Metabolic Syndrome and Growth Hormone Deficiency in Adult Survivors of Childhood Acute Lymphoblastic Leukemia

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BACKGROUND. The purpose of the study was to determine the prevalence of metabolic syndrome, growth hormone deficiency, and cardiovascular risk factors among adult survivors of childhood acute lymphoblastic leukemia (ALL) treated with or without cranial irradiation.

METHODS. Follow-up was undertaken of 75 randomly selected long-term childhood ALL survivors. Testing included fasting insulin, glucose, lipids, and growth hormone (GH) releasing hormone plus arginine stimulation test. The prevalence of metabolic syndrome was compared with population norms from 1999–2002 National Health and Nutrition Examination Study (NHANES) data, and internally between those with and without past cranial irradiation and those with normal (>16.5 μg/L) versus insufficient (9–16.5 μg/L) versus deficient (<9 μg/L) peak GH secretion.

RESULTS. The mean subject age was 30 years and the mean time since ALL diagnosis was 25 years. The prevalence of metabolic syndrome did not differ statistically ($P = .87$) between study subjects (16.6%) and same-age, same-sex population norms (17.5%). However, 60% of subjects treated with cranial irradiation, compared with 20% of those who were not, had 2 or more of the 5 components of metabolic syndrome. Untreated abnormally low GH was present in 64% of subjects overall and 85% of those who received past cranial irradiation. Cranial irradiation was strongly related to GH deficiency, and in turn lower insulin-like growth factor 1 (IGF-1), higher fasting insulin, abdominal obesity, and dyslipidemia, particularly in women.

CONCLUSIONS. Hematologists who treat childhood ALL patients, and particularly those who provide primary care to adult survivors, should be aware of the potential for long-term GH deficiency and adverse cardiovascular and diabetes risk profiles as a consequence of leukemia treatment. ***Cancer*** **2006;107:1303–12.**

KEYWORDS: late effects, survivorship, cancer, neoplasms, pediatrics, insulin resistance, cardiovascular disease, radiation, adverse treatment effects, obesity.

Modern risk-based therapy for childhood acute lymphoblastic leukemia (ALL)[1,2] has resulted in 5-year survival rates of approximately 85% for children age ≤ 14 years at diagnosis.[3] However, the treatment course for childhood ALL is quite arduous, invol-

Presented in part at the 2005 American Society of Pediatric Hematology Oncology (ASPHO) Annual Meeting, May 14–17, 2005, Washington, DC.

Supported by the National Institutes of Health (grants R21-CA106778, M01-RR00400, U24-CA55727, and K23-CA85503).

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Received April 10, 2006; revision received May 22, 2006; accepted June 5, 2006.

DOI 10.1002/cncr.22120
Published online 7 August 2006 in Wiley InterScience (www.interscience.wiley.com).

ving an average of 2 to 3 years of intensive induction, consolidation, and maintenance chemotherapy with high-dose steroids.[4] Understanding the long-term medical and psychosocial consequences of childhood ALL and its treatment is important because there are thousands of young adult survivors of childhood ALL who are confronting a variety of adverse health outcomes, including a higher than expected frequency of obesity[5–9] and early mortality from cardiovascular disease.[10,11] Some evidence indicates that cancer survivors in general,[12] and survivors of childhood ALL in particular,[13–16] are at increased risk for metabolic syndrome. Metabolic syndrome, a constellation of disorders related to insulin resistance, is characterized clinically by central (abdominal) obesity, elevated plasma glucose, dyslipidemia, hypertension, and a prothrombotic and proinflammatory state.[17] Metabolic syndrome is an important risk factor for cardiovascular disease and diabetes mellitus.[17]

Most adult survivors of childhood ALL have the added risk burden of past treatment exposure to cranial irradiation.[4] Although currently limited to high-risk ALL, about 10% to 20% of patients,[18] whole-brain irradiation at 18 grays (Gy) or 24 Gy was historically used as prophylactic treatment against central nervous system (CNS) involvement of leukemia. Long-term hypothalamic-pituitary hormone insufficiency, a potential consequence of cranial irradiation,[19–22] may also be related independently to cardiovascular disease.[23,24] Growth hormone (GH) deficiency has emerged as a likely contributor to central obesity and its related metabolic disorders, including insulin resistance and dyslipidemia. Animal studies have demonstrated that GH is involved in adipocyte development and differentiation, and differential regulation within specific adipose depots, key issues for determining depot-specific adipose mass and insulin sensitivity.[25] Human studies specific to ALL indicate that GH deficiency is related to metabolic syndrome and cardiovascular disease risk factors.[13,15,16,26] Studies in humans have shown that GH replacement reduces abdominal visceral adiposity[27] and improves cardiovascular risk measures[28] and muscle strength.[28,29]

Therefore, in this clinical research study of 75 young adult survivors of childhood ALL we sought to determine the prevalence of metabolic syndrome, GH deficiency, and other cardiovascular risk factors among those with and without past cranial radiation treatment. Our goal was to provide clinical data relevant to risk assessment for cardiovascular disease and diabetes in childhood ALL survivors and to identify possible areas for preventive intervention.

