

CIMT does not identify early vascular changes in childhood acute lymphoblastic leukemia survivors

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Abstract

Background. Childhood acute lymphoblastic leukemia (ALL) survivors are at an increased risk of cardiovascular disease development. It is believed that in the general population, this risk can be predicted with carotid intima-media thickness (CIMT) measurement.

Objectives. The objective of this study was to assess CIMT and to investigate the effects of blood pressure (BP) and lipid profile values on CIMT in childhood ALL survivors.

Material and methods. The study group comprised 81 childhood ALL survivors aged 5–25 years. The control group consisted of 52 age- and sex-comparable healthy children. Carotid intima-media thickness measurement, 24-hour BP monitoring and lipid profiles were evaluated in patients and controls.

Results. Despite significantly higher proportion of subjects with arterial hypertension (AH) (30/81 vs 10/52; $p = 0.0315$), the mean values of CIMT were not statistically different in childhood ALL survivors as compared to controls (0.4303 ± 0.03 vs 0.4291 ± 0.03 ; $p = 0.81$ and 1.096 ± 0.74 vs 1.027 ± 0.55 ; $p = 0.56$, respectively). Carotid intima-media thickness values were not statistically higher in ALL survivors with AH as compared to ALL survivors with normal BP (0.433 ± 0.03 vs 0.428 ± 0.03 ; $p = 0.82$). A significant positive correlation between 24-hour systolic BP standard deviation score (SDS) and CIMT-SDS in childhood ALL survivors was found ($r = 0.29$, $p = 0.009$), whereas such correlation was not observed in healthy controls ($r = 0.12$, $p = 0.39$). A significant correlation between z-score body mass index (BMI) and CIMT was found in controls ($r = 0.29$, $p = 0.031$) but not in childhood ALL survivors ($r = -0.05$, $p = 0.64$). No significant correlations between CIMT and other measured variables were found. Carotid intima-media thickness did not significantly correlate with time since ALL diagnosis ($r = 0.09$, $p = 0.39$).

Conclusions. Carotid intima-media thickness measurement shows limited feasibility and diagnostic accuracy for early assessment of vascular alteration in childhood ALL survivors. Other tests are needed to predict cardiovascular risk in childhood ALL survivors at the early stage of the follow-up.

Key words: children, cardiovascular risk, arterial hypertension, acute lymphoblastic leukemia, carotid intima-media thickness

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Introduction

Carotid intima-media thickness (CIMT) is a recognized marker of endothelial dysfunction. Carotid intima-media thickness measurement has become a useful non-invasive method for cardiovascular risk assessment not only for adults but also for children.¹ Measurement of CIMT has established its utility as an important tool for evaluation of subclinical atherosclerosis.¹ Increased CIMT was found in children with metabolic syndrome, congenital adrenal hyperplasia, obesity, type 1 diabetes mellitus, and also in childhood cancer survivors.^{2–7} However, the lack of pediatric, population-based reference values makes CIMT not a widely accepted marker of subclinical atherosclerosis in youth with cardiovascular risk factors.⁸

The developing cardiovascular system in children is highly susceptible to the toxic effects of chemotherapeutic agents and their administration may cause endothelial damage leading to endothelial dysfunction.^{9–11} It is believed that vascular alteration related to endothelial dysfunction leads to loss of vasodilatory capability and atherosclerosis.¹²

Advances in multimodal chemotherapy and supportive care have substantially improved long-term survival in children with acute lymphoblastic leukemia (ALL).^{13,14} However, an increased number of childhood ALL survivors is accompanied by increased prevalence of cardiovascular disease (including metabolic syndrome and coronary artery disease) in adults who survived childhood ALL.^{15,16} Disorders related to endothelial derangement are initiated early in life since atherosclerosis has its background in childhood.^{1,17} Little is known about this process in children after ALL treatment. Some published reports have confirmed endothelial dysfunction by showing lower flow-mediated vasodilatation (FMD) but not increased CIMT in childhood ALL survivors as compared to controls.^{18,19}

The aim of our study was to assess the CIMT and to investigate the effects of blood pressure (BP) and lipid profile values on CIMT in childhood ALL survivors and healthy controls.

