0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(10):3816–3821

doi: 10.1210/jc.2006-2178

Abdominal Obesity, Liver Fat, and Muscle Composition in Survivors of Childhood Acute Lymphoblastic Leukemia

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Context: Survivors of childhood acute lymphoblastic leukemia (ALL) become obese, and are at increased risk for morbidity and mortality post therapy.

Objective: We determined the association of cranial radiotherapy (CRT) and/or sex with levels of total, regional, and ectopic fat storage, metabolic risk, IGF-I, and leptin in adult ALL survivors.

Design, Setting, Patients: A cross-sectional analysis of 52 male (15 CRT treated) and 62 female (24 CRT treated) young adult ALL survivors was conducted.

Main Outcomes: We assessed levels of visceral fat, sc abdominal and thigh fat, and liver and muscle fat using computed tomography, total fat and lean body mass using dual-energy x-ray absorptiometry, and IGF-I and leptin levels by radioimmunoassay.

Results: Controlled for age and race, ALL survivors treated with CRT had higher levels of abdominal and visceral fat, body fat percentage, metabolic risk (insulin resistance and dyslipidemia), and leptin but lower lean mass and IGF-I levels than non-CRT survivors ($P \leq 0.05$ for each). Levels of IGF-I were inversely associated with total, abdominal, and visceral fat in both sexes ($P < 0.05$ for each). Female ALL survivors had less lean mass and visceral fat but higher total and sc abdominal fat than males ($P < 0.05$ for each). Neither sex nor CRT was associated with muscle and/or liver fat content ($P > 0.1$).

Conclusion: Among young adult ALL survivors, CRT is a risk factor for elevated total, abdominal, and visceral adiposity, a reduced fat-free mass, elevated metabolic risk, and altered IGF-I and leptin levels. (***J Clin Endocrinol Metab* 92: 3816–3821, 2007**)

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) is the most common malignancy of childhood, accounting for 25% of all cancer diagnoses made in children (1). Although prognosis for ALL has significantly improved in recent years, ALL survivors are at elevated risk for obesity (2–7), cardiovascular disease (3, 4, 6, 8), and related mortality (9) in the years after treatment. Cranial radiotherapy (CRT) during ALL treatment has been implicated as a potential cause of excess weight gain among survivors (2, 10). Although the mechanism by which CRT leads to obesity is unknown, hypothalamic damage leading to GH deficiency (GHD) and/or leptin insensitivity has been suggested (4, 5). Furthermore, the risk of obesity after ALL treatment appears to be more pronounced in females than in males (2).

Obesity-related health risk is greatest in those with an abdominal obesity phenotype (11, 12). Specifically, excess accumulation of visceral fat within the abdomen is strongly and independently associated with morbidity (13) and mortality (14). Emerging evidence also suggests that the storage of fat in nonadipose tissues such as liver and skeletal muscle may carry an independent health risk (15, 16). Reports on indirect measurements of abdominal obesity in ALL survivors are inconsistent and limited (3, 4, 7, 8), whereas studies directly characterizing survivors of ALL with respect to specific fat depots are absent. In an effort to explain the elevated health risk and identify specific targets for future intervention, we assessed whether CRT and/or sex among young adult ALL survivors was associated with elevations in abdominal, visceral, liver, and muscle fat accumulation.

Subjects and Methods

A database of potential eligible young adult survivors of childhood ALL was created from three sources. The primary source was patients in the cancer registry at Children's Medical Center Dallas, who were

First Published Online July 24, 2007

Abbreviations: ALL, Acute lymphoblastic leukemia; BMI, body mass index; CRT, cranial radiotherapy; CT, computed tomography; CTL, CT of liver; CTS, CT of spleen; CV, coefficient of variation; GHD, GH deficiency; HDL-C, high-density lipoprotein-cholesterol; HOMA, homeostasis model assessment; HOMA-IR, HOMA-insulin resistance; LDL-C, low-density lipoprotein-cholesterol.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

diagnosed with childhood ALL from 1970–2000. A small group of ALL survivors diagnosed at Cook Children's Hospital in Fort Worth, TX, and treated on a shared, two-institutional protocol [Dallas/Fort Worth-1 (DFW-1)] was also eligible. A third database included a small number of ALL survivors followed in the survivor program at Children's Medical Center Dallas and University of Texas Southwestern (the After the Cancer Experience Program), who were diagnosed and treated at other institutions.

