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Hyperinsulinemia, Impaired Glucose Tolerance, and Diabetes Mellitus in Survivors of Childhood Cancer: Prevalence and Risk Factors

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Context: Hyperinsulinism and its associated metabolic abnormalities, including diabetes mellitus (DM), have been reported in long-term survivors of childhood cancer, mainly after bone marrow transplant (BMT); however, the predisposing factors are unclear, and early markers have not been identified.

Methods: The prevalence of overweight/obesity, abdominal adiposity and hyperinsulinemia (HI), impaired glucose tolerance (IGT), or DM was examined prospectively in 248 survivors of childhood cancer (36 prepubertal, 88 pubertal, and 124 adult subjects; 67 BMT) at a median of 12.9 yr (2.3–33.6) after diagnosis and compared with healthy controls. Potential risk factors for the development of HI, IGT, or DM were sought.

Results: Overweight/obesity was not increased when comparing subjects with controls; however, the prevalence of abdominal adiposity in prepubertal and pubertal subjects was roughly doubled ($P \leq 0.04$). Fasting insulin concentrations were higher in prepubertal and pubertal subjects compared with their controls ($P < 0.001$) and were similar in adult and pubertal subjects. HI, IGT, or DM was detected in 39 of 212 (18%) pubertal or adult subjects (23 BMT). Ten of 88 (11%) pubertal and 14 of 124 (11%) adult subjects had IGT/DM (*vs.* 0 and 4.9% controls, respectively; $P < 0.001$). Total body irradiation, untreated hypogonadism, and abdominal adiposity emerged as independent risk factors for the development of HI, IGT, or DM in multivariate regression analysis.

Conclusions: The risk factors identified suggest the need for reconsideration of BMT protocols and regular screening of survivors. The increased prevalence of abdominal adiposity among prepubertal subjects, none of whom had developed HI/IGT/DM, suggests that a waist to height ratio greater than 0.5 has potential as a clinical screening tool. **(*J Clin Endocrinol Metab* 91: 4401–4407, 2006)**

HYPERINSULINISM AND ITS attendant metabolic abnormalities are associated with the early development of type 2 diabetes mellitus (DM), cardiovascular disease, and cancer (1). An increased prevalence of hyperinsulinism and type 2 DM has been identified in survivors of childhood malignancy (2–6), particularly among those treated with bone marrow transplant (BMT); however, a clear picture of the predisposing factors has not emerged from the handful of studies reported, with conditioning for BMT with total body irradiation (TBI), complications of BMT or chemotherapy, hormonal deficiencies, obesity, and genetic predisposition variably implicated as risk factors (2–6). This may relate to differences in the oncology populations studied and outcome measures used to analyze potential risk factors, and with one exception (6), the relatively small number of patients studied in each.

Identification of the risk factors is critical for the development of prevention strategies. In our cross-sectional study of 248 survivors of childhood malignancy, we grouped hyperinsulinism, impaired glucose tolerance (IGT), and type 2 DM together for analysis of potential risk factors, based on the premise that these three entities are part of the same disease spectrum (7, 8). Although we accepted the definition of hyperinsulinism used in other studies (3, 4), reference ranges for insulinemia in the prepubertal and pubertal population are not well-established, and insulin sensitivity is known to decrease during puberty (9). Moreover, we postulated that, before the development of HI, IGT, or type 2 DM, those at risk might have an unfavorable rather than frankly abnormal metabolic profile compared with the general population. To address these issues, we screened a large population of healthy prepubertal and pubertal children and used published Australian data in adults (10) for comparison with the postmalignancy subjects.

Both body mass index (BMI) and abdominal adiposity are potential clinical markers for metabolic abnormality. Interpretation of BMI in childhood and adolescence is not as straightforward as in adults because of progressive changes with growth (11). Moreover, abdominal adiposity is more strongly associated with the development of insulin resistance and type 2 DM in the general population than is increased BMI (12). Increased total fat mass with or without increased BMI has been described after recovery from malignancy (13–15), although data are conflicting on the risk conferred by increased waist to hip ratio in this population (4, 16). Waist to height ratio has not been studied in postmalignancy subjects but allows for varia-

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Abbreviations: BMI, Body mass index; BMT, bone marrow transplant; DM, diabetes mellitus; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; HI, hyperinsulinemia; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; TBI, total body irradiation.

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tion in height within and outside the normal range, particularly relevant to the postmalignancy children and adolescents in whom abnormal growth is well-described (17). Waist to height ratio correlates well with the volume of visceral fat as measured by computerized tomography (18), and a ratio of more than 0.5 has been found to be a good predictor of complications of abdominal obesity in the general population including children (19–22). We postulated that, if such an association was confirmed in the postmalignancy children, it might serve as a simple clinical screening tool to trigger early intervention to prevent the later development of diabetes.

