. This is important considering the greater ease in obtaining and deriving HOMA-based estimates compared with what generally are considered more precise measures of insulin resistance (i.e. IV or oral glucose tolerance tests or the euglycemic insulin clamp) (12). HOMA-based estimates also can be readily compared across studies as well against normative data from the general population whereas those derived from glucose tolerance tests or insulin clamp studies are rarely directly comparable across studies given significant variations in the testing protocols used.

Prior treatment with cranial or total body irradiation appears to be a consistent risk factor for subsequent obesity and insulin resistance among childhood cancer survivors, particularly among female survivors (2;20;21). This effect is felt to be mediated at least in part by growth hormone insufficiency (20). In our study, we did not find a direct association with cranial radiotherapy, although the small number of radiotherapy exposed participants in our study limited our ability to detect such effects, and given the time such effects take to manifest, it would be unusual for on-therapy participants to develop clinical findings prior to completing leukemia therapy.

Pediatric ALL survivors who did not receive cranial radiotherapy may also experience increased BMI and insulin resistance compared with non-cancer controls. Oeffinger et al. found that 78 non-irradiated adult survivors had substantially greater mean HOMA-IR compared with older population controls even after adjustment for BMI (2). In a prior retrospective analysis that included some off-therapy participants examined in this study (n=13 out of 165), we found a dose-response association between cumulative glucocorticoid dose and risk of obesity (11). In that study, more than 40% of survivors remained overweight or obese 5 years after diagnosis compared with a 25% rate among children from the general population.

Others also have reported that steroid exposure, particularly dexamethasone, may be associated with BMI change (9;10), although this association was borderline (24;25) or not significant (22) in other studies. Although increased cumulative glucocorticoid dose was not associated with increased BMI in the current analysis, children clearly became more insulin resistant while receiving glucocorticoids. However, as our data suggest, there likely is some heterogeneity with many patients gaining a disproportionate amount of weight and becoming primarily more insulin resistant, while a few remain normal weight and relatively insulin sensitive but develop insufficient β-cell function. In a longitudinal series, Mohn et al. reported that recently off-therapy non-obese children may have reduced pancreatic β-cell function affecting glucose tolerance, but which then improves over time (26). However, these children also appeared on average to have increased HOMA-IR values over the same time period suggesting that there may still be increased insulin resistance not completely compensated by increased β-cell function (26).

Other chemotherapeutic agents such as asparaginase typically administered in the earlier phases of ALL therapy also may have some effect, at least acutely. Asparaginase may contribute by depleting insulin and other protein stores, causing a relative insulin insufficiency, as well as being a risk factor for pancreatitis and potential β-cell injury (27). However, investigators have not consistently identified an association between insulin resistance among off-therapy survivors, hyperglycemia during therapy, or asparaginase dose (22).

Changes in adiposity and insulin resistance may also be due to changes in basal metabolism. Children who received a standard 5-day glucocorticoid pulse have been reported to experience a 20% increase in energy intake compared with the immediate pre-steroid time period (28). Given the amount and duration of time children are exposed to high-dose glucocorticoids under most contemporary ALL protocols, this could plausibly explain the changes in adiposity and insulin resistance observed. Other factors such as therapy-related fatigue and musculoskeletal symptoms, which can be associated with both glucocorticoids as well as agents such as vincristine, also may negatively influence physical activity with subsequent adverse effects on adiposity and insulin resistance (29;30).

Our study was limited by an imbalance in select demographic characteristics between our on- and off-therapy groups, although we attempted to adjust for such factors in our

multivariate analysis. A relatively constrained sample also limited our ability to detect statistically significant smaller differences. For example, BMI z-scores of off-therapy survivors examined in this study decreased after completing ALL therapy and were no longer significantly increased compared with values from time of diagnosis. In contrast, in a prior larger study, we found that BMI z-scores of children treated with similar protocols at our institution remained increased even 10 years after diagnosis (11). Nevertheless, the possibility for some reduction in BMI is encouraging and with more focused interventions, it may be possible to further minimize long-term adiposity and insulin resistance in this population. The current COG upfront ALL trial for standard risk patients also is reducing glucocorticoid exposure during maintenance treatment (31). It will be important to determine if such a reduction will be associated with reduced obesity and insulin resistance while preserving therapeutic efficacy.

COG off-therapy health surveillance guidelines recommend close monitoring for development of obesity and other components of the metabolic syndrome among those who have received cranial radiotherapy and prolonged glucocorticoid exposure. This includes consideration of periodic assessment of fasting glucose and lipid profiles (32). Although we do not advocate more routine in-depth assessment of insulin resistance in this population, our results help further define the magnitude of insulin resistance that occurs among children being actively treated for ALL and support the possibility that glucocorticoids may be associated with the development of therapy-related obesity.