A total of 237 potentially eligible participants were identified and contacted. There were 48 potential participants who did not meet eligibility criteria because five had severe cognitive deficits, two had Down's syndrome, seven had major medical problems precluding testing, two were pregnant, one was in jail, two were in the military, and 29 lived out of state. Of the 189 survivors who met eligibility criteria, 16.4% and 21.2% actively and passively refused to participate, respectively. The remaining 118 eligible participants enrolled in the study (62.4%; 118 of 189). Key demographic characteristics, including sex, age, race and ethnicity, age at cancer diagnosis, and interval from cancer diagnosis to present time, were not significantly different ($P > 0.1$) between eligible participants who did not enroll in the study (active and passive refusals; n = 71) and participants (n = 118). Of the 118 who enrolled, 114 completed a computed tomography (CT) scan of the abdomen and are the target population of this analysis.

The mean age of the 114 participants at the time of study was 23.8 ± 4.9 yr (range 18–37). Mean age at ALL diagnosis was 6.2 ± 4.3 yr, with a mean interval from diagnosis to study enrollment of 17.5 ± 6.0 yr. A total of 54% were females, and 23.7% were of an ethnic or racial minority group.

To determine potential differences in body mass index (BMI) (a surrogate of total and abdominal adiposity) between CRT and non-CRT subjects at diagnosis, heights and weights for participants were abstracted. Pretreatment heights and weights were available for 79 (69.3%) of the 114 participants. Using a SAS program from the Centers of Disease Control (17), sex and age-specific BMI z scores were calculated. The gender and age-specific BMI z scores between the CRT and non-CRT were not significantly different at diagnosis ($P = 0.96$), indicating no selection bias of obese children into the CRT group.

Participants were treated on one of several groups of protocols: 45 (39.5%) on DFW-1 protocol; 45 (39.5%) on a Pediatric Oncology Group protocol, including Pediatric Oncology Group 8036, 9201/2/3, and 9404; five (4.4%) on a Children's Cancer Group protocol; and 19 (16.6%) on an institutional or miscellaneous protocol. Of the participants, 34% were treated with CRT (five with 12 Gy; six with 18 Gy; 28 with ≥24 Gy). As a standard, 24 Gy CRT was administered to all patients with ALL at Children's Medical Center Dallas until 1982. After 1982, 18 or 24 Gy was administered to high-risk patients (T cell, overt central nervous system disease, or high-risk cytogenetics), depending upon the era of therapy. Because no differences were observed in the main outcomes between categories of CRT, the study sample was divided into CRT *vs.* non-CRT groups. Six patients with a relapse were treated with 12 Gy total body irradiation before an allogeneic stem cell transplant. Seven also had spinal radiotherapy; three of the males had radiation to the testis. Chemotherapy had been given according to a variety of institutional or consortium protocols. A total of 74% were treated with an anthracycline (<300 mg/m^2, 54.4%; ≥300 mg/m^2, 19.3%). Other key treatment exposures included dexamethasone (11.4%), cytarabine (62.3%), cyclophosphamide (43.0%), etoposide (34.2%), and thioguanine (9.7%). Over 95% of the cohort was treated with vincristine, methotrexate, or prednisone.

All study participants provided written informed consent for study participation and release of medical record information, and the study was approved by the Institutional Review Board at The University of Texas Southwestern Medical Center and The Cooper Institute.

Anthropometric and radiographic measures of body composition

BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Waist circumference was measured at the level of superior iliac crest to the nearest 0.1 cm.

