

Atherogenic low density lipoprotein phenotype in long-term survivors of childhood acute lymphoblastic leukemia

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Abstract Survivors of childhood acute lymphoblastic leukemia (ALL) have an increased risk of cardiovascular disease. Small density lipoproteins are atherogenic but have not been studied in this population. We conducted a cross-sectional analysis of 110 ALL survivors (mean age, 24.3 years) to determine prevalence of small dense LDL (pattern B) phenotype in ALL survivors and identify associated factors. Lipid subfractions were measured using Vertical Auto Profile-II. Participants with greater than 50% of LDL-cholesterol (LDL-c) in small dense LDL fractions (LDL₃₊₄) were classified as LDL pattern B. Visceral and subcutaneous adipose tissue (VAT, SAT) volumes were also measured by computed tomography. While the mean LDL-c level of ALL survivors was 108.7 ± 26.8 mg/dl, 36% (40/110) of survivors had atherogenic LDL pattern B. This pattern was more common in males (26/47; 55%) than in females (14/63; 22%, $P = 0.001$) and more common in survivors treated with cranial radiotherapy (15/33; 45%) than in those who were treated with chemotherapy alone (25/77; 33%; $P = 0.04$, adjusted for age, gender, history of hypertension, and smoking history). VAT was associated with atherogenic lipids: LDL pattern B and LDL₃₊₄ levels. This association was independent of other measures of body fat. **■** We conclude that a substantial proportion of ALL survivors had an atherogenic LDL phenotype despite normal mean LDL-c levels. An atherogenic LDL phenotype may contribute to the increase in cardiovascular mortality and morbidity in this population.—Malhotra, J., E. S. Tonorezos, M. Rozenberg, G. L. Vega, C. A. Sklar, J. Chou, C. S. Moskowitz, D. A. Eshelman-Kent, P. Janiszewski, R. Ross, and K. C. Oeffinger. **Atherogenic low density lipoprotein phenotype in long-term survivors of childhood acute lymphoblastic leukemia.** *J. Lipid Res.* 2012. 53: 2747–2754.

Supplementary key words cancer • dyslipidemias • lipids • lipoproteins • LDL subfractions

Acute lymphoblastic leukemia (ALL) constitutes more than 80% of newly diagnosed acute leukemias in children and has a current five-year overall survival rate exceeding 85 percent (1). At the same time, data from the Childhood Cancer Survivor Study (CCSS) suggest that adult survivors of childhood leukemia are at significantly increased risk for myocardial infarction [Hazard rate (HR) 3.3; 95% CI, range 1.2–8.6] and congestive heart failure (HR 4.2; 95% CI, range 2.3–7.4) compared with their noncancer siblings (2, 3). Therefore, it is imperative to identify potential cardiac risk factors in this population at an early stage in the atherosclerotic process.

Low-density lipoprotein (LDL) is composed of multiple subfractions based on particle size and density. Among these LDL subfractions, small dense LDL is more atherogenic than larger particles (4) and is associated with an increased risk for coronary artery disease (CAD) (5). There are two main subclass patterns of LDL based on predominant LDL particle size: large, buoyant LDL pattern A (particle diameter ≥ 25 nm) and small dense LDL pattern B (particle diameter < 25 nm) (6). LDL pattern B is independently associated with higher rate of CAD progression (7, 8). Conventional lipid panels measure total LDL-cholesterol (LDL-c) level, which is the sum of cholesterol in all LDL subparticles. Elevated LDL-c is a known cardiac

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Abbreviations: ALL, acute lymphoblastic leukemia; BMI, body mass index; CAD, coronary artery disease; CRT, cranial radiotherapy; CT, computerized tomography; GHD, growth hormone deficiency; HDL-c, HDL-cholesterol; HOMA-IR, homeostasis model of assessment-insulin resistance; HR, hazard rate; IDL, intermediate-density lipoprotein; LDL-c, LDL-cholesterol; SAT, subcutaneous adipose tissue; VAP-II, Vertical Auto Profile-II; VAT, visceral adipose tissue.

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risk factor (9), but 30–40% of patients with cardiovascular events have normal LDL-c levels (10). Therefore, patients with CAD may have small dense pattern B despite having normal LDL-c levels (11, 12). This finding represents a potential source of unrecognized atherogenic risk when using a routine lipid panel instead of measuring LDL subfractions. LDL pattern B prevalence in young adults has been reported to be 18.5–29.2% (13, 14).