Material and methods

Patients and controls

Between 1999 and 2012, 168 patients received intensive chemotherapy for ALL in our institution. All patients who survived in first remission and were older than 5 years were invited to participate in this study. Eighty-one patients (32 girls and 49 boys, aged 5–25 years) positively responded and were included into the study group. The control group comprised of 52 children (22 girls and 30 boys, aged 5–17 years) without any known chronic or severe medical condition. Informed consent was obtained from all parents/legal guardians and all children. The study was approved by the Bioethics Committee of Pomeranian Medical University in Szczecin, Poland (approval No. KB-0012/69/12).

Carotid intima-media thickness assessments

Ultrasonographic studies of the common carotid arteries (CCA) were performed using ultrasound system Philips iU22 (Philips Ultrasound, Bothell, USA) with a 3–9 MHz linear array transducer. Carotid intima-media thickness was measured according to the criteria of the Mannheim Consensus.²⁰ Depth of focus was set at 30 mm, frame rate of 25 Hz and gain of 60 dB. The arterial wall was assessed in a longitudinal B-mode view, strictly perpendicular to the ultrasound beam. Carotid intima-media thickness was measured at a distance of 10 mm proximal of the bifurcation and was defined as the distance from the border between the echolucent vessel lumen and the echogenic intima to the border between the echolucent media and echogenic adventitia. A semiautomatic edge detection system was used. All ultrasonographic studies were carried out twice by 2 independent radiologists. Carotid intima-media thickness values from the right and left side were recorded with the Philips iU22 software. Average CIMT values were subsequently recalculated and expressed as CIMT-standard deviation score (CIMT-SDS). This was computed according to the least mean squares (LMS) formula for SDS analysis: $SDS = [(Y/M(t))^{L(t)} - 1]/(L(t) \times S(t))$ where Y is the child's mean CIMT [mm], M(t) is median of Y, L(t) is the measure of skewness, and S(t) is the coefficient of variation. The LMS formula and reference values for the CIMT measurements were extracted from the data published by Doyon et al.²¹

Definition and diagnosis of arterial hypertension

Blood pressure assessments were performed with the use of a standard oscillometric 24-hour ambulatory blood pressure monitoring (ABPM) device (HolCARD CR-07; Aspel S.A., Zabierzów, Poland). Measurements were taken every 20 min during daytime (08:00–22:00) and every 30 min during nighttime (22:00–08:00). Blood pressure values were recorded all day (daytime and nighttime, respectively) as systolic (SBP), diastolic (DBP) and mean arterial blood pressure (MAP). Only readings of SBP < 240 mm Hg and >70 mm Hg, and DBP < 140 mm Hg and >40 mm Hg were considered valid. Arterial hypertension (AH) was defined as either mean SBP and/or mean DBP $\geq 95^{\text{th}}$ percentile for age, height and sex during any recorded (daytime and/or nighttime) period.

All mean ABPM values (SBP, DBP and MAP) were recalculated using the LMS formula and expressed as 24-hour SBP-SDS, DBP-SDS and MAP-SDS. The LMS formula and reference values for the ABPM measurements were extracted from the data published by Wühl et al.²²

Clinical and biochemical evaluation

All patients and subjects from the control group underwent a complete physical examination with assessment

