CLINICAL STUDY

Body composition in young adult survivors of childhood acute lymphoblastic leukaemia

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Abstract

Objective: Obesity is frequently reported in patients treated for childhood leukaemia. Obesity, particularly abdominal obesity, is one of the main characteristics of the metabolic syndrome and a risk factor for cardiovascular disease and non-insulin-dependent diabetes mellitus (NIDDM).

Design: All patients treated for acute lymphoblastic leukaemia (ALL) before the onset of puberty in the region of western Sweden, between 1973 and 1985, and in first remission, were included. 35 out of 47 patients aged 20–32 years participated. 19 patients had received cranial radiotherapy, and the median follow-up time was 20 years. The focus of this report was to study body composition and signs of the metabolic syndrome and correlate the findings to spontaneous growth hormone (GH) secretion.

Methods: Body composition was assessed using dual-energy X-ray absorptiometry (DEXA). We analyzed serum concentrations of insulin, glucose, leptin and lipids.

Results: No patient was obese according to World Health Organization criteria (body mass index, BMI ≥ 30 kg/m²) but one-third were overweight (BMI 25–29.9 kg/m²). The maximal GH peak during 24 h (GH_{max}) was correlated to percentage of total body fat ($r = -0.42$; $P = 0.017$), trunk fat ($r = -0.5$; $P = 0.005$) and fat-free mass ($r = 0.42$; $P = 0.017$). GH_{max} was also correlated to s-triglycerides ($r = -0.54$; $P = 0.001$), low-density lipoprotein-cholesterol ($r = -0.382$; $P = 0.024$) and high-density lipoprotein-cholesterol ($r = 0.45$; $P = 0.007$).

Conclusions: We found little effect on BMI but an increased percentage of total body fat, especially trunk fat, and a tendency for an unfavourable lipid profile in adult survivors of childhood leukaemia. These findings were related to low endogenous GH secretion due to cranial irradiation.

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Introduction

For how long should patients cured of childhood cancer be followed? What late effects may be expected after the patients have grown out of paediatric care? As a consequence of improved survival rate after childhood cancer, these questions are now often raised. Clarification is therefore needed regarding which patients and what symptoms and organ functions need to be followed into adulthood. Acute lymphoblastic leukaemia (ALL) is the most common form of malignancy in childhood and has a high survival rate (>70%) (1). Survivors of ALL therefore constitute the largest group of long-term survivors from childhood cancer. However, survivors of ALL are a heterogeneous group. Differences depend on the treatment given, especially whether or not it included prophylactic cranial irradiation. Several studies have reported increased

risk of obesity or overweight in children and young adults previously treated for ALL (2–9). In a previous report we found that 47% of young adult patients who had received cranial radiotherapy (CRT +) for childhood ALL had a maximal growth hormone (GH) peak (GH_{max}) of below 3.3 µg/l during a 24-h spontaneous GH profile, suggestive of GH deficiency in adults (10). However, final height was in the expected range for midparental height in 34 out of 35 patients. All patients who had not received cranial radiotherapy (CRT –) had GH_{max} levels within the normal range.

The aim was to study body composition and predisposing factors of the metabolic syndrome in a homogeneous population-based group of young adult survivors of ALL, and to relate our findings to the GH status of the patients. Our study group was narrowed down to include only patients in their first remission and with treatment concluded before onset of puberty.

Subjects and methods

Records from all patients treated for ALL before onset of puberty in the region of western Sweden between 1 January 1973 and 31 December 1985 were reviewed. For inclusion, patients had to be at least 20 years old and in first remission. The ALL treatment had to have been completed before the onset of puberty. 47 young adults aged between 20 and 32 years, of whom seven patients were lost to follow up, fulfilled those criteria. Thus 40 patients were contacted, 35 of whom agreed to participate. The median follow-up time in the group was 20 years, with a minimum of 15 years (Table 1). All patients were Caucasian and stated that they were in good health and were either employed or engaged in studies. Two women were on antidepressant therapy. Eight women were taking oral contraceptives; they were equally divided between the CRT + and CRT – groups.