Although ALL survivors have a high prevalence of obesity, including visceral adiposity, and are at an increased risk for cardiovascular disease (15–18), studies have not shown any significant difference in mean LDL-c and HDL-cholesterol (HDL-c) levels between ALL survivors and noncancer controls (15, 19). We are unaware of any prior study of subfraction lipid analysis in this population. The objectives of the current analysis were *i*) to estimate the prevalence of small dense LDL (pattern B) phenotype in ALL survivors and identify associated treatment factors and *ii*) to assess the relationship between measures of body fat and LDL pattern B in this cohort of survivors.

METHODS

Study population

Between May 2004 and January 2007, a cohort of 118 adult survivors of childhood ALL participated in the ALLIFE Study, as described in prior reports (15, 18, 20). Eligible survivors (N = 189) were based upon the cancer registry, diagnosed between 1970 and 2000, and lived in the Dallas-Fort Worth metropolitan area. Nonparticipants (passive nonrespondents, 21.2%; active refusals, 16.4%) were not significantly different than participants with respect to sex, race and ethnicity, age at study, age at ALL diagnosis, interval from diagnosis to study, or history of attending a long-term follow-up program (all $P > 0.1$). All 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.

Seven participants who received total body irradiation before an allogeneic hematopoietic cell transplant were excluded, as this group has an increased prevalence of fatty liver (21) and might have an alternate mechanism for development of insulin-related lipid aberrations. One participant was excluded due to

missing lipid subfraction data. Our study population included 110 survivors of childhood leukemia at median of 17.6 (4.9–34.0) years from cancer diagnosis (**Table 1**).

Measurements

Fasting laboratory testing. Venous blood samples were taken after a 12 h overnight fast and stored frozen at -80 C until sent for batch analysis. Glucose was measured at the University of Texas Southwestern Medical Center GCRC Core Laboratory. Insulin was measured using commercial radioimmune assays (Linco Research, St. Charles, MO). Insulin resistance was estimated using the homeostasis model for assessment of insulin resistance (HOMA-IR) (22); subjects were categorized as being insulin resistant when HOMA-IR was equal to or greater than 2.86 (the 75th percentile for HOMA-IR derived from the Third National Health and Nutrition Examination Survey) (23). Patients were considered as having metabolic syndrome if they had three or more of the following as per Adult Treatment Program III guidelines issued by the National Cholesterol Education Program (NCEP-ATP III): fasting blood glucose ≥ 100 mg/dl or drug treatment for elevated blood glucose; HDL < 40 mg/dl in men or HDL < 50 mg/dl in women; triglycerides ≥ 150 mg/dl; waist circumference ≥ 102 cm in men or waist circumference ≥ 88 cm in women; blood pressure $\geq 130/85$ mmHg or drug treatment for hypertension (24).

Lipoproteins and their subfractions were determined using the Vertical Auto Profile-II (VAP-II, Atherotech, Birmingham, AL) method (25, 26). VAP-II is an inverted rate zonal, single vertical spin, density gradient ultracentrifugation technique that simultaneously measures cholesterol concentrations of all five lipoprotein classes [LDL, HDL, very low density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and triglycerides] and their subclasses. LDL subclasses include LDL₁ and LDL₂ (large, buoyant) and LDL₃ and LDL₄ (small, dense, and more atherogenic). In addition, VAP identifies predominant LDL density pattern based on LDL max time value (25, 26). Patients with greater than 50% of LDL-c in small dense LDL particles (LDL₃₊₄) were categorized as more atherogenic LDL pattern B (LDL max time ≤ 115 s) (25, 26). Patients with greater than 50% of LDL-c in predominantly large or intermediate LDL particles (LDL₁₊₂) were categorized as LDL pattern A (LDL max time > 115 s). Our primary study outcomes to measure atherogenic small dense LDL were *i*) prevalence of LDL pattern B and *ii*) mean LDL₃₊₄ levels.