Table 1. Characteristics of study patients and controls

Parameters	ALL (n = 81)	Controls (n = 52)	p-value
Mean age [years], median	12.1 ±4.6 (12)	11.7 ±4.2 (12)	0.63
Sex, female/male	32/49	22/30	0.59
Mean age at ALL diagnosis [years], median	6.6 ±4.27 (6)	NA	–
Mean follow-up time [years], median	5.7 ±3.96 (5)	NA	–
Follow-up time ≤5 years, number of patients (%)	36 (44.44)	NA	–
Follow-up time >5 years, number of patients (%)	45 (55.56)	NA	–
AH, number of patients (%)	30 (37)	10 (19.2)	0.0315
24-hour SBP, mean	114.6 ±9.2	113.7 ±7.6	0.53
24-hour DBP, mean	65.8 ±7.5	64.0 ±5.7	0.14
24-hour MAP, mean	89.5 ±7.5	88.2 ±5.7	0.28
24-hour SBP-SDS	0.336 ±1.26	0.284 ±1.05	0.81
24-hour DBP-SDS	–0.26 ±1.28	–0.569 ±1.09	0.15
24-hour MAP-SDS	1.415 ±1.31	1.205 ±0.96	0.32
BMI [kg/m ²]	19.6 ±3.99	18.9 ±4.39	0.41
BMI, z-score	0.44 ±1.03	–0.10 ±1.40	0.01
BMI-for-age (≥90 percentile), number of patients (%)	20 (24.7)	7 (13.5)	0.13
BMI-for-age (≥95 percentile), number of patients (%)	10 (12.3)	3 (5.8)	0.34
Total cholesterol [mg/dL]	162.9 ±34.6	144.7 ±33.2	0.003
Triglycerides [mg/dL]	96.8 ±71.2	80.7 ±46.9	0.15
LDL [mg/dL]	92.0 ±28.6	85.1 ±26.9	0.17
HDL [mg/dL]	60.5 ±14.9	51.4 ±16.1	0.001

ALL – childhood acute lymphoblastic leukemia survivors; AH – arterial hypertension; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; MAP – mean arterial pressure; SDS – standard deviation score; NA – not applicable; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

of weight and height. Body mass index (BMI) as well as z-score BMI were subsequently calculated. Fasting blood samples were collected from all study subjects for serum total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) measurements.

Statistical analysis

The data was expressed as mean ± standard deviation (SD). Continuous variables between groups (age, age at diagnosis, time of follow up, z-score BMI values, and SDS values) were compared using the two-tailed Mann–Whitney test. Fisher's exact test was used to compare unpaired, nominal variables. Pearson's coefficients or Spearman's coefficients were used to estimate correlations between longitudinal data. P-values ≤0.05 were considered significant.

The statistical analysis was performed using STATISTICA v. 13 (StatSoft, Inc., Tulsa, USA) software.

Results

Patient and control characteristics are presented in Table 1.

Mean age at evaluation of CIMT was 12.1 years and 11.7 years in the ALL and control cohort, respectively.

The number of patients with AH was significantly higher in the ALL cohort (30/81) as compared to controls (10/52) ($p = 0.0315$; odds ratio (OR) = 2.47; 95% confidence interval (95% CI) = 1.08–5.63). Body mass index was not statistically different in the study groups; however, z-score BMI was statistically higher in the ALL cohort. Numbers of patients with BMI-for-age above or equal to 90th and 95th percentile were not different in both cohorts.

It was found that right CIMT, left CIMT and average CIMT as well as CIMT-SDS were not statistically different between childhood ALL survivors and the control group. This data is presented in Table 2.

Right CIMT, left CIMT and average CIMT as well as CIMT-SDS were found not to be statistically higher in childhood ALL survivors and controls with AH

Table 2. Comparison of CIMT in childhood ALL survivors and controls

Variables	ALL (n = 81)	Controls (n = 52)	p-value
CIMT R [mm]	0.4305 ±0.03	0.4297 ±0.03	0.89
CIMT L [mm]	0.4300 ±0.03	0.4285 ±0.03	0.78
CIMT average [mm]	0.4303 ±0.03	0.4291 ±0.03	0.81
CIMT-SDS	1.096 ±0.74	1.027 ±0.55	0.56

ALL – childhood acute lymphoblastic leukemia survivors; CIMT – carotid intima-media thickness; L – left; R – right; SDS – standard deviation score.