Treatment

The patients had been treated on the basis of three subsequent protocols from the Swedish childhood leukaemia group (11). All patients had been treated with intrathecal injections of methotrexate and 19 (10 men and nine women), had received cranial radiotherapy (CRT +), with a dose of 18–24 Gy. The majority of the CRT + patients had received a radiation dose of 24 Gy; two men and three women had received 18–22 Gy. The remaining 16 patients, seven men and nine women, who had not received cranial radiotherapy (CRT –), were treated with high-dose methotrexate (500 mg/m², three times) as central-nervous-system prophylaxis. All patients had received prednisolone 60 mg/m² for approximately 6 weeks during the induction treatment. Seven patients were treated with additional pulses of prednisolone (three CRT + men, three CRT + women and one CRT – woman) and one CRT + man with dexamethasone. No patient had been treated for relapse. The mean age at follow up was somewhat higher in the CRT + than in the CRT – group (Table 1), owing to a greater proportion of CRT + patients diagnosed early in the inclusion period.

The height of the patients has been reported previously; in summary, the final height of CRT + patients

was –0.8 S.D. compared with midparental height. In contrast, the CRT – patients were taller than expected for midparental height (median 0.6 S.D.) (10).

Clinically and biochemically, all patients were euthyroid, with normal free thyroxine and thyrotropin (TSH). One patient was euthyroid on thyroxine-replacement therapy after total thyroidectomy due to a thyroid adenoma. Blood-pressure measurements using a mercury sphygmomanometer were done in the hospital by the same investigator (M J), with the patients in a supine position before getting up in the morning. The average result from three measurements with 1-min intervals was used. One patient was found to have hypertension with a pressure of 160/100 mmHg, confirmed with an echocardiogram. Apart from this patient, no-one had a systolic pressure of more than 140 mmHg or a diastolic blood pressure of more than 80 mmHg. The GH secretory status of the patients has been reported previously (10). Two women were currently smokers.

Informed consent was obtained from all participants. The study was approved by the ethics committee at the Sahlgrenska Academy at Göteborg University.

Anthropometry and clinical investigations

All patients had reached final height. Height was measured with an Ulmer stadiometer (Visopan, Elchingen, Germany) and weight with calibrated electronic scales. The World Health Organization (WHO) definitions of obesity (body mass index, BMI ≥ 30 kg/m²) and overweight (BMI 25–29.9 kg/m²) were used. The results were also compared with Swedish population-based reference data for BMI based on 5439 (2762 men, 2677 women) normal Swedish young adults aged 16–34 years, collected during the same time period (Statistics, Sweden). Waist circumference (cm) was measured by the same investigator (M J) at the level midway between the most caudal part of the lateral costal arch and the iliac crest. Hip circumference (cm) was measured at the symphysis–trochanter femoris level. Waist-to-hip ratio was calculated as the ratio between the circumference of waist and hip.

Dual-energy X-ray absorptiometry (DEXA)

DEXA was performed using a LUNAR-DXP-IQ scanner (Scanexport Medical, Helsingborg, Sweden). The system

Table 1 Clinical details of the patients and anthropometrical results. Data are shown as medians and ranges. * $P < 0.05$.

	CRT + men	CRT – men	<i>P</i> value	CRT + women	CRT – women	<i>P</i> value
Age at diagnosis (years)	4.5 (2.0–7.0)	3.0 (1.0–5.0)	0.13	5.0 (1.0–6.0)	6.0 (3.0–8.0)	0.19
Age at follow up (years)	27.0 (22.0–32.0)	21.0 (20.0–24.0)	0.001*	28.0 (23.0–32.0)	23.0 (21.0–29.0)	0.006*
Height (cm)	179.8 (170.5–187.0)	184.0 (180.8–194.0)	0.024*	161.7 (152.5–167.4)	170.7 (157.0–178.9)	0.009*
BMI (kg/m ²)	26.2 (22.3–28.6)	21.4 (18.7–23.8)	0.002*	23.4 (20.2–29.1)	23.6 (20.6–28.9)	0.90
Waist (cm)	97.0 (76.0–102.0)	77.0 (72.5–87.0)	0.003*	76.0 (65.0–93.0)	78.0 (69.0–86.0)	0.79
Waist-to-hip ratio	0.88 (0.75–0.92)	0.76 (0.71–0.94)	0.005*	0.79 (0.64–0.85)	0.75 (0.70–0.81)	0.42