MATERIALS AND METHODS

Sampling and Subject Recruitment

Eligibility included being an active participant in the Childhood Cancer Survivor Study (CCSS) and having received treatment for ALL at age $\leq$20 years at the University of Minnesota Children's Hospital or Children's Hospitals and Clinics of Minneapolis/St. Paul. CCSS is an epidemiologic follow-up study of 14,000 5-year or longer survivors of childhood cancer who were diagnosed and treated between 1970 and 1986 at 1 of 26 collaborating institutions. As described in detail previously,[30] each CCSS participant had treatment data abstracted from their medical record.

We identified 207 individuals who were eligible for the present study. From these, subjects were stratified into 3 groups by cranial radiation treatment dose (none, $<$24 Gy, $\geq$24 Gy) in blocks of 25 persons each, assigned a random number within treatment group and block, and contacted in random number order. The sampling scheme was designed to minimize the potential for favoring "fast responders" who may not fairly represent the target study population. Twenty-nine (14%) subjects actively or passively refused, 22 (10.6%) were lost to follow-up, 10 (4.8%) agreed to participate but were never scheduled because accrual was met, and 71 (34.3%) were not contacted because their random number was not reached in our sampling scheme. Subjects were offered $300 for participation. Written informed consent was obtained for each subject as approved by the Human Subjects Review Committees at the University of Minnesota and Children's Hospitals and Clinics of Minneapolis/St. Paul.

Population-Based Comparison Group

Data from the 1999–2002 National Health and Nutrition Examination Study (NHANES) were used to compare the prevalence of metabolic syndrome and its components to that of the study subjects. NHANES subjects, sampled to be representative of the civilian, noninstitutionalized U.S. population, underwent both an in-home interview and an onsite evaluation at a mobile examination center where they provided a blood sample for laboratory testing (available at URL: http://www.cdc.gov/nchs/nhanes.htm [accessed July 14, 2006]). To coincide with the demographics of our subjects, we included from NHANES only non-Hispanic white males and females ages 20–45 years and restricted the analysis to those who were not pregnant, who reported no history of cancer (except for nonmelanoma skin cancer), who were not diabetic, and who fasted for the required 8 hours before their laboratory samples were obtained ($n = 730$).

Measurements

After an overnight fast, subjects provided a urine sample for microalbumin and a venous blood sample for plasma measurement of insulin, glucose, triglycerides, high-density lipoproteins (HDL-C), and other tests. Circulating blood levels of creatinine and C-reactive protein were measured with rate nephelometry[31]; insulin, insulin-like growth factor I (IGF-I), thyroxine, and thyroid-stimulating hormone with chemiluminescent immunoassays[32]; and homocysteine with fluorescence polarization immunoassays.[33] The homeostasis model assessment of insulin resistance index (HOMA) was calculated from fasting plasma insulin and glucose values as described by Matthews et al.[34] Waist circumference was measured between the anterior superior iliac spine and the lower rib margin. Hip girth was measured at the maximum hip width over the greater trochanters. Body composition was measured by dual energy X-ray absorptiometry (DXA) (Prodigy [software version. 6.7]; 3M, Madison, WI). Blood pressure measurements were taken after 5 minutes of quiet sitting with the right arm supported at the level of the heart. Two blood pressure readings were taken and their values averaged for analysis.

The GH-releasing hormone with arginine stimulation test (GHRH/ARG) for measuring peak GH secretion[35,36] was completed for 72 of the 75 subjects. GH-releasing hormone was administered at 1 μg/kg as an intravenous bolus followed immediately by an intravenous infusion of arginine HCL (0.5 g/kg, maximum 30 g) given over 30 minutes. GH levels were obtained at 30 minutes, 40 minutes, 60 minutes, 90 minutes, and 120 minutes after completion of the arginine infusion. Consistent with previous studies using the GHRH/ARG stimulation test,[13,36] we categorized peak GH level into 3 categories: normal GH (>16.5 μg/L), GH-insufficient (9–16.5 μg/L), and GH-deficient (<9 μg/L).