CT scans of the abdomen and thigh were acquired using an electron beam CT scanner (Imatron; General Electric, Milwaukee, WI). Images were obtained using standard procedures and analyzed using specialized image analysis software (Tomovision, Montreal, QC, Canada). A contiguous series of five to seven CT images between the L4–L5 and L3–L4 vertebral disc spaces were analyzed for determination of visceral and sc abdominal fat mass, whereas 11 contiguous images of the midthigh were analyzed to determine thigh sc fat mass using procedures described elsewhere (14).

Liver fat was determined using the ratio of liver (CTL) to spleen (CTS) attenuation values (CTL/CTS), as described in detail elsewhere (18). A lower CTL to CTS ratio is an indication of fatty infiltration of the liver (19).

Skeletal muscle composition was derived using the mean CT attenuation of thigh skeletal muscle (range 0–149 HU) averaged from 11 CT images of the midthigh. A reduced mean muscle attenuation is associated with an increased muscle lipid content (20).

A full-body dual-energy x-ray absorptiometry scan was acquired to determine total body fat mass, lean mass, and percent body fat using a Lunar DPX scanner (MEC, Minster, OH).

Blood pressure measurement

Five blood pressure measurements were taken in the seated position using an automatic oscillometric device (series no. 52,000; Welch Allyn, Inc., Arden, NC) that has been validated against direct catheter-based measurements of intraarterial pressure.

Laboratory analysis

Venous blood samples were taken after a 12-h overnight fast and stored frozen at −80 C until sent for batch analysis. Commercial RIAs were used to measure serum IGF-I and leptin levels (Linco Research, Inc., St. Charles, MO). For leptin, the intraassay coefficient of variation (CV) was 4.7%, interassay CV was 3.0%, detection limit was 0.5 ng/ml, and specificity was 100%. The performance characteristics of the IGF-I kit were: sensitivity, 2.06 ng/ml; specificity, 100%; intraassay CV, 3.9%; and interassay CV 3.8%. Although insulin tolerance testing is the recommended standard for diagnosing GHD, IGF-I is a reliable surrogate of GH status among childhood-onset GHD adults (21). A low IGF-I level strongly suggests GHD or GH insufficiency, but a normal IGF-I level does not exclude the diagnosis of GHD.

Lipoproteins [total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglycerides) were determined using the Vertical Auto Profile-II (Atherotech, Birmingham, AL). The Vertical Auto Profile-II is a single test direct measurement method, with no estimations involved.

A commercial RIA was used to measure insulin levels (Linco). The human insulin assay intraassay CV was 3.1%, interassay CV was 6.0%, detection limit was 2 μU/ml, and sensitivity was 100%. The glucose levels were determined through the General Clinical Research Center Core Laboratory using a Beckman Synchron CX9 ALX system (Beckman Coulter, Inc., Fullerton, CA). Insulin resistance was estimated, using the fasting glucose and insulin levels, with the Homeostasis Model Assessment 2 (HOMA2) computer model (HOMA Calculator version 2.2) (22).

Statistical analysis

A 2 × 2 analysis of covariance for main effect and interaction of sex and CRT using age and race as covariates was applied to assess differences between group means. Data not normally distributed were normalized using transformations. Spearman's ρ and linear regression were used to explore relationships among hormone and body composition measures. Statistical analyses were performed using SPSS 13.0 (SPSS, Inc., Chicago, IL).

Results

Anthropometrics

Body composition measurements are given in Table 1. Participants treated with CRT were significantly older and shorter than non-CRT participants ($P < 0.01$). Males were

TABLE 1. Anthropometrics, body composition, and hormone and metabolic status in a sample of young adult survivors of ALL