Table 3. Comparison of CIMT in childhood ALL survivors and controls with AH and with normal blood pressure

Variables	ALL AH(+) (n = 30)	ALL AH(-) (n = 51)	p-value	Controls AH(+) (n = 10)	Controls AH (-) (n = 42)	p-value	*p-value
CIMT R [mm]	0.435 ±0.04	0.428 ±0.04	0.78	0.431 ±0.04	0.429 ±0.04	0.89	0.89
CIMT L [mm]	0.431 ±0.03	0.429 ±0.03	0.89	0.426 ±0.04	0.429 ±0.03	0.78	0.78
CIMT average [mm]	0.433 ±0.03	0.428 ±0.03	0.82	0.428 ±0.03	0.429 ±0.02	0.93	0.93
CIMT-SDS	1.291 ±0.91	0.981 ±0.61	0.07	1.034 ±0.49	1.024 ±0.57	0.95	0.95

ALL – childhood ALL survivors; AH (+) – arterial hypertension; AH (-) – normal blood pressure; CIMT – carotid intima-media thickness; L – left; R – right; SDS – standard deviation score; *p-values for comparison of CIMT in childhood ALL survivors with AH and normal blood pressure controls.

Table 4. Comparison of CIMT, blood pressure values as well as lipid profile in childhood ALL survivors in relation to the follow-up time

Variables	Follow-up ≤5 years (n = 45)	Follow-up >5 years (n = 36)	p-value
CIMT R [mm]	0.4276 ±0.03	0.4342 ±0.04	0.39
CIMT L [mm]	0.4248 ±0.03	0.4365 ±0.04	0.10
CIMT average [mm]	0.4262 ±0.03	0.4353 ±0.03	0.18
CIMT-SDS	1.167 ±0.78	1.00 ±0.67	0.34
24-hour SBP, mean	113.4 ±9.9	116.2 ±8.0	0.17
24-hour DBP, mean	65.9 ±8.8	65.7 ±5.5	0.91
24-hour MAP, mean	88.7 ±8.5	90.6 ±5.9	0.26
24-hour SBP, SDS	0.545 ±1.29	0.073 ±1.18	0.09
24-hour DBP, SDS	-0.193 ±1.43	-0.345 ±1.07	0.60
24-hour MAP, SDS	1.451 ±1.41	1.369 ±1.19	0.78
Total cholesterol [mg/dL]	161.9 ±34.6	164.2 ±33.2	0.76
Triglycerides [mg/dL]	102.5 ±71.2	89.6 ±46.9	0.42
LDL [mg/dL]	91.0 ±28.6	93.3 ±26.9	0.72
HDL [mg/dL]	58.3 ±14.9	63.2 ±16.1	0.14

CIMT – carotid intima-media thickness; L – left; R – right; SBP – systolic blood pressure; DBP – diastolic blood pressure; MAP – mean arterial pressure; SDS – standard deviation score.

as compared to cohorts with normal BP. Carotid intima-media thickness values were found not to be statistically higher in childhood ALL survivors with AH when compared only to normal BP controls. This data is presented in Table 3.

Numbers of subjects with high (≥ 1 SDS) and low (< 1 SDS) CIMT were not different in childhood ALL survivors group compared to control group (37/81 vs 24/52 and 44/81 vs 28/52; RR = 0.901, 95% CI = 0.755–1.305 and RR = 1.008, 95% CI = 0.766–1.325, $p = 1$, respectively).

There were no significant differences in CIMT and BP values as well as lipid concentrations with respect to the follow-up in childhood ALL survivors. This data is presented in Table 4.