Metabolic syndrome was defined using the recommended revisions of the NCEP/ATP III criteria.[17] Participants with 3 or more of the following criteria were considered positive for metabolic syndrome: 1) waist circumference >102 cm in men or >88 cm in women; 2) triglyceride levels ≥150 mg/dL; 3) HDL-C <40 mg/dL in men or <50 mg/dL in women or on current treatment for high cholesterol; 4) blood pressure ≥130/85 mmHg or on current treatment for hypertension; or 5) glucose ≥100 mg/dL (changed in the new criteria from 110 mg/dL). Our sample size of 75 subjects was designed to detect a 10% difference in prevalence of metabolic syndrome between the study and NHANES populations with 80% power and a 2-sided type I error level of 5%.

Statistical Analysis

Prevalences were weighted to account for both the sampling fractions and the participation levels in each of the 3 treatment blocks. Prevalences from the NHANES data were standardized to mirror the sex, race, and age group distributions in our study sample and adjusted to account for the complex, multicluster sampling design.

The frequency and proportions of metabolic syndrome were calculated for each GH category and compared with chi-square statistics. Mean values and standard deviations for other cardiovascular disease risk factors were also calculated by GH category and compared between groups using 1-way analysis of variance. A multivariable linear regression model was conducted to assess the difference in mean peak GH among those who were treated versus not treated with cranial irradiation, after controlling for body mass index (BMI), sex, age at diagnosis, and age at study date.

Metabolic syndrome prevalence and other risk factors for cardiovascular disease were initially compared statistically across the 3 levels of cranial radiation dose. Because we found no indication of a dose response or meaningful differences in the measures of interest between the 2 irradiated groups, we present cranial irradiation only as a dichotomous variable (yes or no cranial irradiation).

RESULTS

No statistical differences were found in any demographic or treatment measure between the 75 study participants and the 132 eligible nonparticipants, with the exception of radiation treatment group and brain radiation field, which differed by sampling design (Table 1). Among participating study subjects, 59% were female, the mean age at study date was 30 years, the mean age at diagnosis was 5.6 years, and the mean time since ALL diagnosis was 25 years. No cardiovascular events had occurred among subjects. All male subjects had testosterone levels in the normal range, although 1 was on active testosterone treatment. One female subject tested below normal range for estradiol, and 15 female subjects were taking estrogen, all for birth control purposes. Medication for hypertension was currently being taken by 2 male subjects, both of whom were counted as having hypertension in the metabolic syndrome analyses as per ATP III revised criteria. Likewise, 1 male was taking medication for elevated cholesterol and he was counted as positive for the HDL cholesterol component of metabolic syndrome. No one in the study was on insulin.

TABLE 1
Demographic and Treatment Variables between Study Participants and Eligible Nonparticipants

	Participants (n = 75)		Nonparticipants (n = 132)		
	No.	**(%)**	**No.**	**(%)**	***P***
Sex					.42
Male	31	(41.3)	64	(48.5)	
Female	44	(58.7)	68	(51.5)	
Age group at interview					.19
19–29 y	40	(53.3)	61	(46.2)	
30–39 y	27	(36.0)	63	(47.7)	
40–45 y	8	(10.7)	8	(6.1)	
Mean age at interview (SD) in years	30.2	(7.1)	30.9	(6.3)	.50
Mean age at diagnosis (SD) in years	5.6	(4.3)	5.4	(4.0)	.72
Mean years of survival (SD) in years	24.6	(4.8)	25.5	(4.6)	.20
Body mass index,1995–1996 survey: mean (SD)	23.6	(5.9)	24.5	(4.6)	.28
Race					.98
White	74	(98.7)	127	(96.2)	
Nonwhite	1	(1.3)	6	(4.5)	
Radiation treatment group					.001
None	25	(33.3)	17	(12.9)	
<24 Gy	25	(33.3)	70	(53.0)	
24+ Gy	25	(33.3)	45	(34.1)	
Body areas in radiation fields					
Brain	50	(66.7)	115	(87.1)	<.001
Spine	17	(22.7)	27	(20.5)	.71
Pelvis or testes	11	(14.7)	11	(8.3)	.15
Total body	5	(6.7)	4	(3.0)	.22
Chemotherapy agents received					
Actinomycin	1	(1.3)	0	(0.0)	.18
Cytoxan	33	(44.0)	64	(48.5)	.53
Ara-C	33	(44.0)	58	(43.9)	.99
Daunorubicin	21	(28.0)	30	(22.7)	.39
Dexamethasone	11	(14.7)	20	(15.2)	.92
Doxorubicin	21	(28.0)	51	(38.6)	.12
Isofosfomide	1	(1.3)	1	(0.8)	.68
L-aspariginase	72	(96.0)	122	(92.4)	.31
6-mercaptopurine	69	(92.0)	119	(90.2)	.66
Methotrexate	75	(100.0)	132	(100.0)	.99
Prednisone	74	(98.7)	129	(97.7)	.64
6-thioguanine	18	(24.0)	29	(22.0)	.74
Vincristine	75	(100.0)	131	(99.2)	.45
Teniposide	2	(2.7)	1	(0.8)	.27
Allopurinol	2	(2.7)	1	(0.8)	.27
Anthracycline dose					
None	46	(61.3)	77	(58.3)	.07
1–100 mg/m^2	10	(13.3)	6	(4.5)	
101–300 mg/m^2	11	(14.7)	31	(23.5)	
301+ mg/m^2	8	(10.7)	18	(13.6)	
Cardiovascular events*					
Congestive heart failure	0	(0.0)			
Myocardial infarction	0	(0.0)			
Stroke	0	(0.0)			
Hypogonadism*	2	(2.7)			
Current medications*					
Testosterone (males)	1	(3.2)			
Estrogen (females, all birth control)	15	(34.1)			
Antihypertensives	2	(2.7)			
Lipid lowering agent	1	(1.3)			
Insulin	0	(0.0)			
Current habits*					
Smoker	15	(20.0)			
Drink alcohol	7	(9.3)			