Anthropometrics	Men		Women		*P* value		
	Non-CRT (n = 37)	CRT (n = 15)	Non-CRT (n = 38)	CRT (n = 24)	Main effect of CRT	Main effect of sex	Interaction effect
Age (yr)	22.0 (3.5)	27.1 (5.7)	23.1 (4.2)	25.3 (6.0)	<0.01	0.90	0.11
Height (cm)	175.5 (6.8)	171.6 (8.5)	162.7 (5.2)	154.8 (7.4)	<0.01	<0.01	0.23
Weight (kg)	80.8 (15.2)	81.9 (22.1)	71.9 (18.8)	76.3 (23.5)	0.70	<0.05	0.29
BMI (kg/m^2)	26.2 (4.5)	27.8 (7.4)	27.2 (7.2)	31.6 (8.6)	0.16	0.35	0.08
Waist circumference (cm)	89.2 (12.1)	94.6 (16.3)	89.0 (15.3)	96.4 (16.7)	0.28	0.82	0.30
Dual-energy x-ray absorptiometry							
Total fat mass (kg)	18.0 (9.9)	23.9 (11.4)	26.0 (12.7)	32.5 (13.0)	0.06	<0.01	0.93
Total lean mass (kg)	60.9 (8.1)	56.9 (11.1)	44.6 (6.5)	42.2 (9.5)	<0.01	<0.01	0.32
Percent body fat (%)	21.7 (8.7)	28.5 (6.3)	35.1 (7.8)	42.4 (4.9)	<0.01	<0.01	0.53
CT							
Abdominal fat (kg)	1.00 (0.64)	1.38 (0.65)	1.09 (0.59)	1.47 (0.54)	<0.05	0.67	0.58
(Visceral fat (kg))	0.25 (0.17)	0.37 (0.22)	0.17 (0.13)	0.33 (0.17)	<0.01	<0.05	0.09
(Subcutaneous fat (kg))	0.75 (0.52)	1.01 (0.51)	0.93 (0.49)	1.15 (0.41)	0.09	<0.05	0.88
Liver fat (CTL/CTS)	1.22 (0.15)	1.17 (0.28)	1.24 (0.13)	1.23 (0.17)	0.67	0.70	0.74
Muscle attenuation (HU)	55.1 (3.2)	54.2 (3.8)	54.1 (3.3)	52.4 (4.3)	0.12	0.14	0.42
Thigh sc fat (kg)	0.76 (0.38)	0.91 (0.50)	1.39 (0.70)	1.66 (0.63)	0.12	<0.01	0.76
Hormone status							
IGF-I (μg/liter)	463.1 (175.1)	315.3 (155.5)	434.3 (190.4)	254.8 (110.7)	0.01	0.49	0.16
Leptin (μg/liter)	6.2 (6.9)	12.9 (15.5)	19.6 (14.3)	28.9 (14.6)	<0.05	<0.01	0.48
Leptin/fat mass (μg/liter·kg)	0.3 (0.2)	0.5 (0.3)	0.7 (0.3)	0.8 (0.3)	<0.05	<0.01	0.79
Metabolic							
Fasting glucose (mg/dl)	91.5 (7.4)	94.3 (7.9)	87.8 (6.6)	90.8 (7.3)	0.15	<0.01	0.73
Fasting insulin (μU/ml)	16.4 (8.0)	20.5 (14.5)	16.7 (8.3)	22.6 (11.2)	0.06	0.60	0.26
HOMA-IR	2.1 (1.0)	2.6 (1.7)	2.1 (1.0)	2.8 (1.4)	<0.05	0.84	0.39
Total cholesterol (mg/dl)	176.8 (29.6)	186.7 (27.3)	168.9 (25.4)	184.1 (29.4)	<0.05	0.30	0.64
HDL-C (mg/dl)	44.8 (9.0)	42.2 (8.7)	51.4 (11.6)	48.8 (9.8)	0.12	<0.01	0.90
LDL-C (mg/dl)	113.1 (26.4)	121.0 (27.2)	99.8 (21.7)	114.8 (29.0)	<0.05	<0.05	0.56
Triglyceride (mg/dl)	114.5 (84.5)	150.0 (86.5)	97.9 (54.0)	134.0 (95.9)	0.05	0.23	0.95
Systolic blood pressure (mm Hg)	117.4 (9.7)	112.9 (11.5)	111.1 (11.4)	108.1 (11.9)	<0.05	<0.01	0.62
Diastolic blood pressure (mm Hg)	70.3 (7.9)	70.7 (8.4)	72.1 (8.5)	71.1 (9.2)	0.24	0.36	0.97