uses a constant-potential X-ray source and a K-edge filter to achieve a congruent beam of stable dual-energy radiation. Whole-body scans were performed at the scan speed suggested by the system for each subject. Body fat, lean tissue mass, total bone mineral content and density mass were analyzed using software version 4.7 C. Fat-free mass (FFM) was defined as the sum of lean tissue and bone mineral content. Trunk fat was defined as fat mass in the trunk region of the whole-body scan. FFM and body fat are presented as percentages of body weight, and trunk fat as a percentage of trunk mass. We used the prediction model of Gallagher *et al.* (12) for comparison with our results concerning total body fat mass. Gallagher *et al.* (12) made prediction models for percentage of total body fat mass related to BMI by measuring DEXA and total body water on 192 healthy, white men and 225 healthy, white women in the USA and UK (12). Gallagher *et al.*'s equation was:

$$\begin{aligned} \text{Percentage body fat} = & 76.0 - (1097.8 \times 1/\text{BMI}) \\ & - (20.6 \times \text{sex}) + (0.053 \times \text{age}) \\ & + (154 \times \text{sex} \times 1/\text{BMI}) \\ & + 0.034 \times \text{sex} \times \text{age} \end{aligned}$$

where male sex = 1 and female sex = 0.

Assays

Blood samples for glucose, insulin, leptin and serum lipids were collected after overnight fasting. Serum leptin concentrations were determined by RIA (Human Leptin Kit; Linco Research, St Charles, MO, USA). The intra-assay coefficients of variation were 5.5% at 2.4 µg/l and 5.4% at 15.1 µg/l. Concentrations of glucose, insulin and lipid (including serum concentrations of cholesterol, triglycerides and high density lipoprotein-cholesterol (HDL-cholesterol)) were analyzed in the accredited laboratory of Sahlgrenska University Hospital. Low-density lipoprotein-cholesterol (LDL-cholesterol) was calculated from the equation of Friedwald *et al.* (13). As an estimate of insulin sensitivity, we used the Homeostasis Model of Assessment (HOMA) (14). This index was calculated using the formula:

$$\begin{aligned} \text{HOMA index} = & \text{fasting insulin (mU/l)} \\ & \times \text{fasting plasma glucose (mM)} / 22.5 \end{aligned}$$

This model has been evaluated in both diabetic and non-diabetic individuals, and shows a high correlation with the glucose-clamp technique (15). A HOMA index of >2 has been shown to be associated with an increased risk of stroke and cardiovascular disease.

Definition of the metabolic syndrome

According to the National Cholesterol Education Program Adult Treatment Panel III guidelines (NCEP APT III) the metabolic syndrome is defined as at least three of the following criteria (16): (1) abdominal obesity defined as waist circumference >102 cm in men and >88 cm in women; (2) fasting plasma glucose ≥ 6.1 mM; (3) blood pressure ≥ 130/85 mmHg; (4) s-triglycerides ≥ 1.7 mM; (5) HDL-cholesterol < 1.0 mM in men and < 1.3 mM in women.

Statistical methods

Data are presented as medians with ranges in brackets, unless otherwise stated. Correlations between variables (GH_{max} versus body-composition variables, HOMA index and serum lipids, and dose of corticosteroids versus body-composition variables, HOMA index and serum lipids) were tested using Pitman's non-parametric test (17). Multivariate linear-regression analyses were performed in order to elucidate how GH_{max} affected different variables of body composition. Additional correlations were assessed using univariate linear regression analysis, stated in connection to the result. Statistical significance between groups was calculated using the Mann-Whitney-Wilcoxon Sum Rank test. For all statistical tests a *P* value of <0.05 was considered significant, using two-tailed tests.