SD indicates standard deviation, Gy, grays.

* Data not available for nonparticipants.

TABLE 2
Prevalence* of Metabolic Syndrome and Its Components among Adult Survivors of Childhood ALL and U.S. Adults Age 18–45 Years (NHANES 1999–2002) by Gender

	Metabolic syndrome			Abdominal obesity			High triglycerides			Low HDL cholesterol			High blood pressure			High glucose		
	%	SE	*P*	%	SE	*P*	%	SE	*P*	%	SE	*P*	%	SE	*P*	%	SE	*P*
Total																		
U.S. population† ($n = 730$)	17.45	3.02		30.78	3.44		23.05	3.41		42.13	4.71		16.23	3.04		14.16	2.95	
Subjects ($n = 75$)	16.59	4.74	.87	41.72	6.16	.11	20.60	5.09	.67	63.49	5.84	.002	21.21	5.15	.37	9.87	3.88	.35
Females																		
U.S. population‡ ($n = 348$)	15.68	2.72		36.69	2.84		18.50	3.35		46.39	4.76		10.80	2.41		8.01	2.28	
Subjects ($n = 44$)	21.81	7.00	.27	52.82	8.11	.02	17.47	6.24	.85	69.15	7.19	.001	14.93	6.02	.38	9.10	5.06	.78
Males																		
U.S. population‡ ($n = 382$)	19.97	3.43		22.38	4.29		29.51	3.49		36.08	4.64		23.95	3.93		22.90	3.91	
Subjects ($n = 31$)	9.37	5.54	.03	26.81	8.27	.47	24.79	8.40	.27	55.90	9.42	<.001	29.65	8.73	.01	10.90	6.05	.03

ALL indicates acute lymphoblastic leukemia; NHANES, National Health and Nutrition Examination Study; HDL, high-density lipoprotein; SE, standard error.

* Case data weighted for sampling distribution and response rates, NHANES data weighted for sampling probabilities, strata, and primary sampling units.

† Standardized to the distributions of age and gender and race in the study population.

‡ Standardized to the distributions of age and race in the study population.

Metabolic Syndrome and Components

Metabolic syndrome was present in 11 study subjects, 3 males and 8 females. The prevalence of metabolic syndrome did not differ statistically ($P = .87$) between study subjects (16.6%) and age- and sex-standardized population norms (17.5%; Table 2). The prevalences of high triglycerides, hypertension, and elevated glucose were similar overall between study subjects and the normative population, but abnormally low HDL-C was present in a substantially higher prevalence of study subjects than in the normative population (63.5% vs. 42.1%; $P = .002$). Male subjects had a higher prevalence of hypertension (29.7%) than did males in the normative population (23.9%; $P = .01$), and a lower prevalence of elevated glucose (10.9% vs. 22.9%, respectively; $P = .03$). The prevalence of abdominal obesity, as measured by waist circumference, was 41.7% in study subjects compared with 30.8% in the normative population ($P = .11$). However, abdominal obesity was present in 20 of the 44 female study subjects, with a prevalence higher than that of same-age females in the normative population (52.8% vs. 36.7%; $P < .02$). In contrast, 9 of 31 male subjects had abdominal obesity, with the difference in prevalence not statistically different from that of same-age males in the normative population (26.8% vs. 22.4%; $P = .47$).