Patients and Methods

Sixteen hundred children were treated for childhood cancer at Sydney Children's Hospital Australia between 1971 and 2000, and approximately 600 attended follow-up clinics regularly. From this cohort, individuals attending routine review in either the endocrine or the long-term follow-up clinic between February 2002 and July 2004 were offered enrollment in the study if they had been disease-free for a minimum of 1 yr since completing treatment and were at least 2 yr from diagnosis. None of those approached declined enrollment. The study protocol was approved by the institution's research ethics committee. Written informed consent was obtained from subjects over the age of 14 yr and from a parent/guardian of all those 14 yr or younger.

The median age (range) of the 248 subjects enrolled was 18.0 yr (5.8–39.4), and the median time since initial diagnosis was 12.9 yr (2.3–33.6), with 232 subjects 5 or more years from diagnosis. Details of the diagnoses and treatment were obtained from the medical record and are listed in Table 1. Birth weight and length were recorded, and a history was sought from the subject and/or family of type 2 DM and dyslipidemia in siblings, parents, or grandparents.

Subjects were classified as prepubertal (n = 36), pubertal (n = 88), or adult (n = 124) at the time of screening (Table 2). Pubertal staging was performed by clinical examination by an endocrinologist. The pubertal group included all subjects less than 18 yr old with clinical features of puberty [≥4 ml testes (boys) or Tanner stage 2 or more breast development (girls) and/or Tanner stage 2 or more pubic hair]. One girl aged over 12 yr and one boy aged over 13 yr who were clinically prepubertal but had raised gonadotropins were included in the pubertal group. All subjects 18 yr and older were classified as adults.

Based on the age spread of the prepubertal and pubertal oncology subjects, healthy prepubertal (n = 85) and pubertal (n = 90) children aged 5–17 yr (Table 2) who were fasting for minor surgical procedures or were siblings of patients (n = 4) were recruited as controls after their assent and parental consent had been obtained. Height, weight, waist circumference, and pubertal status were determined by a single observer (K.A.N.), and a fasting blood sample was obtained.

For comparison with the oncology subjects aged 18 yr or older, data from the 1999–2000 Australian National Diabetes Survey (10) (AusDiab Study) were used. Because of the known association of risk factors for IGT and type 2 DM with age and sex in adulthood, the anthropomorphic and biochemical data available on the 2541 adult population controls were weighted based on the proportion of the 124 adult subjects of each sex at each year of age. BMI, waist to height ratio, fasting glucose, lipids, and the results of a standard oral glucose tolerance test (OGTT) were available in all individuals from the AusDiab study; however, fasting insulin concentrations were not.

The prevalence of overweight and abdominal adiposity in subjects and controls was compared. Adults (≥18 yr) were classified as overweight/obese if their BMI was 25 kg/m^2 or greater. In those 18 yr and younger, the International Obesity Task Force Standards were used to define overweight and obese (11). Abdominal adiposity was defined as a waist to height ratio more than 0.5 (18, 20–22).

The prevalence of hypertension was assessed in subjects by comparison with published standards, defined as a systolic and/or diastolic blood pressure greater than or equal to 140 or 90 mm Hg, respectively, in subjects 18 yr or older, or a systolic and/or diastolic blood pressure 95th percentile or more for age, sex, and height in those less than 18 yr (23).

A fasting blood sample was obtained in all subjects and controls for the measurement of insulin, glucose, cholesterol [total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL)], triglycerides, insulin, and glycosylated hemoglobin (HbA_{1c}). Thyroid function tests (free T_4, TSH), FSH, LH, and either estradiol or testosterone were also measured in the subjects.

Hyperinsulinemia (HI) was defined as a fasting insulin 20 mU/liter or greater (24) or a peak insulin during a standard OGTT of 150 mU/liter or more (25). In those with a fasting insulin 20 mU/liter or greater or acanthosis nigricans, a standard OGTT performed after a 12-h overnight fast was used to define IGT (fasting glucose < 7.0 mmol/liter, 2-h glucose ≥ 7.8 and < 11.1 mmol/liter) or DM (fasting glucose ≥ 7.0 mmol/liter and 2-h glucose