Results

BMI

According to the WHO definition of obesity, no patient was obese (BMI ≥ 30 kg/m²); however, 12 out of 35 patients fulfilled the criteria for overweight (BMI 25–29.9 kg/m²) (18) (Table 1). The CRT+ men had significantly higher BMI than the CRT– men (*P* = 0.002). There was no difference among the women (Table 1). Compared with Swedish population-based reference data for BMI, four men and four women had BMI values above +2 S.D. for BMI, which is 22% of the patients as compared with the expected frequency of 2.5% (Fig. 1; Statistics, Sweden).

Waist circumference and waist-to-hip ratio

No man had a waist circumference of more than 102 cm. Two women had waist circumferences of more than 88 cm. The CRT+ men had higher waist circumference than the CRT– men (*P* = 0.003). There was no difference among the women (Table 1). Three men had a waist-to-hip ratio of more than 0.9 but no woman had a waist-to-hip ratio of more than 0.85 (Table 1). The CRT+ men had higher waist-to-hip ratio than the CRT– men (*P* = 0.005). There was no difference between the two groups of women

(Table 1). In a linear-regression analysis there was a correlation between waist circumference and trunk fat mass ($r = 0.4$; $P = 0.016$).

FFM

The CRT + men had significantly lower FFM than the CRT – men ($P = 0.001$). There was no difference between the two groups of women (Table 2). $\text{GH}_{\max}$ was significantly correlated with FFM ($r = 0.42$; $P = 0.017$). There was no correlation between corticosteroid dose used during the ALL treatment and FFM ($P = 0.626$).

Body fat mass

The CRT + men had significantly higher total body fat than the CRT – men ($P = 0.001$). There was no difference among the women (Table 2). The CRT + men had significantly higher percentage of trunk fat than the CRT – men ($P = 0.001$). There was no difference among the women (Table 2). $\text{GH}_{\max}$ was negatively correlated to both percentage total body fat ($r = -0.42$; $P = 0.017$) and percentage trunk fat ($r = -0.5$; $P = 0.005$). To explore whether $\text{GH}_{\max}$ influenced all

three components (percentage FFM, percentage total body fat and percentage trunk fat) to the same extent, or if one of the variables was affected primarily and the other two secondarily, we performed a multiple linear-regression analysis where $\text{GH}_{\max}$ was the dependent variable and fat components were the three independent variables. This analysis revealed that only the partial regression coefficient for percentage trunk fat remained significant ($r = -0.5$; $P = 0.005$; Fig. 2). The corticosteroid dose did not correlate with percentage total body fat ($P = 0.63$) or percentage trunk fat ($P = 0.61$). The estimated percentage total body fat in the patients was calculated with the equation of Gallagher *et al.* (12), as given in the Subjects and methods section. The estimated body-fat percentages in men were 21.6% (range 15.5–24.4) and 12.0% (6.8–17.6) in the CRT + and CRT – groups, respectively. The estimated body-fat percentages in women were 30.4% (23.0–39.9) and 30.6% (23.9–39.3) in the CRT + and CRT – groups, respectively. The differences between the percentage total body fat mass measured using DEXA and the estimated total body fat mass from the Gallagher equation were calculated and found to have medians of 8.9% (4.0–15.5) and 8.4% (–4.2–8.6) in the CRT + and CRT – men, respectively. In the

Table 2 Results of body-composition analyses and laboratory findings. Data are shown as medians and ranges. * $P < 0.05$.