Anthropometric measures. Upon entry to the study, height, weight, and waist circumference (at the level of superior iliac

TABLE 1. Characteristics of 110 survivors of childhood ALL

Characteristic	All (n = 110)	Male (n = 47)	Female (n = 63)
Age at time of study, years	24.3 (5.0)	23.9 (5.0)	24.6 (5.0)
Age at diagnosis, years	6.6 (4.2)	7.3 (4.3)	6.1 (4.2)
Time since cancer, years	17.6 (6.0)	16.6 (5.8)	18.4 (6.0)
Ethnicity, n (%)			
African American	13 (11.8%)	4 (8.5%)	9 (14.3%)
White, non-Hispanic	79 (71.8%)	38 (80.9%)	41 (65.1%)
Hispanic	16 (14.6%)	4 (8.5%)	12 (19.1%)
Height, m	1.7 (0.1)	1.7 (0.07)	1.6 (0.07)
Weight, kg	78.4 (19.7)	82.7 (16.9)	75.2 (21.2)
BMI, kg/m ²	28.4 (7.4)	27.1 (5.6)	29.4 (8.4)
Cranial radiotherapy, n (%)	33 (30.0%)	11 (23.4%)	22 (34.9%)
Cumulative anthracycline dose, n (%)			
None	32 (29.1%)	10 (21.3%)	22 (34.9%)
1–249 mg/m ²	59 (53.6%)	29 (61.7%)	30 (47.6%)
≥ 250 mg/m ²	19 (17.3%)	8 (17.0%)	11 (17.5%)

Data presented as mean (SD) or as a number (%).

crest, to the nearest 0.1 cm) were measured using standard techniques (27). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Radiographic measures. Computed tomography (CT) scans of the abdomen were performed on all subjects using an electron beam CT scanner (Imatron; General Electric, Milwaukee, WI) (18). Images were analyzed using specialized software (Tomovision, Montreal, Canada). A contiguous series of five to seven CT images between the L4-L5 and L3-L4 vertebral disc spaces were used to calculate visceral (VAT) and subcutaneous (SAT) abdominal fat mass. Subjects were categorized as having a visceral pattern of obesity if VAT/SAT ratio was equal to or greater than 0.4 (28).

Statistical analysis

Continuous variables were compared using the Student *t*-test, and discrete variables were compared using Fisher's exact test. Logistic regression analysis was used to examine whether select factors were associated with the presence of LDL pattern B. Linear regression models were used to explore relationships between LDL_{3+4} and covariates. Regression analyses were adjusted for age, gender, history of hypertension, and smoking history. Statistical analyses was performed using STATA version 9.1 (College Station, TX) (29) with a two-sided $P < 0.05$ considered statistically significant.

RESULTS

Characteristics of participants

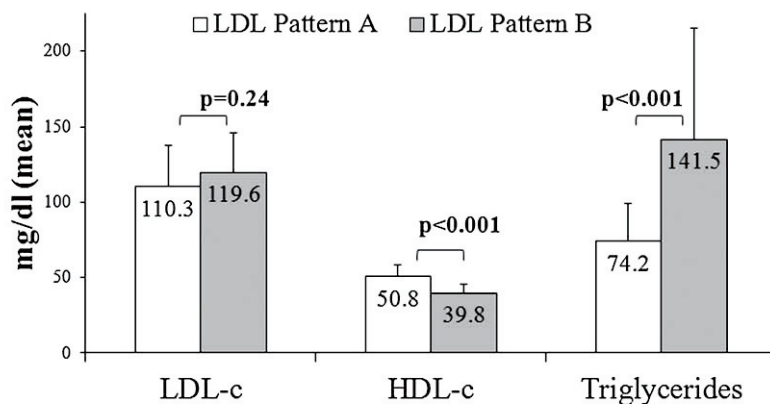
Of the 110 participants, 47 (42.7%) were male (Table 1). Non-Hispanic white patients made up 80.9% of the males and 65.1% of the females. Median age at ALL diagnosis was 5.2 years (range 0.9–17.7 years), and median number of years since initial cancer diagnosis was 17.5 years (range 4.9–34.0 years). Two subjects were receiving lipid therapy.

LDL-c, HDL, triglycerides, and LDL pattern B

On average, participants in this study had normal mean LDL-c levels (Fig. 1; 108.7 ± 26.8 mg/dl). Mean levels of HDL-c (48.3 ± 10.3 mg/dl) and triglycerides (108.4 ± 70.0 mg/dl) were also within normal range. However, 36.4% (40/110) of the study participants were found to have atherogenic LDL pattern B; mean LDL_{3+4} level for the 110 participants was 50.9 ± 20.0 mg/dl.