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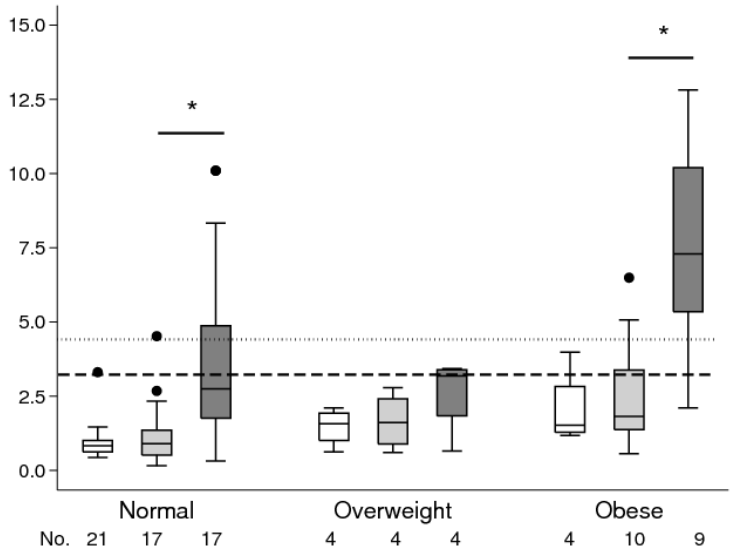

FIGURE 1.

HOMA-IR values associated with off-therapy (white), on-therapy pre-glucocorticoid (medium gray), and on-therapy on-glucocorticoid (dark gray) status stratified by body mass index (BMI) category. Boxes show median value and interquartile range with whiskers denoting upper/lower adjacent values; outside values denoted by circles. Dashed line denotes upper quartile (HOMA>3.29) based on US population-based adolescent sample and dotted line denotes upper 2.5th percentile (HOMA>4.39) based on normal weight adolescents, as defined by Ref (17). ANOVA $p<0.05$ for each therapeutic group across BMI categories. (*) Difference between pre- and on-glucocorticoid values for on-therapy group, $p<0.01$.

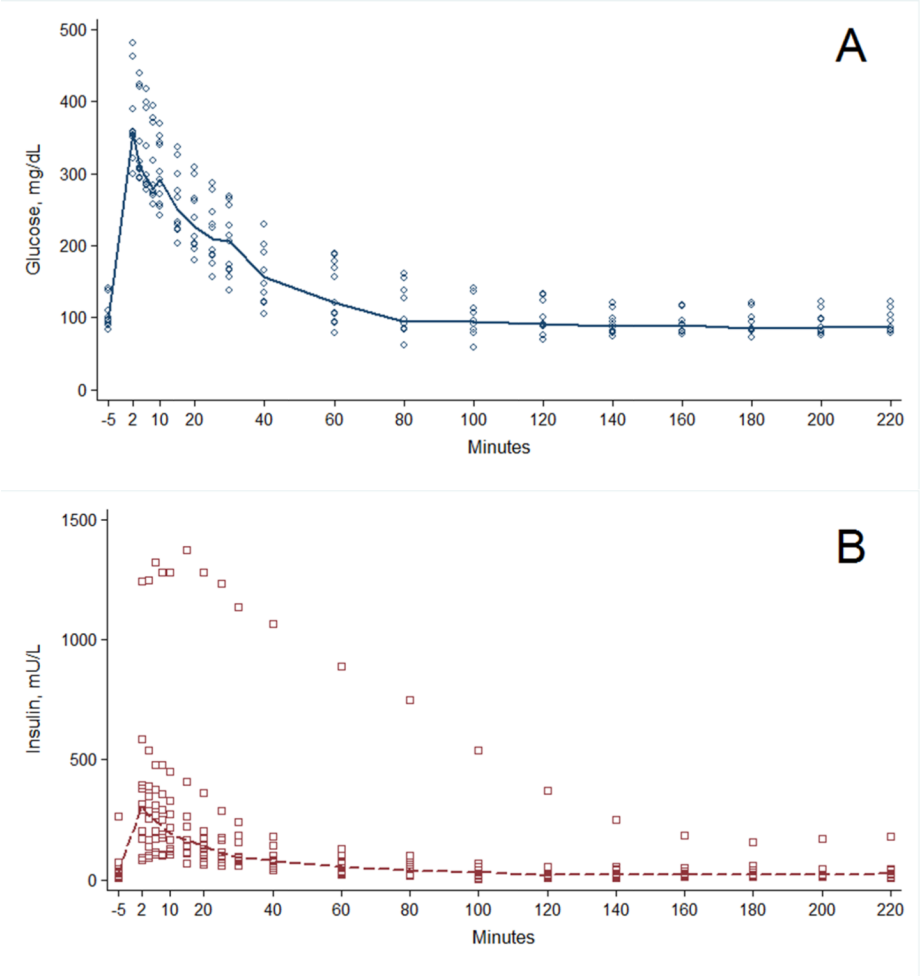

FIGURE 2.