TABLE 1. Diagnoses and treatment modalities

Diagnosis	No. of subjects (no. of males)	Median age (yr) at initial diagnosis (range)	Median age (yr) at screening (range)	Median years since diagnosis (range)	BMT (n)	TBI (n)	Pituitary irradiation (n)[a]	Abdominal irradiation (n)
ALL	116 (68)	3.8 (0.6–15.4)	20.4 (6.9–37.1)	15.0 (2.9–33.6)	21	13	92	
AML	19 (10)	5.1 (0.4–13.7)	17.5 (8.1–37.9)	14.7 (3.6–26.5)	17	7	5	
NHL	20 (15)	7.9 (1.4–16.9)	18.0 (13.6–30.7)	12.3 (4.3–25.8)	6	5	6	2
Hodgkins' disease	5 (1)	12.4 (8.6–13.8)	23.7 (21.4–37.8)	11.7 (7.8–29.3)				
Stage 4 neuroblastoma	10 (9)	2.7 (1.3–5.7)	12.0 (6.5–21.3)	9.5 (4.7–17.8)	10	10		6
Stage 2/3 neuroblastoma	8 (1)	1.2 (0.1–4.0)	14.6 (9.0–23.6)	12.9 (8.5–20.5)				2
Wilm's tumor	14 (5)	3.2 (1.0–11.1)	15.2 (11.4–37.0)	12.8 (7.7–30.5)				10
Bone tumors[b]	7 (5)	9.3 (3.0–15.2)	23.1 (13.4–31.2)	16.0 (6.7–20.2)	1[c]			
Soft tissue tumors[b]	13 (7)	4.8 (1.9–15.7)	19.4 (8.9–39.4)	15.4 (6.9–26.4)	3[d]		10	
Brain tumors[b]	23 (15)	7.1 (1.1–13.7)	15.3 (5.8–26.5)	7.1 (2.3–15.2)	1[e]		23	
Other[b]	13 (7)	5.0 (0.1–13.5)	16.7 (9.5–29.5)	9.6 (4.9–18.6)	8[f]		1	

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; NHL, non-Hodgkin's lymphoma.

[a] Subjects that received pituitary irradiation, either in addition to or independent of TBI.

[b] Bone tumors: Osteogenic sarcoma, n = 4; Ewings sarcoma, n = 3. Soft tissue tumors: Head and neck rhabdomyosarcoma, n = 7; nasopharyngeal carcinoma, n = 2; nasopharyngeal endodermal sinus tumor, n = 1; nasopharyngeal lymphoepithelioma, n = 1; sarcoma (limb), n = 1, (parameningeal), n = 1. Brain tumors: Medulloblastoma, n = 15; ependymoma, n = 5; primitive neuroectodermal tumor, n = 2; pineal, n = 1. Other: Chronic myeloid leukemia, n = 3; myelodysplasia, aplastic anemia, Fanconi anemia, familial erythrophagocytic lymphohistiocytosis, hemangioendothelioma, hemophagocytic syndrome, Langerhans histiocytosis, desmoid tumor, hepatoblastoma, and mesonephroma.

[c] Indication for BMT, Ewings sarcoma.

[d] Indication for BMT, secondary AML, n = 2; recurrent rhabdomyosarcoma, n = 1.

[e] Five additional children with brain tumors received stem cell-supported nonmyeloablative chemotherapy but were not classified as receiving a BMT.

[f] Indication for BMT, chronic myeloid leukemia, n = 3; aplastic anemia, myelodysplasia, hemophagocytic syndrome, Fanconi anemia, familial erythrophagocytic lymphhistiocytosis.