A significant positive correlation between CIMT [mm] and z-score BMI in the control group only was found ($r = 0.299$, $p = 0.031$). A significant positive correlation between CIMT-SDS and systolic BP-SDS was found exclusively in the ALL cohort ($r = 0.29$, $p = 0.009$). We also found a significant positive correlation between z-score BMI and 24-hour SBP in the ALL cohort as well as in controls

($r = 0.23$, $p = 0.034$ and $r = 0.29$, $p = 0.031$, respectively). No significant correlations between CIMT [mm] or CIMT-SDS and the other measured variables (including mean 24-hour BP as well as total cholesterol, triglycerides, and LDL and HDL concentrations) were found. Furthermore, no significant correlations between CIMT [mm]/CIMT-SDS and the follow-up time in the ALL cohort were found ($r = 0.09$, $p = 0.39$ and $r = 0.122$, $p = 0.28$). The correlations between CIMT and all variables measured are presented in Table 5.

The correlation between 24-hour SBP-SDS and carotid intima-media thickness SDS (CIMT-SDS) in the ALL cohort is shown in Fig. 1.

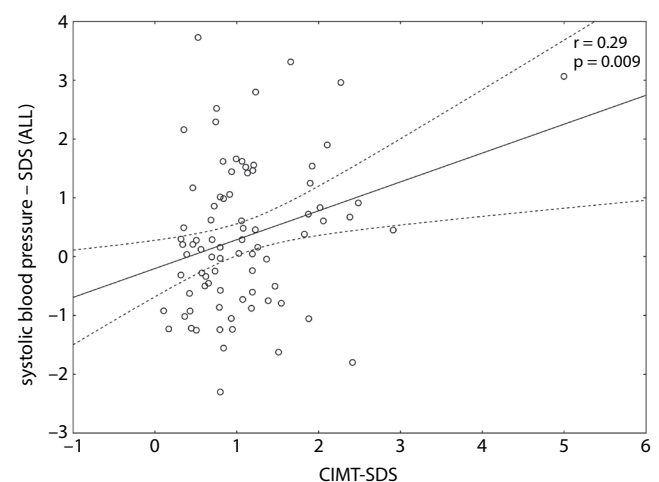


Fig. 1. The correlations between 24-hour systolic blood pressure (SBP-SDS) and carotid intima-media thickness SDS (CIMT-SDS) in childhood ALL survivors

Discussion

Assessment of cardiovascular risk in a population of childhood ALL survivors is challenging. A good, sensitive and commonly available method of early evaluation of subclinical cardiovascular disease in ALL survivors is strongly warranted and CIMT measurement as a direct estimation of arterial thickening seems to be promising. This non-invasive technique is commonly accepted as a credible instrument for cardiovascular risk assessment in adults. However, its use in the pediatric population is most commonly reserved for scientific purposes since

Table 5. Correlations between CIMT [mm]/CIMT-SD, blood pressure values and lipid profile in childhood ALL survivors and controls

Variables	CIMT [mm]		CIMT-SDS	
	ALL	controls	ALL	controls
z-score BMI				
r	-0.0532	0.2999	0.0611	0.1598
p-value	0.64	0.031*	0.59	0.25
24-hour SBP, mean				
r	0.2096	0.1889	0.314	0.0236
p-value	0.06	0.18	0.19	0.87
24-hour DBP, mean				
r	0.1298	0.0444	0.066	-0.0468
p-value	0.25	0.755	0.56	0.74
24-hour MAP, mean				
r	0.2133	0.0348	0.1316	-0.1109
p-value	0.056	0.81	0.24	0.43
24-hour SBP-SDS				
r	0.1731	-0.0828	0.2904	0.1219
p-value	0.12	0.56	0.009*	0.39
24-hour DBP-SDS				
r	0.1358	-0.0228	0.1179	-0.0376
p-value	0.23	0.87	0.29	0.79
24-hour MAP-SDS				
r	0.1655	-0.1411	0.1988	-0.0438
p-value	0.14	0.318	0.07	0.76
Total cholesterol [mg/dL]				
r	0.0098	-0.0605	-0.0198	0.1314
p-value	0.93	0.67	0.86	0.35
Triglycerides [mg/dL]				
r	0.1869	0.1455	0.0906	0.1545
p-value	0.09	0.303	0.42	0.27
LDL [mg/dL]				
r	0.0063	-0.0087	-0.0028	0.1568
p-value	0.956	0.95	0.98	0.27
HDL [mg/dL]				
r	0.0275	-0.1155	-0.0148	-0.0214
p-value	0.8	0.41	0.89	0.88
Follow up [years]				
r	0.09	NA	0.122	NA
p-value	0.39	NA	0.28	NA