	CRT + men	CRT – men	P value	CRT + women	CRT – women	P value
Fat-free mass (%)	70.8 (62.5–76.0)	82.9 (74.0–90.4)	0.001*	62.5 (55.5–74.8)	64.1 (57.7–76.6)	0.29
Total fat mass (%)	29.2 (24.0–37.5)	17.1 (9.6–26.0)	0.001*	37.5 (25.2–44.5)	35.9 (23.4–42.3)	0.42
Trunk fat mass (%)	33.4 (23.5–39.0)	16.2 (11.0–25.8)	0.001*	37.3 (19.8–43.3)	36.1 (23.4–42.3)	0.42
Leptin/kg fat	0.42 (0.22–0.58)	0.38 (0.17–0.52)	0.20	0.75 (1.16–3.14)	0.75 (0.69–2.65)	0.84
s-Insulin (mU/l)	7.3 (3.2–11.0)	6.4 (4.9–11.0)	0.77	6.3 (3.3–9.7)	6.1 (4.4–12.0)	0.79
p-Glucose (mM)	5.0 (4.4–5.3)	4.9 (4.7–5.4)	0.73	4.9 (4.5–5.4)	4.8 (4.3–5.6)	0.42
HOMA index	1.6 (0.7–2.5)	1.4 (1.2–2.4)	0.96	1.3 (0.8–2.2)	1.3 (0.9–2.6)	0.82
s-Triglycerides (mM)	1.4 (0.6–2.2)	0.7 (0.4–1.0)	0.011*	1.4 (0.7–1.6)	0.9 (0.6–1.4)	0.14
s-Cholesterol (mM)	4.6 (3.2–5.9)	3.7 (3.1–4.4)	0.095	4.5 (3.6–5.6)	3.9 (3.2–5.0)	0.13
LDL-cholesterol (mM)	3.0 (2.0–4.2)	2.2 (1.3–3.0)	0.031*	2.6 (1.3–3.9)	2.3 (1.2–2.9)	0.29
HDL-cholesterol (mM)	1.0 (0.6–1.2)	1.5 (1.0–1.8)	0.014*	1.5 (0.9–1.9)	1.5 (0.7–1.7)	0.62

Figure 2 Relation between percentage trunk fat and GH_{max} . Trunk-region fat = $36.34 - 0.81 \times \text{GH}_{\text{max}}$; $r = -0.5$ (s.d. around the regression function is 7.81); $P = 0.005$.

women the differences were 4.7% (0.2 – 8.8) and 4.2% (– 2.5–10.8) in the CRT + and CRT – groups, respectively. There was a higher percentage of total body fat measured by DEXA than estimated according to the equation of Gallagher *et al.* (12) in 32 out of 35 patients (Fig. 3). All eight men with peak GH secretion below $3.3 \mu\text{g/l}$ had a percentage total body fat greater than 21%, which is the predicted percentage of total body fat in men aged 20–39 years with a BMI of $25\text{--}30 \text{ kg/m}^2$ according to Gallagher *et al.* (12). On the other hand, although only one woman in our study had a GH_{max} below $3.3 \mu\text{g/l}$, the women overall had a high percentage of total body fat. 14 (seven CRT + and seven CRT –) out of the 18 women had a percentage fat of more than 33%, which is the predicted percentage of fat mass for these women (12).

Leptin

There was no difference between leptin/kg fat mass among the CRT + and CRT – groups in men and women (men, $P = 0.2$; women, $P = 0.84$; Table 2). There was a linear correlation between GH_{max} and

leptin ($r = -0.57$; $P = 0.017$), but not between GH_{max} and leptin/kg fat mass. We also compared the difference in leptin/kg fat mass between the men with normal GH secretion and the men with low GH secretion; there was no difference ($P = 0.9$). It was not possible to do this comparison in the women since there was only one woman with low GH secretion.

Insulin resistance

There were no differences in concentrations of s-insulin or fasting p-glucose, or in the calculated HOMA index between the CRT + and CRT – patients (Table 2). 20% of the patients had a HOMA index of >2.0 . There was no correlation between GH_{max} and HOMA index ($P = 0.91$) or between dose of corticosteroids and HOMA index ($P = 0.17$). There was no correlation between HOMA index and percentage total fat (men, $P = 0.73$; women, $P = 0.29$) or percentage trunk fat (men, $P = 0.54$; women, $P = 0.22$).