Metabolic Syndrome and Cranial Irradiation

The influence of cranial irradiation on metabolic syndrome is shown in Table 3. Of the 11 subjects with metabolic syndrome, 9 received cranial irradiation. The difference in prevalence of metabolic syndrome by cranial irradiation (18.0% irradiated vs. 8.0% nonirradiated) was not statistically significant ($P = .25$), albeit with a small sample size. Sixty percent of subjects who received cranial irradiation, versus 20% who did not, had 2 or more components of metabolic syndrome. For the 2 metabolic components with important differences by irradiation status (i.e., waist circumference and HDL-C), the differences were observed in females but not in males. In females, mean waist circumference was more than 10 cm larger ($P = .04$) and mean plasma HDL-C nearly 10 mg/dL lower ($P = .007$) in those who were treated with cranial irradiation compared with those who were not.

Mean BMI was higher overall in the irradiated subjects (Table 3), but this difference was entirely limited to female subjects (BMI of 30.3 for those irradiated vs. 24.1 for those not irradiated, $P = .01$). Significantly higher mean levels of total cholesterol and LDL-C were found in the irradiated subjects. Fasting insulin and HOMA index were significantly higher, and IGF-1 significantly lower, among those who received cranial irradiation. A very substantial difference was observed for peak GH among subjects who received cranial irradiation (11 μg/L) compared with those who did not (62 μg/L, $P < .001$, Table 3).

Peak GH Secretion and Cranial Irradiation

GH deficiency (<9 μg/L) was present in 33 of the 72 subjects (46%) with GH tests; 28 of these 33 subjects received cranial irradiation. An additional 13 subjects

TABLE 3
Frequencies and Proportions of Metabolic Syndrome and Its Components and Other Cardiovascular and Diabetes Risk Factors by Cranial Radiation Exposure Status

	Total		No radiation		Radiation		
	(n = 75)		(n = 25)		(n = 50)		
	No.	(%)	No.	(%)	No.	(%)	*P*
Metabolic syndrome	11	(14.67)	2	(8.00)	9	(18.00)	.25
No. of metabolic syndrome components							
None	16	(21.33)	8	(32.00)	8	(16.00)	.05
1	24	(32.00)	12	(48.00)	12	(24.00)	
2	24	(32.00)	3	(12.00)	21	(42.00)	
3–5	11	(14.67)	2	(8.00)	9	(18.00)	
Meets criteria for abnormal metabolic syndrome component							
Waist circumference	29	(38.67)	7	(28.00)	22	(44.00)	.18
Triglycerides	14	(18.67)	2	(8.00)	12	(24.00)	.09
HDL cholesterol	44	(58.67)	11	(44.00)	33	(66.00)	.07
Glucose	6	(8.00)	0	0.00	6	(12.00)	.07
Blood pressure	15	(20.00)	4	(16.00)	11	(22.00)	.54
	Mean	(SD)	Mean	(SD)	Mean	(SD)	*P*
Metabolic syndrome components							
Waist circumference (cm)							
Males	93.16	(13.21)	92.64	(13.13)	93.35	(13.52)	.89
Females	91.00	(17.53)	84.08	(12.89)	95.36	(18.83)	.04
Triglycerides (mg/dL)	124.05	(86.35)	98.48	(67.51)	136.84	(92.35)	.07
HDL cholesterol (mg/dL)							
Males	37.81	(12.54)	39.37	(17.48)	37.26	(10.77)	.69
Females	44.54	(12.19)	50.64	(11.91)	40.7	(10.90)	.007
Glucose (mg/dL)	83.69	(10.32)	80.68	(8.41)	85.2	(10.92)	.07
Systolic blood pressure (mm Hg)	117.60	(14.03)	116.18	(11.15)	118.33	(15.35)	.54
Diastolic blood pressure (mm Hg)	68.05	(9.60)	67.02	(7.51)	68.57	(10.54)	.51
Other risk factors							
Body mass index (kg/m^2)	27.43	(7.04)	24.97	(5.01)	28.67	(7.61)	.03
Males	26.78	(5.25)	26.77	(4.69)	26.79	(5.53)	.99
Females	27.90	(8.09)	24.12	(5.07)	30.27	(8.79)	.01
Waist-to-hip ratio	0.90	(0.07)	0.88	(0.07)	0.91	(0.08)	.06
Total cholesterol (mg/dL)	184.20	(40.67)	164.48	(31.13)	194.06	(41.55)	.002
LDL cholesterol (mg/dL)	116.95	(34.30)	97.76	(25.55)	126.73	(34.26)	<.001
VLDL cholesterol (mg/dL)	23.00	(11.71)	19.68	(13.45)	24.73	(10.43)	.08
C-reactive protein (mg/dL)	0.33	(0.48)	0.35	(0.69)	0.31	(0.35)	.77
Homocysteine (μmol/L)	8.18	(1.67)	8.29	(1.73)	8.12	(1.66)	.7
Microalbumin (mg/L)	10.18	(16.58)	13.44	(14.73)	9.33	(13.11)	.22
Insulin (mu/L)	8.15	(7.88)	4.68	(2.61)	9.88	(9.01)	.006
Peak growth hormone (μg/L)	27.75	(35.02)	61.96	(40.31)	10.65	(12.71)	<.001
IGF-1 (ng/mL)	157.99	(65.92)	189.3	(72.28)	143.29	(57.81)	.005
Thyroxine (ng/dL)	1.07	(0.17)	1.1	(0.15)	1.05	(0.17)	.18
Thyroid-stimulating hormone (mu/L)	2.57	(3.93)	1.78	(0.82)	2.95	(4.72)	.23
Homeostasis model assessment (HOMA)	1.65	(1.89)	0.87	(0.53)	2.04	(2.19)	.01
Height (cm)	165.71	(9.27)	168.43	(8.75)	164.35	(9.31)	.07
Weight (kg)	75.41	(20.21)	71.27	(17.15)	77.48	(21.43)	.21