Data are presented as mean (SD). Age and race were used as covariates in the analysis. Variables not normally distributed [age (median 23.0, range 18.0–37.0 yr), BMI (26.6, 18.2–60.2 kg/m^2), waist circumference (91.3, 62.0–150.0 cm), total fat mass (22.3, 4.4–74.9 kg), visceral fat (0.22, 0.03–0.91 kg), sc abdominal fat (0.84, 0.10–2.60 kg), liver fat (1.26, 0.79–1.53 CTL/CTS), muscle attenuation (54.3, 41.4–62.2 HU), thigh sc fat (1.13, 0.18–4.07 kg), fasting insulin (15.0, 6.0–54.0 μU/ml), HOMA-IR (2.0, 0.8–9.9), and triglycerides (90.5, 38.0–502.0 mg/dl)] were normalized using transformations.

significantly taller and heavier than female participants ($P < 0.01$). Neither the exposure to CRT nor sex had an effect on BMI and/or waist circumference ($P > 0.1$).

Regional adipose tissue distribution

Controlled for age and race, CRT ALL survivors had greater abdominal ($P < 0.05$) and visceral fat ($P < 0.01$), but not sc abdominal fat ($P = 0.09$; Fig. 1), compared with non-CRT survivors. In female survivors only, CRT was associated with greater visceral fat ($P < 0.01$) but similar sc abdominal fat ($P > 0.1$) after further control for total fat mass (data not shown). Although abdominal fat did not differ between the sexes ($P > 0.1$), males had more visceral fat but less sc fat than females ($P < 0.05$). Additional control for height did not alter these observations. Finally, the amount of sc fat in the thigh did not differ by treatment ($P > 0.1$) but was higher in the female than male survivors ($P < 0.01$).

Dose of CRT did not modify outcomes. Cumulative dose of an anthracycline and therapy with any specific chemotherapeutic agent was not significantly associated with an increase in visceral or abdominal sc fat. When adjusted for age at study, the interval from cancer diagnosis to study was not associated with an increase in visceral or abdominal sc fat.

Liver fat and skeletal muscle composition

Neither CRT nor sex was associated with liver fat (CTL to CTS ratio, $P > 0.1$) or muscle fat (mean muscle attenuation, $P = 0.07$).

Total body fat and lean mass

Controlled for age and race, CRT survivors had a higher body fat percentage than non-CRT survivors ($P < 0.01$), consequent to a higher total fat mass ($P = 0.06$) and reduced lean mass ($P < 0.01$; Fig. 1). Females had a higher total fat mass ($P < 0.01$) and lower lean mass ($P < 0.01$), and, thus, a higher body fat percentage compared with males ($P < 0.01$).

IGF-I and leptin levels

Although both the male and female CRT groups had total IGF-I z scores within expected ranges for their age (z = 0.45 and −0.20 for male and female CRT survivors, respectively; $P > 0.1$), IGF-I levels were significantly lower in CRT than in non-CRT survivors ($P = 0.01$). CRT survivors had higher absolute and relative (expressed per kg of fat mass) leptin levels than non-CRT counterparts ($P < 0.05$). Furthermore, females had greater absolute and relative leptin levels compared with the males ($P < 0.01$).