ALL – childhood acute lymphoblastic leukemia survivors; SBP – systolic blood pressure; DBP – diastolic blood pressure; MAP – mean arterial pressure; BMI – body mass index; SDS – standard deviation score; r – Pearson correlation coefficient; * statistically significant; NA – not applicable; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

pediatric data regarding the usefulness of CIMT is still limited.¹

It is believed that cancer survivors, including children treated for ALL, are at particular risk of AH development.^{16,23,24} The main finding of the presented paper is that CIMT expressed as mean values [mm] and SDS is not statistically different in childhood ALL survivors as compared to controls and between those ALL survivors with AH and normal BP. This is surprising since there is a lot of published data which implies a strong association between CIMT and disorders associated with atherosclerosis development. Increased CIMT was found in children with type 1 diabetes mellitus, familial hypercholesterolemia, hypertension, and metabolic syndrome.^{2,4,7,25,26} Children

after therapy of ALL are also at substantial risk of cardiovascular disease development in adulthood.^{15,16,27} It was also confirmed that cancer childhood survivors are approx. 8 times more likely to die due to cardiac-related events as compared to the general population.²⁸

Our observations are in line with data published by Giordano et al. They demonstrated that children after ALL treatment had lower FMD of the brachial artery but not different CIMT as compared to healthy controls.¹⁸ Moreover, the study of Järvelä et al. revealed similar results since they did not find a difference in CIMT between childhood ALL survivors aged 16–30 years as compared to controls, although it needs to be stressed that one of the main aims of their study was to compare the CIMT values before and after a 16-week home-based exercise program.¹⁹

It should also be highlighted that most available pediatric studies regarding CIMT included older children and compared the mean values of CIMT in healthy subjects with a population at risk (hypertension, obesity, metabolic syndrome, and dyslipidemia). Doyon et al. established reference charts which allow a comparison CIMT-SDS in children with chronic conditions and healthy controls.²¹ In our study, all mean values of CIMT were computed using the LMS formula, which makes it possible to convert the measurements for specific characteristics of a child (sex, age, height).

The relationship between AH and CIMT has been confirmed in many studies.^{29,30} This convincing association is not in line with our results. Despite an increased number of individuals with AH in childhood ALL survivors as compared to controls, the CIMT values in these 2 populations were not statistically different.

If CIMT represents subclinical and asymptomatic atherosclerotic vascular disease which is also associated with AH, the only explanation why CIMT is not increased in hypertensive childhood ALL survivors, as compared to controls, is that CIMT displays only morphological alterations of the vascular wall, whereas one of the earliest components of atherosclerosis is endothelial dysfunction.²¹ It results from the predominance of a pro-vasoconstrictory state and, if sustained and not reversed, may finally progress to morphological changes of the vascular wall including plaque formation.³¹

Several functional changes of the vascular wall in childhood ALL survivors may be present earlier, leading to abnormal regulation of vascular tone, and are responsible for AH development.³² Even though we found a significant positive correlation between CIMT-SDS and 24-hour SBP-SDS in the ALL cohort, such a correlation was not found in controls. This may indicate some causative impact of BP on CIMT in children with ALL.