TABLE 2. Comparisons of oncology subjects *vs.* controls

	Prepubertal		Pubertal		Adult	
	Controls (n = 85)	Subjects (n = 36)	Controls (n = 90)	Subjects (n = 88)	Controls (n = 2541)[a]	Subjects (n = 124)
Age in yr (range)[b]	7.3 (5.0–12.1)	9.8 (5.8–13.5) $P < 0.001$	13.2 (9.1–18.0)	15.3 (9.0–18.0) $P < 0.001$	25 (25–39)	24.5 (18.1–39.4)
Sex (males/females)	45/40	27/9 $P = 0.02$	41/49	49/39	54/46	67/57
Measures of obesity						
BMI (kg/m^2)[c]	17.5 (3.9)	18.1 (3.1)	21.7 (4.2)	22.5 (4.8)	25.6 (5.0)	25.1 (4.9)
Overweight/obese	21 (25%)	11 (31%)	37 (41%)	34 (39%)	(47%)	50 (40%)
Waist to height ratio[c]	0.46 (0.05)	0.48 (0.05) $P = 0.02$	0.46 (0.06)	0.48 (0.06) $P = 0.003$	0.50 (0.08)	0.51 (0.08)
Waist to height > 0.5	14 (17%)	12 (33%) $P = 0.04$	21 (23%)	38 (43%) $P = 0.005$	(43%)	62 (50%)
Fasting plasma concentrations						
Insulin (mU/liter)[b]	2 (<2–4)	5 (2–7) $P < 0.001$	5 (3–8)	9 (6–15) $P < 0.001$	Unavailable	8 (5–12)
Glucose (mmol/liter)[c]	4.6 (0.7)	4.6 (0.5)	4.8 (0.5)	4.9 (0.9)	5.2 (0.5)	4.8 (0.9) $P = 0.02$
Total cholesterol (mmol/liter)[c]	4.1 (0.7)	4.9 (0.9) $P < 0.001$	3.9 (0.7)	4.5 (0.9) $P < 0.001$	5.1 (1.0)	5.0 (0.9)
HDL cholesterol (mmol/liter)[c]	1.2 (0.3)	1.4 (0.4) $P = 0.002$	1.2 (0.3)	1.2 (0.3)	1.4 (0.3)	1.2 (0.3) $P = 0.002$
Cholesterol to HDL ratio[c]	3.5 (0.8)	3.6 (1.1)	3.5 (0.9)	3.9 (1.2) $P = 0.05$	3.9 (1.2)	4.5 (1.4) $P = 0.03$
LDL cholesterol (mmol/liter)[c]	2.6 (0.6)	3.2 (0.9) $P < 0.001$	2.4 (0.6)	2.8 (0.8) $P < 0.001$	3.2 (0.9)	3.3 (0.8)
Triglycerides (mmol/liter)[b]	0.5 (0.4–0.9)	0.6 (0.4–0.8)	0.7 (0.5–1.0)	0.9 (0.5–1.2) $P = 0.06$	1.0 (0.7–1.5)	0.9 (0.6–1.3)
HI, IGT, and DM						
HI alone	0	0	1 (1%)	10 (11%) $P < 0.001$	Unavailable	5 (4%)
IGT	0	0	0	8 (9%) $P < 0.001$	4.2%	9 (7%) $P < 0.001$
DM	0	0	0	2 (2%)	0.7%	5 (4%) $P < 0.001$
IGT/DM	0	0	0	10 (11%) $P < 0.001$	4.9%	14 (11%) $P < 0.001$
HI/IGT or DM	0	0	1 (1%)	20 (23%) $P < 0.001$	Unavailable	19 (15%)

[a] Data are weighted to reflect age and sex distribution of the oncology adult survivors.
[b] Median (interquartile range).
[c] Mean (SD).

≥ 11.1 mmol/liter) (26), except in those who were diabetic by fasting/random blood glucose levels and/or HbA_{1c}. For analysis, subjects and controls were classified as having HI with normal glucose tolerance, IGT, or DM.

The historical, anthropometric, and biochemical results of the subjects who had developed HI, IGT, or DM were compared with those who had not, to determine potential risk factors. The potential treatment-related risk factors examined were BMT (67 of 248), TBI (35 of 67), acute/chronic graft *vs.* host disease more than grade 2 (16 of 67 and 16 of 67, respectively), pituitary irradiation 30 Gy or more (n = 73), and chemotherapy agents known to be associated with pancreatic toxicity, hyperglycemia, and/or abnormalities in metabolic parameters, namely asparaginase (27), cisplatinum (28), and busulfan (29). Corticosteroids were not included in the analysis because of their widespread use off protocol.

The potential endocrine risk factors considered were GH deficiency, hypogonadism, and hypothyroidism. Subjects who had been investigated for growth failure with GH stimulation tests (glucagon and clonidine) or 24-h 20-min GH sampling, were classified as GH deficient if the peak GH concentration was less than 10 mU/liter (5 ng/ml). If GH testing had not been performed, GH deficiency was presumed in those whose pituitary gland would have received 30 Gy or more irradiation and in whom growth failure had been documented over a minimum of 2 yr after cessation of therapy.

Hypogonadism was defined as failure to progress through puberty without hormone replacement therapy, or a raised FSH or LH with no clinical signs of puberty in girls older than 12 yr and boys older than 13 yr. In subjects aged 18 yr and older who had undergone spontaneous puberty, hypogonadism was defined in men as a subnormal testosterone level (<8.4 nmol/liter) drawn between 0800 and 1400 h, and in women as a history of menstrual irregularity associated with a subnormal estradiol (<90 pmol/liter). Forty-four of 212 pubertal or adult subjects were hypogonadal, 17 of whom were untreated.

Hypothyroidism was defined as a free T_4 less than 9.8 pmol/liter. Five subjects were hypothyroid at the time of screening and untreated. A further 18 patients had been diagnosed with hypothyroidism but were euthyroid at the time of screening as they were receiving T_4 treatment.