Serum lipids

The CRT + men had higher s-triglycerides than the CRT – men ($P = 0.011$), but there was no difference among the women (Table 2). Two men had hypertriglyceridemia according to NCEP ATP III ($\geq 1.7 \text{ mM}$). There were no differences in total s-cholesterol between the CRT + and CRT – patients (Table 2). The CRT + men had a higher LDL-cholesterol than the CRT – men ($P = 0.031$), but there was no difference between the two groups of women (Table 2). A linear-regression analysis revealed no correlation between total cholesterol and GH_{max} but a negative correlation between LDL-cholesterol and GH_{max} ($r = -0.382$; $P = 0.024$) meaning that high LDL-cholesterol concentration was associated with low peak GH secretion. The CRT + men had lower HDL-cholesterol than the CRT – men ($P = 0.014$), but there was no difference among the women (Table 2). There were five men and six

Figure 3 Relation between $\Delta\text{-fat}$ and GH_{max} in men and women. $\Delta\text{-Fat}$ is the difference between percentage total body fat mass measured by DEXA and total body fat mass calculated with Gallagher *et al.*'s (12) equation, as given in the Subjects and methods section.

women with HDL-cholesterol values below the level defined as entry criteria for the metabolic syndrome. s-Triglycerides and HDL-cholesterol in relation to GH_{max} were compared with the NCEP APT III reference group in the age interval 20–34 years (Fig. 4). We found a negative correlation between GH_{max} and s-triglycerides ($r = -0.54$; $P = 0.001$) and a positive correlation between GH_{max} and HDL-cholesterol ($r = 0.45$; $P = 0.007$). This is shown in Fig. 4, where most subjects with low serum HDL-cholesterol and high serum triglyceride concentration also had low GH_{max} . We found no correlation between corticosteroid dose and s-triglycerides ($P = 0.73$) or between corticosteroid dose and HDL-cholesterol ($P = 0.50$).

Discussion

In the present study the percentage of trunk fat and total body fat was increased, whereas the percentage of FFM was decreased, a median 20 years after treatment for childhood ALL. We also found a tendency for unfavourable lipid profiles. These findings were related to low spontaneous secretion of GH, secondary to cranial radiotherapy. Obesity is one of the major threats to general health in the western world. Reports on long-term survivors of ALL in childhood have claimed that obesity, defined by WHO as $\text{BMI} \geq 30 \text{ kg/m}^2$, is a common finding (2–4, 6, 8, 19–21). Several explanations have

been proposed including cranial radiotherapy, GH insufficiency, use of corticosteroids and reduced energy expenditure (2–4, 6, 20–23). In this population-based study, all patients were treated before the onset of puberty, and were all in first remission. No patient fulfilled the WHO BMI criteria for obesity, but one-third of the patients were overweight. Furthermore, a larger number of patients than expected had a BMI value of > 2 s.d. compared with a normal Swedish age-matched reference population collected during the same time period. These findings extend those of Nysom *et al.* (24) who found a high BMI at follow up of Danish children and young adults, median 10 years after diagnosis. Earlier studies have found that high BMI values correlate to the corticosteroid treatment applied during the induction of remission (5, 6, 20), a finding that could not be confirmed in this study. The duration of follow up in previous studies has been shorter than in our study, indicating that corticosteroids might influence body weight during treatment and up to the attainment of final height, but not in early adulthood. BMI is only a crude indicator of body fat mass. The amount of fat and FFM, and the distribution of fat, are more important risk factors for prediction of cardiovascular disease and non-insulin-dependent diabetes mellitus (NIDDM) (25–28). Both Brennan *et al.* (23) and Nysom *et al.* (24) found higher relative fat mass in patients than controls at follow up and correlated this to GH insufficiency or cranial radiotherapy. Unfortunately there are no Swedish

Figure 4 s-Triglycerides (A, B) and HDL-cholesterol (C, D) of the patients compared with a healthy American population 20–34 years (grey shading; NCEP ATP III Guidelines, appendix IIIA (16)). ■, Patients with low GH secretion; ●, patients with normal GH secretion. Horizontal lines are the means of the population data.

reference data for body composition in this age group. We therefore used Gallagher *et al.*'s equation (12), based on healthy American and British young adults, and found a higher fat mass in our patients than predicted in the model. Men with low GH secretion all had body fat percentage of more than 21%, which is predicted for this age group, and 78% of the women had more than 33% total body fat mass, which is the predicted value for fat mass in women of this age group (12). These findings are difficult to explain and are contradictory to those of van de Sluis *et al.* (29), who found no difference in total body fat mass in patients who had not received CRT compared with controls 9.6 years after treatment. The majority of previous reports have studied cranially irradiated patients who have been found to have increased total body fat mass (30, 31).