HDL indicates high-density lipoprotein; SD, standard deviation; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; IGF-1, insulin-like growth factor 1; HOMA, homeostasis model assessment of insulin resistance index.

were GH insufficient (9–16.5 μg/L), all of whom were treated with cranial irradiation. Thus, 64% of study subjects had untreated abnormally low GH. Among the 48 subjects who received cranial irradiation and GH testing, 41 (85%) had either insufficient or deficient GH secretion, compared with 5 of 24 (21%) subjects with GH deficiency (none with insufficiency) who were not treated with cranial irradiation ($P <$ .0001, data not shown). Results from regression modeling showed that mean peak GH was 48 μg/L

TABLE 4
Frequencies and Proportions of Metabolic Syndrome and Its Components and Other Cardiovascular and Diabetes Risk Factors by Peak Growth Hormone Secretion

			Peak growth hormone levels						
	Total		>16.5 μg/L		9–16.5 μg/L		<9 μg/L		
	(*n* = 72)		(*n* = 26)		(*n* = 13)		(*n* = 33)		
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	*P*
Metabolic syndrome	10	(13.89)	1.00	(3.85)	4.00	(30.77)	5.00	(15.15)	.07
No. of metabolic syndrome indicators									.004
None	15	(20.83)	8.00	(30.77)	5.00	(38.46)	2.00	(6.06)	
1	25	(34.72)	12.00	(46.15)	0.00	0.00	12.00	(36.36)	
2	23	(31.94)	5.00	(19.23)	4.00	(30.77)	14.00	(42.42)	
3–5	10	(13.89)	1.00	(3.85)	4.00	(31.77)	5.00	(15.15)	
Meets criteria for metabolic syndrome indicator									
Waist circumference	28	(38.89)	6.00	(23.08)	7.00	(53.85)	15.00	(45.45)	.10
Triglycerides	12	(16.67)	1.00	(3.85)	3.00	(23.08)	8.00	(24.24)	.09
HDL cholesterol	42	(58.33)	10.00	(38.46)	8.00	(61.54)	24.00	(72.73)	.03
Glucose	5	(6.94)	1.00	(3.85)	2.00	(15.38)	2.00	(6.06)	.39
Blood pressure	15	(20.83)	7.00	(26.92)	2.00	(15.38)	6.00	(18.18)	.62
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	*P*
Metabolic syndrome indicators									
Waist circumference (cm)									
Males	92.61	(13.22)	83.32	(5.25)	93.57	(11.37)	96.00	(14.27)	.10
Females	91.22	(17.67)	86.26	(15.20)	91.30	(12.21)	97.89	(22.40)	.18
Triglycerides (mg/dL)	122.33	(86.28)	96.46	(63.45)	154.61	(154.27)	122.00	(86.27)	.10
HDL cholesterol (mg/dL)									
Males	38.41	(12.74)	45.00	(15.69)	40.67	(10.11)	35.63	(11.53)	.24
Females	44.16	(12.06)	51.10	(12.17)	40.80	(11.24)	37.14	(6.71)	.001
Glucose (mg/dL)	83.44	(10.28)	79.26	(7.90)	88.15	(14.38)	84.87	(9.09)	.02
Systolic blood pressure (mm Hg)	117.59	(14.33)	116.17	(14.63)	115.23	(14.46)	119.70	(14.17)	.53
Diastolic blood pressure (mm Hg)	67.84	(9.73)	66.69	(9.77)	63.92	(11.54)	67.83	(9.72)	.09
Other risk factors									
Body mass index (kg/m^2)	27.52	(7.12)	25.00	(5.65)	27.23	(4.82)	29.61	(8.31)	.04
Males	26.71	(5.34)	22.68	(1.44)	27.33	(2.51)	28.10	(5.88)	.06