Laboratory methods

Plasma glucose, urea, creatinine, uric acid, cholesterol, and triglycerides were measured by standard automated diagnostic laboratory methods (Beckman LX20 analyzer; Beckman Coulter Inc., Fullerton, CA). Serum insulin, FSH, LH, TSH, and free T_4 were measured on the Immulite 2000 (Diagnostic Products Corporation, Los Angeles, CA). HbA_{1c} was measured by the variant HbA_{1c} program (Bio-Rad Laboratory Diagnostics Group, Hercules, CA). Estradiol was measured by time resolved fluoroimmunoassay (Wallac Oy, Turku, Finland) and testosterone by an in-house RIA after celite chromatography separation.

Statistics

All statistical analyses were performed using SPSS for Windows. Results were expressed as either mean (SD) or median (range or interquartile range, as indicated), unless otherwise indicated. Means between two groups were compared by independent *t* tests, and medians were compared by the Mann-Whitney *U* test. Categorical data were analyzed using cross-tabulation and the χ^2 test or Fischer's Exact test where appropriate. One-way χ^2 test was used to compare proportions between the adult survivors and AusDiab population. Univariate and multivariate logistic regression analyses with both "backward: conditional" and "enter" method were used to assess the relationship between a variety of treatment and complications factors and anthropometric measures and the development of HI, IGT, or DM. Statistical significance was defined as a P value less than 0.05.

Results

Measures of obesity

Prepubertal and pubertal subjects had similar mean BMIs compared with controls, but the mean waist to height ratio was higher, and the percentage with abdominal adiposity was approximately double that observed in the controls ($P \leq 0.04$; Table 2). No differences were observed comparing the adult subjects with controls (Table 2); however, adult subjects who had undergone a BMT were less likely to be overweight/obese by BMI [4 of 23 (17%)] than either non-BMT subjects [46 of 101 (46%); $P = 0.01$] or controls (47%; $P = 0.03$), despite similar prevalence of abdominal adiposity, suggesting a tendency for differential accumulation of abdominal fat.

Hypertension

Hypertension was documented in 11% (4 of 36) of prepubertal and 10% (9 of 88) of pubertal subjects. Nineteen percent (24 of 124) of adult subjects were hypertensive, compared with the expected rate of 4.8% in the AusDiab cohort, with similar rates in males and females.

Lipid profile

The lipid profiles of the subjects were unfavorable compared with controls (Table 2).

HI, IGT, and DM

The median fasting insulin concentrations in the prepubertal and pubertal subjects were approximately twice those of controls (Table 2), although well below the arbitrary cutoff for HI of 20 mU/liter. Fasting insulin levels were similar in adult and pubertal subjects ($P = 0.24$; Table 2).

None of the prepubertal subjects or controls had HI, IGT, or DM (Table 2), and only one of the pubertal controls had HI, whereas 20 of 88 (23%) of the pubertal subjects had HI, IGT, or DM (Table 2). Compared with the AusDiab study, the prevalence of IGT/DM among the adult oncology subjects was more than double (Table 2). None of the subjects with DM was insulin dependent.

Overall, HI, IGT, or DM was detected in 39 of 212 (18%) of the pubertal and adult subjects (Table 2). Of the 24 with either IGT or DM, 14 were asymptomatic and diagnosed on screening; thus, the time of onset in relation to the initial diagnosis or treatment modalities could not be determined. The oncological diagnoses, treatment modalities, and complications of treatment for these 39 subjects are shown in Table 3. BMT subjects accounted for over half of those affected (23 of 39). Among the 28 of 54 pubertal or adult BMT subjects whose conditioning included TBI, 18 (64%) had HI/IGT/DM compared with five of 26 (17%) conditioned by other means ($P < 0.001$).

Compared with the 173 pubertal and adult subjects without HI, IGT, or DM, those affected had unfavorable changes in waist to height ratio, BMI, blood pressure, and lipid profile (Table 4).

Risk factors for developing HI, IGT, or DM on univariate and multivariate analysis

All prepubertal children were excluded from univariate and multivariate logistic regression analysis because none had HI, IGT, or DM. The risk factors associated with the development of HI, IGT, or DM in univariate logistic regression analysis are shown in Table 5. The following factors were not found to be significant: a family history of type 2 DM ($P = 0.053$), asparaginase-related hyperglycemia ($P = 0.06$), diagnosis ($P = 0.74$), age at time of study ($P = 0.6$), age at first diagnosis ($P = 0.9$),