Change in median plasma concentrations of (A) glucose and (B) insulin among ALL survivors receiving glucocorticoid therapy during a frequently sampled intravenous glucose tolerance test (n=10).

TABLE I

Characteristics of the Study Population

Characteristic, n (%)	On-therapy		Off-therapy N=29
	All, N=31[a]	IVGTT, N=10	
Male	26 (83.9)	10	11 (37.9)
White/non-Hispanic	20 (64.5)	6	22 (76)
Age at diagnosis, median (range)	7.7 (2.8-14.9)	8.7 (5.0-14.9)	4.1 (1.6-15.4)
Age at study, median (range)	9.4 (5.2-16.5)	9.6 (8.2-16.5)	15.8 (8.1-21.5)
Current pubertal status			
Tanner 1	23 (74.2)	6	4 (13.8)
Tanner 2-3	5 (16.1)	1	4 (13.8)
Tanner 4-5	3 (9.7)	3	21 (72.4)
Years since diagnosis, median (range)	1.6 (0.7-3.2)	1.2 (0.6-3.2)	10.6 (4.2-16.0)
ALL risk group			
Standard	18 (58.1)	5	21 (72.4)
High	13 (41.9)	5	8 (27.9)
Cranial radiotherapy	8 (25.8)	4	4 (13.8)
Glucocorticoid dose, median (range)[b]	5528 (2975-10245)	4285 (2975-8978)	7594 (3400-11600)
Growth hormone deficiency	-	-	2 (7)
BMI z-score, mean (SD)			
Leukemia diagnosis	0.02 (1.20)	0.38 (1.38)	0.36 (0.98)
End of therapy	-		0.93 (0.90)[c]
Study enrollment	1.00 (1.01)[c]	0.72 (1.17)	0.63 (0.80)

IVGTT, intravenous glucose tolerance test.

[a] Includes subset (n=10) who underwent an IVGTT;

[b] Cumulative dose received (prednisone equivalence, mg/m^2) at time of study;

[c] Compared with diagnosis value, $p<0.05$.

TABLE II

Insulin Resistance Between Baseline and on Glucocorticoid Conditions among On-therapy Participants (n=31), and among On-therapy and Off-therapy (n=29) Participants

Measures, median (range)	On-therapy, baseline	On-therapy, glucocorticoids	P-value[a]	Off-therapy, baseline	P-value[b]
Glucose, mg/dL	87 (50-109)	97 (75-138)	<0.01	82 (65-96)	<0.01
Insulin, mIU/L	8.0 (1.2-45.2)	22.8 (2.0-265.8)	<0.01	6.0 (2.8-26.9)	0.42
HOMA-IR[c]	1.26 (0.16-6.49)	3.39 (0.32-12.82)	<0.01	0.93 (0.44-3.98)	0.38
>3.29, n (%)	4 (12.9)	17 (54.8)	<0.01	2 (6.9)	0.67
>4.39, n (%)	3 (9.7)	14 (45.2)	<0.01	0	0.24
HOMA-%S	80 (15-635)	30 (8-310)	<0.01	108 (25-228)	0.38
HOMA-%B	115 (52-395)	234 (46-635)	<0.01	128 (67-298)	0.79

HOMA, homeostatic model assessment; IR, insulin resistance; %S, insulin sensitivity, %B, β-cell function.

[a] On-therapy baseline vs. on-therapy glucocorticoid values;

[b] Off-therapy vs. on-therapy baseline participants;

[c] US population-based cut-offs defined by Ref (17): 3.29, upper quartile among all adolescents; 4.39, upper 2.5th percentile among normal weight adolescents.

TABLE III

Correlation between Minimal Model IVGTT vs. HOMA-based Estimates of Insulin Sensitivity and β-cell Function (n=10)

	Correlation (p-value)	
Minimal Model	**HOMA2**	**Original HOMA**
Insulin sensitivity, Si	0.09 (0.83)	0.67 (0.03)
Excluding outliers[a]	0.71 (0.05)	0.74 (0.03)
β-cell function, AIR	0.58 (0.10)	0.72 (0.02)
Excluding outliers[a]	0.70 (0.05)	0.69 (0.06)

AIR, acute insulin response.

[a] N=8 after minimum and maximum Si values excluded.