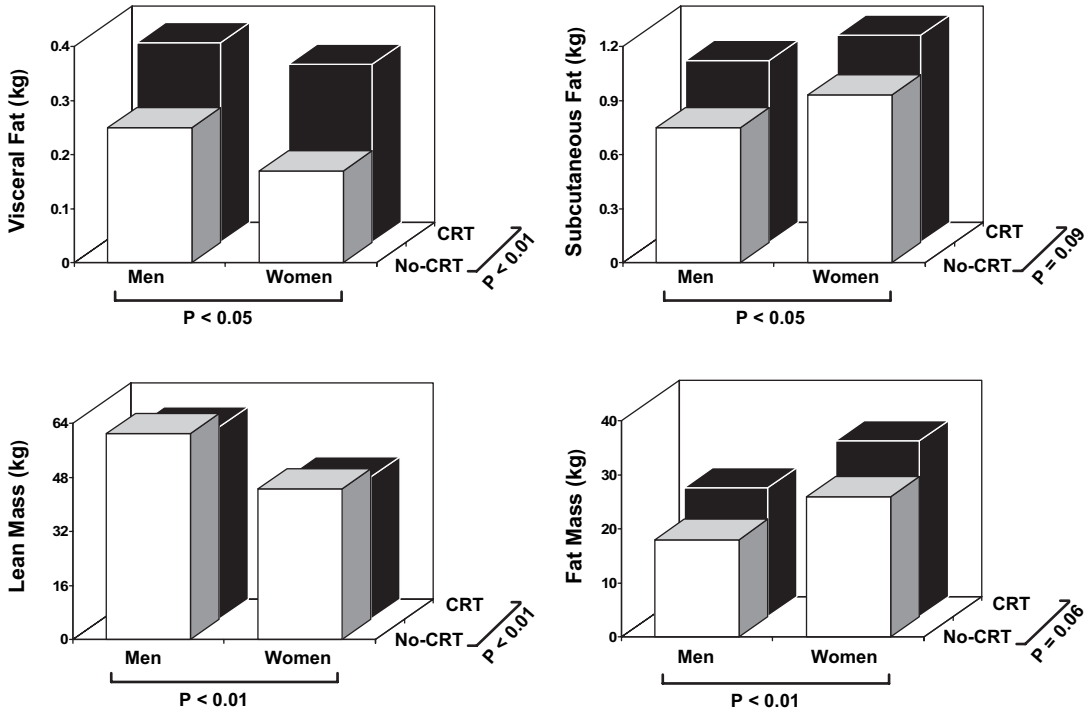

FIG. 1. Main effects of CRT and sex on visceral and sc abdominal fat, fat mass, and lean mass in men and women ALL survivors.

Metabolic variables

After control for age and race, Homeostasis Model Assessment-insulin resistance (HOMA-IR) score ($P < 0.05$), total cholesterol ($P < 0.05$), LDL-C ($P < 0.05$), and triglyceride levels ($P = 0.05$) were higher, whereas systolic blood pressure was lower ($P < 0.05$) in the CRT *vs.* the non-CRT survivors. In addition, fasting glucose ($P < 0.01$), LDL-C ($P < 0.05$), and systolic blood pressure ($P < 0.01$) were higher, whereas HDL-C ($P < 0.01$) was lower in the males compared with females.

Relationship between IGF-I, leptin levels, and body composition

In both genders, IGF-I was negatively related to absolute and relative levels of leptin ($\rho = -0.38$ to -0.56; $P < 0.01$), as well as total, abdominal, and visceral fat mass ($\rho = -0.35$ to -0.54; $P < 0.05$). In female survivors only, low levels of IGF-I were also associated with a higher BMI and reduced height ($P < 0.01$). Absolute leptin levels were positively correlated with all measures of total, regional adiposity, and muscle fat ($P < 0.05$), but not with liver fat ($P > 0.1$).

Discussion

This is the first report in young adult ALL survivors to quantify specific fat depots that are independent predictors of health risk. The novel finding is that abdominal adiposity, specifically visceral fat, is greater in CRT *vs.* non-CRT ALL survivors independent of sex, age, and race. Furthermore, the elevated visceral adiposity among CRT survivors is associated with a deteriorated metabolic risk profile compared with non-CRT survivors. These results underscore the heightened health risk among ALL survivors treated with CRT.

Independent of BMI, those with abdominal obesity exhibit greater risk of hypertension, type 2 diabetes, dyslipidemia, and mortality (11, 12). Of the two abdominal fat depots, visceral fat has emerged as an independent predictor of cardiovascular disease (13) and mortality (14). In this study, despite similar BMI and waist circumference values, ALL survivors treated with CRT had 65% more visceral fat, and were insulin resistant and dyslipidemic by comparison to non-CRT survivors. These observations highlight visceral adiposity as a primary target for intervention strategies designed to attenuate obesity related morbidity and mortality among ALL survivors treated with CRT.