TABLE 3. Primary diagnoses and treatment and hormonal and anthropometric risk factors for the 39 subjects diagnosed with HI, IGT, or DM

	n	BMT	TBI	Total pituitary irradiation dose ≥ 30 Gy	Abdominal irradiation[a]	GHD	Untreated hypogonadism	Untreated hypothyroidism	Overweight/ obese	Abdominal adiposity
Total	39	23 (59%)	18 (46%)	15 (38%)	3 (8%)	15 (38%)	13 (33%)	4 (10%)	28 (72%)	35 (90%)
ALL	15	10	8	6		4	5	1	11	14
AML	5	5	4	1		3	1		1	3
NHL	5	3	3	1	1	1	1	1	5	5
Hodgkins' disease	1							1	1	1
Stage 4 neuroblastoma	3	3	3		2	1	1	1		2
Brain tumor	4			4		4	2		4	4
Soft tissue tumors	3[b]	1		3		2	3		3	3
Wilm's tumor	1								1	1
Ewings sarcoma	1								1	1
Fanconi's anemia	1	1							1	1

Data are expressed as number of patients. The diagnoses associated with type 2 DM were acute lymphoblastic leukemia (ALL) (n = 3), acute myeloid leukemia (AML) (n = 2), non-Hodgkin`s lymphoma (NHL) (n = 1), and stage 4 neuroblastoma (n = 1). All seven received TBI conditioning for a BMT.

[a] In addition to or independent of TBI.

[b] One transplanted for secondary AML.

TABLE 4. Comparison of clinical and laboratory data for the pubertal and adult subjects with and without HI, IGT, or DM

	HI, IGT, or DM (n = 39)	Normal (n = 173)	*P* value
Age at diagnosis (range)	6.1 (1.2–13.9)	5.0 (0.1–16.9)	0.70
Age at screening (range)	17.8 (9.2–37.9)	20.3 (9.0–39.4)	0.93
Time since diagnosis (range)	14.5 (2.4–33.6)	13.4 (5.4–31.9)	0.96
Waist to height ratio[a]	0.56 (0.06)	0.49 (0.07)	<0.001
Percent waist to height ratio > 0.5 (n)	90% (35)	38% (65)	<0.001
BMI (kg/m^2)	26.7 (4.7)	23.4 (4.9)	<0.001
Percent overweight/obese (n)	72% (28)	32% (56)	<0.001
Systolic blood pressure[a]	120 (16)	113 (16)	0.02
Diastolic blood pressure[a]	75 (13)	71 (12)	0.08
Total cholesterol (mmol/liter)[a]	5.2 (1.0)	4.7 (0.9)	0.004
HDL cholesterol (mmol/liter)[a]	1.0 (0.2)	1.2 (0.3)	0.001
Cholesterol to HDL ratio[a]	5.3 (1.6)	4.0 (1.2)	<0.001
LDL cholesterol (mmol/liter)[a]	3.2 (0.9)	3.0 (0.8)	0.22
Triglycerides (mmol/liter)[b]	1.6 (1.2–2.5)	0.8 (0.6–1.1)	<0.001
Uric acid (mmol/liter)[a]	0.35 (0.07)	0.32 (0.08)	0.05

[a] Mean (95% confidence interval).
[b] Median (interquartile range).

time since diagnosis ($P = 0.7$), gender ($P = 0.8$), small birth size ($P = 1.0$), more than one malignancy ($P = 0.9$), asparaginase ($P = 0.6$), cisplatinum ($P = 0.5$), and abdominal ($P = 0.97$) or testicular irradiation ($P = 0.7$).

Because there are a number of treatment modalities specific to BMT, univariate logistic regression analysis was performed separately for the 54 pubertal and adult BMT subjects. Conditioning with TBI increased the risk; however, busulfan was protective against the development of HI/IGT/DM (Table 5). BMT-specific variables found not to be significant included time since BMT ($P = 0.08$), more than one BMT ($P = 0.7$), the type of transplant (allogeneic *vs.* autologous; $P = 0.2$), total lymphoid irradiation ($P = 0.2$; although both subjects so treated have HI or IGT), acute or chronic graft *vs.* host disease ($P = 0.5$, $P = 0.9$), or any specific diagnosis for which they were transplanted.

Multivariate logistic regression models were developed, including all variables significant in univariate analyses. A family history of type 2 DM was also included, as population data would suggest it should be a risk factor. The model of best fit included TBI ($P < 0.001$), abdominal adiposity ($P < 0.001$), and untreated hypogonadism ($P < 0.001$). A family history of dyslipidemia was found to be significant ($P = 0.03$), but was excluded because it did not add to the predictive value of the model. A family history of type 2 DM, GH deficiency, and untreated hypothyroidism did not emerge as significant risk factors ($P = 0.09$, 0.16, and 0.09, respectively). Inclusion of TBI excluded BMT from the model, and waist to height removed overweight/obesity.