Females	28.05	(8.12)	25.85	(6.38)	27.20	(5.43)	31.66	(10.69)	.12
Waist to hip ratio	0.90	(0.07)	0.86	(0.07)	0.90	(0.08)	0.93	(0.07)	.00
Total cholesterol (mg/dL)	183.99	(40.83)	171.96	(32.39)	211.38	(47.94)	182.67	(39.90)	.01
LDL cholesterol (mg/dL)	116.96	(34.53)	103.19	(27.59)	137.17	(36.37)	120.45	(35.20)	.01
VLDL cholesterol (mg/dL)	22.57	(11.31)	19.31	(12.60)	22.58	(6.76)	25.22	(11.16)	.14
C-reactive protein (mg/dL)	0.33	(0.49)	0.33	(0.68)	0.24	(0.23)	0.36	(0.40)	.75
Homocysteine (μmol/L)	8.23	(1.68)	8.50	(1.61)	7.97	(2.03)	8.12	(1.60)	.58
Microalbumin (mg/L)	10.30	(16.94)	11.65	(14.56)	8.54	(9.31)	10.81	(15.17)	.81
Insulin (mu/L)	8.08	(7.86)	4.77	(2.63)	12.00	(13.90)	9.15	(6.56)	.01
Peak growth hormone (μg/L)	27.75	(35.02)	65.65	(33.30)	12.25	(2.58)	4.01	(2.64)	
IGF-1 (ng/mL)	157.10	(65.45)	183.54	(71.61)	138.38	(57.49)	144.88	(58.91)	.04
Thyroxine (ng/dL)	1.07	(0.17)	1.10	(0.14)	1.06	(0.25)	1.05	(0.14)	.53
Thyroid-stimulating hormone (mu/L)	2.60	(4.01)	2.04	(1.15)	4.64	(9.11)	2.23	(0.97)	.13
Homeostasis model assessment (HOMA)	1.63	(1.88)	0.85	(0.49)	2.69	(3.60)	1.82	(1.34)	.01
Height (cm)	165.57	(9.39)	166.31	(9.67)	163.49	(8.41)	165.81	(9.68)	.67
Weight (kg)	75.51	(20.43)	68.92	(14.73)	73.12	(15.16)	81.65	(24.38)	.05

HDL indicates high-density lipoprotein; SD, standard deviation; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; IGF-1, insulin-like growth factor 1; HOMA, homeostasis model assessment of insulin resistance index.

lower (95% CI: −31.5, −64.8; $P < .001$) among those who received cranial irradiation compared with those who did not, after controlling for sex, current age, age at diagnosis, and BMI (R^2 for model = 0.55). The BMI parameter estimate in this model was −0.62 (95% CI: −0.16, −1.08; $P = .01$), indicating a modest effect of BMI on GH after accounting for the cranial radiation effect (data not shown).

Peak GH Secretion and Metabolic Syndrome

Of the 72 subjects who were tested for GH secretion, 10 had metabolic syndrome and 9 of those were either GH insufficient or deficient ($P = .07$) (Table 4). An additional 23 subjects had 2 components of metabolic syndrome, 18 of whom had either GH insufficiency or deficiency. We found a pattern similar to that observed with cranial irradiation treatment, in that the number of metabolic components increased with decreasing peak GH level ($P = .004$). Abnormal waist circumference ($P = .10$) and low HDL-C ($P = .03$) were substantially more prevalent among those with abnormal GH secretion compared with subjects who had normal GH secretion. Similarly, BMI, waist-to-hip ratio, LDL-C, mean fasting insulin, and HOMA index were all higher among those with lower than normal peak GH levels.