Although liver and skeletal muscle fat are independently associated with metabolic risk (15, 16), CRT was not associated with elevations in either of these depots among ALL survivors. Because the duration of obesity predicts health risk independent of the degree of obesity (23), and because the study sample was young and predominantly obese, our results do not preclude the possibility of future development of liver and muscle fat infiltration and associated metabolic disturbance. Furthermore, the lack of association between visceral fat and liver fat has been reported by others (15) and suggests that these two depots function independently to predict metabolic risk.

Previously, Jarfelt *et al.* (7) documented a higher fat mass and lower lean mass in male but not female CRT *vs.* non-CRT ALL survivors. We extend these earlier findings to both male and female CRT-treated survivors of ALL, in-

dependently of age and race. With the exception of non-CRT males, all the groups in our study had markedly higher fat mass (+5.5 to + 12.0 kg) compared with age-specific population norms established using bioelectrical impedance in the third National Health and Nutrition Examination Survey (24). The most notable discrepancy was seen in the CRT females, whose fat mass was 60% higher than seen among age-matched females from the normal population. Only CRT males had a notably lower lean mass (−4 kg) compared with corresponding third National Health and Nutrition Examination Survey values (24).

The mechanism by which CRT-treated ALL survivors accrue excess fat remains unclear. It is proposed that CRT may induce damage at the radiosensitive hypothalamus with consequent GHD and/or leptin insensitivity. A significant proportion of CRT-treated survivors will exhibit varying degrees of GHD (4, 25). As suggestive of GHD or GH insufficiency, reduced IGF-I levels in our study were associated with elevated total, abdominal, and visceral fat concurrent with reduced lean body mass and height, particularly in those treated with CRT. Furthermore, consistent with GH insufficiency (26), we observed greater levels of visceral fat in relation to reduced IGF-I levels among CRT *vs.* non-CRT participants, but no differences in sc abdominal fat. Thus, CRT ALL survivors not only accumulate more fat abdominally but do so preferentially in the visceral depot as a possible consequence of relative GH insufficiency.

Consistent with prior reports (3–5), our findings illustrate that treatment with CRT among ALL survivors is associated with increased plasma leptin levels, even when expressed per unit of fat mass. These observations suggest that the pathogenesis of obesity subsequent to treatment with CRT may involve radiation-induced hypothalamic resistance to leptin (5). Alternatively, the hyperleptinemia seen in CRT-treated ALL survivors may simply be a result of GHD, rather than a manifestation of leptin resistance, *per se* (5).

Limitations of the present report include the use of total, rather than free IGF-I level as a surrogate for GH action, as well as lack of reference data for our primary outcomes, including visceral fat, liver fat, and muscle composition. Furthermore, although the direct effects of radiation at other sites, chemotherapy, and glucocorticoid administration on the primary outcomes could not be assessed, the effect of CRT was independent of these potentially confounding factors.

In summary, our study demonstrates that CRT among ALL survivors is associated with excess accumulation of abdominal fat, particularly visceral fat, and elevated metabolic risk. Furthermore, our findings corroborate previous reports of increased total fat mass, reduced lean body mass, altered IGF-I levels, and hyperleptinemia as a consequence of CRT. Because abdominal obesity and visceral fat are independent predictors of morbidity and mortality, they present as novel targets for future interventions aimed at reducing the increased health risk among ALL survivors.

Acknowledgments

We thank the nursing staff and Robert Butsch of Informatics Core at the General Clinical Research Center, and Janice Rookstool and Jessica Scarf of the Department of Family and Community Medicine, University of Texas Southwestern Medical Center, for their assistance and expertise. The authors also appreciate the insightful comments of Charles A. Sklar, M.D.

Received October 5, 2006. Accepted July 12, 2007.

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This work was supported by research grants from the National Institutes of Health (R01-CA-100474 and M01-RR-00633), the Howard J. and Dorothy Adleta Foundation, the Canadian Institutes of Health Research (MT-13448, to R.R.), and the Heart and Stroke Foundation of Ontario.

Disclosure Statement: The authors have nothing to disclose.

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