TABLE 5. Significant risk factors from univariate logistic regression analysis for the development of HI, IGT, or DM in 212 pubertal and adult oncology subjects

	Odds ratio (95% CI)	*P* value
BMT (n = 54) *vs.* all others (n = 158)	6.6 (3.1–13.9)	<0.001
ALL BMT (n = 16) *vs.* no BMT (n = 82)[a]	25.6 (6.6–100)	<0.001
TBI	13.8 (5.7–34.3)	<0.001
Pituitary irradiation dose ≥ 30 Gy	4.5 (2.1–10.0)	<0.001
GH deficiency	5.1 (2.3–11.3)	<0.001
Untreated hypogonadism	21.1 (6.4–69.7)	<0.001
Untreated hypothyroidism	19.7 (2.1–181.2)	0.009
Overweight or obese (BMI)	5.3 (2.5–11.4)	<0.001
Abdominal adiposity[b]	14.5 (4.9–42.8)	<0.001
Family history of dyslipidemia	2.1 (1.0–4.2)	0.04
Hypertension	2.6 (1.1–5.8)	0.03
BMT survivors only (n = 54)		
TBI	7.6 (2.2–26.2)	<0.001
Busulphan	0.2 (0.1–0.8)	0.02

[a] The 98 patients with acute lymphoblastic leukemia (ALL) were analyzed separately to look at the potential impact of BMT in a homogeneous population.
[b] The effect of abdominal adiposity defined as a waist to height ratio more than 0.5 was independent of short stature, defined as a height less than 10th percentile [odds ratio 13.5 (1.6–110) *vs.* 15.2 (4.3–54) in those 10th percentile or greater].

Predictive value of abdominal adiposity for biochemical abnormality in the subjects

To determine whether a waist to height ratio greater than 0.5 could be a useful clinical marker for metabolic abnormality in the oncology population, the prepubertal, pubertal, and adult subjects with and without a waist to height ratio greater than 0.5 were compared.

Among the prepubertal subjects, there were no differences in insulinemia or lipid profiles on the basis of a ratio greater than 0.5 (12 of 36 subjects), although the median (interquartile range) concentration of triglycerides tended to be higher [0.9 mmol/liter (0.4–1.4) *vs.* 0.5 mmol/liter (0.4–0.7); $P = 0.053$] and the mean (SD) concentration of HDL cholesterol lower [1.3 (0.3) mmol/liter *vs.* 1.5 (0.4) mmol/liter; $P = 0.07$]. In contrast, in the pubertal subjects, a ratio more than 0.5 (38 of 88 subjects) was associated with higher fasting insulin [median 15 mU/liter (9–23) *vs.* 7 mU/liter (5–9); $P < 0.001$], total cholesterol [mean 4.7 (0.9) mmol/liter *vs.* 4.3 mmol/liter (0.9); $P = 0.04$] and triglycerides [median 1.1 mmol/liter (0.9–1.7) *vs.* 0.7 mmol/liter (0.5–0.9); $P < 0.001$] with lower HDL cholesterol [mean 1.1 (0.2) mmol/liter *vs.* 1.3 (0.3); $P < 0.001$]. Similarly, adult subjects with a ratio more than 0.5 (62 of 124) had higher fasting insulin [median 10 mU/liter (7–18) *vs.* 6 mU/liter (4–9); $P < 0.001$], total cholesterol [mean 5.2 mmol/liter (1.0) *vs.* 4.7 mmol/liter (0.8); $P = 0.004$], and triglycerides [median 1.2 mmol/liter (0.8–1.7) *vs.* 0.7 mmol/liter (0.6–1.1); $P < 0.001$] with lower HDL cholesterol [mean 1.1 (0.3) mmol/liter *vs.* 1.2 (0.3); $P = 0.02$].

Discussion

Our study confirms that the rates of HI, IGT, and DM are increased in survivors of childhood cancer. Moreover prepubertal subjects, none of whom had HI, IGT, or DM, showed unfavorable changes in waist to height ratio, insulinemia, and lipid profiles compared with controls. The most prominent risk factor for the development of HI, IGT, or DM was conditioning for BMT with TBI. The risk was not limited to subjects who had undergone BMT, however, and untreated hypogonadism and abdominal adiposity also emerged as important. Our study is the first to document increased rates of abdominal adiposity in prepubertal and pubertal children who have survived malignancy despite similar prevalence of overweight/obesity compared with controls.