An important risk factor for NIDDM and cardiovascular diseases and a major criteria in the definition of the metabolic syndrome is abdominal obesity (25–28). We found a negative correlation between the percentage of trunk fat and physiological GH secretion, indicating that at this stage in life impaired GH secretion in young adult survivors of ALL may have adverse metabolic consequences. This is in agreement with Talvensaari & Knip (32) and Link *et al.* (33) who found an increased risk for the metabolic syndrome in patients treated for malignancy in childhood associated with low GH secretion. Therefore, with older age we postulate that our patients may be at risk for the metabolic syndrome characterised by abdominal obesity, insulin resistance, hypertension, dyslipidemia, dysfibrinolysis and endothelial dysfunction. In adults with GH deficiency abdominal fat accumulation is a core feature (34) and in healthy adults there is a strong inverse relationship between endogenous GH secretion and visceral abdominal fat mass (35) that is stronger than the association between GH secretion, age and gender. In healthy adults it is not possible to determine what is the cause and what is the consequence. In young adult survivors from ALL who have received CRT it is most likely that the reduced GH secretion is the result of previous intervention and therefore the cause of abdominal fat accumulation and its metabolic consequences.

Leptin, the product of the adipocyte-specific *ob* gene (36), is produced in the adipose tissue and the circulating level is proportional to total fat mass and is thought to act as a satiety signal to the hypothalamus. There is a sex-related difference in leptin concentration, being higher in women than men even after correction for absolute fat mass (37). Like earlier studies, we found a negative correlation between circulating GH and leptin levels (38). Furthermore, Brennan *et al.* (39) found higher leptin concentrations per kg fat mass in adults with hypothalamic-pituitary disease compared with normal controls and hypothesised that the relative hyperleptinemia in these patients could be caused by radiation damage to the hypothalamus. We could not confirm this finding, since we did not find any difference in

leptin concentration/kg fat mass, either between the GH-deficient and non-GH-deficient patients or between the CRT + and CRT – patients in our study. Link *et al.* (33) did not find higher leptin/kg fat mass in men, but did in women adult survivors of childhood ALL who all had received CRT compared with healthy controls (33). Bulow *et al.* (40) found higher leptin/kg in patients (predominantly women) than controls and this difference remained after 1 year with GH treatment. Bulow *et al.* (40) also found impaired glucose tolerance in GH-deficient young adult survivors of ALL and this impairment remained after 1 year with GH treatment (40). Using the less-sensitive HOMA index for investigating glucose metabolism, we did not detect similar abnormalities. No patients in our study fulfilled the NCEP APT III criteria for the metabolic syndrome, but several patients had unfavourable lipid profile and increased trunk fat according to DEXA measurements. We found that low GH secretion was related with high serum triglycerides, low HDL-cholesterol and high LDL-cholesterol concentrations, but not to HOMA index. However, since the patients in this study are still young the cholesterol composition could be a premonition of more serious conditions later in life. This lipid pattern is both associated with abdominal obesity and GH deficiency in adults (41). Therefore, both the increased fat mass and its abdominal distribution and/or the low endogenous GH secretion may have induced this pattern that probably has a deleterious impact on long-term cardiovascular health in this population (42). In conclusion, we found little effect on BMI but increased fat mass, especially trunk fat mass as well as a tendency of impaired lipid profile in young adult survivors of childhood ALL treated before puberty. These findings were related to low spontaneous GH secretion and indicate that the impaired GH secretion may have caused secondary metabolic events of importance for future health. For these reasons patients who have received cranial irradiation for ALL in childhood should be followed in adulthood and considered for treatment with GH. On the other hand, patients who have not received cranial irradiation and have a normal GH secretion may still be at risk for overweight and obesity, with secondary morbidity later in life. For this reason we find it justified to follow also this large and increasing group of young adult survivors of ALL.

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