Our data cannot support a strong relationship between BP and CIMT in the patients studied. It is in contrast to data reported by Dawson et al., who found that SBP was independently associated with CIMT in a population of children older than 11 years.³³ Kollias et al., who found

that BP was an independent determinant of increased CIMT in healthy children aged 8–18, made a similar observation. It is worth noting that the correlation coefficient observed in that study was low ($r = 0.12$), suggesting that CIMT is only partially predicted by BP.⁸

Carotid intima-media thickness is particularly influenced by a patient's age; thus, the time of first CIMT assessment may be crucial for proper adaptation of this method.²¹ Our study population consisted of subjects with a median age of 12 years and a median time of CIMT analysis of 5 years from ALL diagnosis. It might be too early to find structural abnormalities in the arterial wall. However, we did not find any significant correlation between CIMT and time from diagnosis of ALL, which might be explained by the relatively short time of the follow-up in the study group. The length of time that could result in morphological remodeling of the vascular wall in childhood ALL survivors still needs to be estimated. This is in line with data published by Baroncini et al., who found no significant difference in CIMT in healthy children younger than 15 years and relatively constant values of CIMT in children younger than 10 years.³⁴ The hypothesis that our study population was examined too early also cannot be ruled out.

Dawson et al. confirmed a direct association of CIMT with total cholesterol and triglycerides in a healthy population of adolescents and young adults.³³ We did not find any significant correlations of CIMT (mm/SDS) with total cholesterol, triglycerides, and LDL and HDL concentrations in childhood ALL survivors as well as in controls, even though the concentration of total cholesterol was higher in the ALL cohort.

This finding supports the observation of Giordano et al., who also did not confirm such a correlation although concentrations of total cholesterol, triglycerides and LDL were higher, and HDL was lower in ALL survivors as compared to controls.¹⁸ But the truth is also that we found higher HDL concentration in ALL survivors, which would have protective effect for early vascular changes in this population.

Vijayarathi et al. showed that the only risk factor which had a negative significant correlation with CIMT was HDL concentration. In this study, total cholesterol, LDL and triglyceride concentrations were not significantly correlated with CIMT.²⁵

Metabolic syndrome, obesity and hyperlipidemia are widely recognized causative factors of atherosclerosis in youths. Published data indicates their relation with intima-media thickening, making CIMT evaluation a useful tool for prediction of cardiovascular events in such patients.^{1,25} We found that z-score BMI was significantly higher in childhood ALL survivors. However, a significant correlation between z-score BMI and CIMT was found exclusively in the controls. Moreover, higher z-score BMI did not result in carotid intima-media thickening in the ALL cohort. Mean BMI as well as numbers of patients with obesity were also not different between the 2 groups. This

is in line with the results of a study by Juonala et al. They found that the strength of the associations between childhood risk factors (total cholesterol, triglycerides, BP, and BMI) and CIMT is dependent on childhood age and becomes evident only in children older than 8 years.¹⁷

We are aware that our study has several limitations. The study sample was relatively small as well as the follow-up too short. These factors probably have had an impact upon the results. Moreover, measurements of CIMT require extreme precision, since Wiegman et al. found that CIMT increases by only 0.001 mm per year in healthy controls.³⁵ Finally, since reference values of CIMT for children have not yet been set, matched-case control is required for every measurement, which is not feasible in clinical practice.

Considering the results presented in this paper as well as the abovementioned study limitations, we conclude that measurement of CIMT cannot be used as an early indicator of endothelial dysfunction in childhood ALL survivors. Based on the observations presented in this study, one may speculate that in childhood ALL survivors with AH, the vascular wall retains its elasticity and probably responds to vasodilators. If this is so, these agents should be considered as first-line treatment of AH in young ALL survivors.

Although there are some clinical practice guidelines which provide recommendations for cardiac toxicity screening of late effects in survivors of pediatric malignancies using echocardiography, other tests are needed to predict cardiovascular risk in childhood ALL survivors at the early stage of the follow-up, in particular those with AH.³⁶ This would probably help in designing early intervention programs intended to prevent, reduce or delay cardiovascular disease in childhood and adolescence.

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