DISCUSSION

We found that the prevalence of metabolic syndrome in long-term survivors of childhood ALL did not differ from that of population norms. Of concern, however, is the finding that 60% of those who were treated with cranial irradiation, compared with 20% of those who were not, had 2 or more of the five components of metabolic syndrome. A pattern of dyslipidemia and abdominal obesity was evident, particularly in women, which may foreshadow future cardiovascular problems. A large prevalence of ALL survivors in our study, 63.5% (weighted for the sampling method), had abnormally low HDL-C. Triglycerides, total cholesterol, and LDL-C also tended to be abnormal in those who received cranial irradiation. We found essentially no evidence for a dose difference between the 18 Gy and 24 Gy levels for any of the biochemical outcome measures considered, implying that the threshold effect from cranial radiation exposure occurs somewhere less than 18 Gy.

Consistent with other research,[13,21,22,26,37] GH deficiency was strongly associated with cranial radiation treatment in these young adults and was associated with a pattern of dyslipidemia and abdominal obesity. Abnormally low GH was also deleteriously associated with higher fasting insulin, lower IGF-1, and higher HOMA index. Large waist circumference is a strong independent risk factor for insulin resistance,[38,39] and untreated GH deficiency is associated with an array of unfavorable cardiovascular risk factors and outcomes[23,24,40–43] and may also be a risk factor for insulin resistance.[13,23,44,45] The risk profile for diabetes that we observed in ALL survivors with GH deficiency is notable. Whether or not GH treatment is advisable for GH-deficient ALL survivors[19,46] is beyond the scope of our study, but assessment of hypothalamus and pituitary functioning and GH secretion among ALL survivors appears warranted, even in those who did not receive cranial irradiation, given that 20% of those subjects were found to be GH-deficient.

Our study has limitations that should be considered. First, some studies suggest that the GHRH/ARG stimulation test may underdiagnose GH deficiency in the early years after cranial irradiation.[21,47] The patients in our study, however, had a mean time of 25 years from diagnosis, thus minimizing the likelihood of false-negative results. Second, the findings attributable to cranial irradiation are important to the thousands of childhood ALL survivors alive today who were treated ≥20 years ago, but have less contemporary relevance because of the substantially reduced reliance on cranial radiation treatment in current ALL therapy.[2,4,18] Nevertheless, cranial irradiation is still in use for high-risk ALL, for many types of childhood brain and spinal cord tumors, and as a conditioning agent for hematopoietic stem cell transplantation. Lastly, our study was not designed to evaluate etiologic mechanisms of insulin resistance or abnormalities in the biochemical measures studied. Damage to the hypothalamic-pituitary axis from cranial irradiation presumably is largely responsible for the long-term adverse effects on GH secretion observed in our study and others,[13,26,37] and contributes substantially to the cardiovascular disease risk factors that we found. Our data, however, are not sufficient to draw definitive conclusions on etiologic pathways.

Our findings are consistent with a study that compared 50 long-term childhood cancer survivors, including 28 with ALL, with 50 sex- and age-matched healthy controls.[16] Compared with controls, survivors had significantly higher weight and body fat, higher fasting glucose and insulin levels, and significantly decreased HDL-C. A combination of obesity, hyperinsulinemia, and low HDL-C was seen in 8 (16%) of the survivors, but none of the controls. Of the 8 cases with indicators of metabolic syndrome, 4 received cranial radiation and 4 did not. Similarly, Link et al.[13] evaluated GH deficiency and cardiovascular risk fac-

tors in 44 adult survivors of childhood ALL, all of whom were treated with cranial irradiation. They found that all subjects, using the same cutoff points as in our study, were either GH-deficient (91%) or GH-insufficient (9%). They found childhood ALL survivors to have significant dyslipidemia, insulin resistance, increased fat mass, and a marked reduction in cardiac dimensions and performance. Neither the Link et al.[13] study nor the Talvensaari et al.[16] study, however, reported sex-specific findings. Our observation of significant differences in abdominal obesity and lipid profile by gender needs to be explored in future studies.

In conclusion, we found that cranial irradiation in long-term childhood ALL survivors was strongly related to GH deficiency, and in turn lower IGF-1, higher fasting insulin and HOMA index, abdominal obesity, and dyslipidemia, particularly in women. Hematologists who treat and follow childhood ALL patients, and particularly healthcare professionals who provide primary care to young adults once treated for childhood ALL, should be aware of the potential for long-term GH deficiency and adverse cardiovascular and diabetes risk profiles as a consequence of their leukemia treatment.

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