Despite recruitment from a clinic population, the prevalence of HI, IGT, and DM we observed was similar to (3, 5) or less than (4, 6) that reported in other studies. The actual prevalence of abnormal glucose tolerance may be greater, because based on the ranges of fasting insulin we observed in normal prepubertal and pubertal children, the arbitrary concentration of 20 mU/liter for the performance of an OGTT may have been too high. The unfavorable differences in biochemical profile observed in the prepubertal subjects *vs.* controls, together with the similar prevalence of HI, IGT, or DM in the pubertal and adult subjects, suggest the early establishment of metabolic abnormality, although longitudinal studies would be required to confirm this. There may be a genetic contribution to this, as suggested by the risk conferred by a family history of dyslipemia in our study and of type 2 DM in other studies (6).

Our finding of TBI as a major risk factor for metabolic abnormality is in keeping with one (2) but not two other studies (4, 6). The grouping together of HI, IGT, and DM as the outcome measure may account for this difference. Our spectrum of metabolic abnormality was also detected on prospective screening as opposed to by self-report, and in more broad ranging diagnoses than documented in the survey of hematopoietic cell transplant recipients by Hoffmeister *et al.* (6), in which transplant diagnosis excluded TBI as a risk factor. The importance of our finding is that if alternative conditioning therapies for BMT can be considered without compromising survival, the risk of metabolic abnormality may be decreased.

The emergence of hypogonadism as an independent metabolic risk factor underlines the need for screening of patients at risk and appropriate replacement therapy. This finding is consistent with reports in children after BMT (4), adults after testicular cancer (30), and of studies of the relationship of testosterone (31, 32) or estrogen (33) to cardiovascular risk factors in healthy adults.

Similar to other studies (3), GH deficiency was identified as a risk factor for HI, IGT, and DM in univariate analysis, but, unexpectedly, was not an independent risk factor in multivariate analyses. This may be because increased abdominal adiposity, a known feature of GH deficiency (34), or the cooccurrence of hypogonadism captured these subjects.

We and others (4) did not find a family history of type 2 DM predictive of metabolic abnormality in contrast to the relationship reported in the general population and by Hoffmeister *et al.* (6). The latter sought a wider family history, and the ethnicity of our subjects was probably different; however, we suspect that if we had larger numbers, family history of type 2 DM would have emerged as significant.

Waist to height ratio emerged as a more important risk factor for metabolic abnormalities than BMI in both univariate and multivariate analysis. The prevalence of abdominal adiposity was increased in prepubertal and pubertal oncology subjects compared with controls despite similar prevalence of overweight/obesity. Preferential accumulation of abdominal fat was also observed in adult BMT subjects. Their waist to height ratio was similar to that of controls, but the likelihood of overweight/obesity was less, as has been observed previously (14). In keeping with the known association between abdominal fat accumulation and metabolic risk factors (35), a waist to height ratio greater than 0.5 was associated with a tendency to dyslipidemia in prepubertal subjects and with significantly raised insulinemia and unfavorable lipid profiles in pubertal and adult subjects. The increased prevalence of abdominal adiposity in the prepubertal subjects compared with controls in association with raised plasma insulin concentrations suggests that a waist to height ratio greater than 0.5 may be an early and simple clinical marker for the later development of the metabolic disturbance.

A variety of treatment and complication factors may contribute to abnormal fat distribution and the development of insulin resistance in survivors of childhood malignancy. Prolonged catabolism and malnutrition are common during many treatment regimens for childhood cancer. These may predispose to long-term changes in body composition, lower lean body mass, and muscles that remain insulin resistant, analogous to the state proposed by the Barker hypothesis after intrauterine growth retardation (36). Subsequent weight gain may exacerbate this (37), as may the development of hormonal deficiencies (32, 34, 38). The mechanisms underlying the increased risk associated with TBI remain unclear. A direct irradiation effect on pancreatic β-cells alone seems unlikely from the available animal (39) and human data (40). Irradiation has been shown to alter mitochondrial function (41), abnormalities of which in muscle, liver, and pancreas have been implicated in the development of insulin resistance and type 2 DM (42). Adipose tissue is not only an energy store but also a complex endocrine organ, secreting a number of adipocytokines (43), including adiponectin, TNFα, and IL-6 that can modulate glucose homeostasis. To our knowledge, the effect of irradiation on the function of adipose tissue has not been studied.

Prevention of late complications has become a significant consideration in the development of oncology treatment protocols. Our findings suggest that the use of conditioning with TBI for BMT deserves reconsideration and underline the need for regular, long-term screening of survivors of malignancy. Early identification of abdominal adiposity and/or hormonal deficiency may allow the institution of dietary and lifestyle measures and therapeutic regimens that have been shown to modify the tendency toward increased metabolic risk (44) and type 2 DM (45).

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