In analyses that were adjusted for age, gender, history of smoking, and hypertension history, mean LDL-c levels were not significantly different between participants with LDL pattern B (Fig. 1; 114.8 mg/dl) and those with pattern A (105.3 mg/dl; adjusted $P = 0.18$). In contrast, mean

A Males



B Females

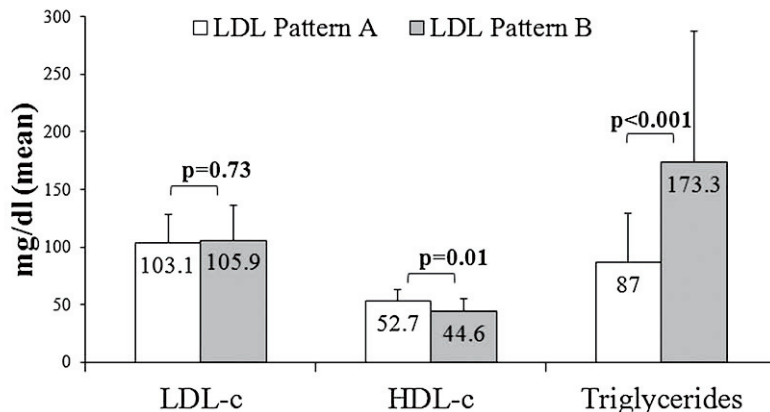


Fig. 1. Mean LDL-c, HDL-c, and triglyceride levels among survivors of childhood ALL with LDL pattern A and LDL pattern B. *P* adjusted for age, history of hypertension, and smoking history.

HDL-c was lower in those with LDL pattern B (41.5 mg/dl) compared with those with pattern A (52.1 mg/dl; adjusted $P < 0.001$). HDL subfractions (HDL₂ and HDL₃) were also lower in survivors with LDL pattern B compared with survivors with LDL pattern A (Table 2). Participants with LDL pattern B also had higher triglyceride levels (152.6 versus 83.2 mg/dl; adjusted $P < 0.001$) and higher triglyceride/HDL-c ratio than those with pattern A (3.9 versus 1.7; adjusted $P < 0.001$).

Males had a higher prevalence of LDL pattern B (26/47, 55.3%) than females (14/63, 22.2%; $P = 0.001$). There was no difference in prevalence of LDL pattern B by race or ethnicity.

Atherogenic lipids and cancer therapy factors

Participants receiving cranial radiotherapy (CRT) had higher prevalence of LDL pattern B (Table 3; 15/33, 45.5%) compared with those who did not receive CRT (25/77, 32.5%; $P = 0.04$, adjusted for age, gender, history of hypertension, and smoking history). CRT also showed a significant association with LDL₃₊₄ levels (mean, 57.7 versus 48.0 mg/dl; adjusted $P = 0.02$). However on a linear

TABLE 2. Lipid subfractions among 110 survivors of childhood leukemia with LDL pattern A and LDL pattern B

	LDL pattern A (n = 70)	LDL pattern B (n = 40)
Total cholesterol	173.9 (28.3)	178.6 (30.5)
Triglycerides	83.2 (37.8)	152.6 (89.6) ^a
LDL	105.3 (25.5)	114.8 (28.2)
LDL ₁	14.6 (5.3)	16.6 (5.5)
LDL ₂	36.3 (13.8)	15.1 (6.8) ^a
LDL ₃	36.4 (12.1)	51.3 (15.7) ^a
LDL ₄	4.7 (2.5)	16.7 (9.5) ^a
LDLR	92.1 (22.7)	99.8 (25.6)
HDL	52.1 (9.6)	41.5 (7.8) ^a
HDL ₂	12.6 (4.1)	7.8 (3.0) ^a
HDL _{2a}	9.0 (3.5)	6.2 (2.2) ^a
HDL _{2b}	2.5 (1.0)	1.4 (1.2) ^a
HDL _{2c}	1.1 (0.2)	0.2 (0.9) ^a
HDL ₃	39.5 (6.2)	33.8 (5.4) ^a
HDL _{3a}	12.8 (3.9)	8.7 (2.9) ^a
HDL _{3b}	6.9 (1.5)	6.5 (1.9)
HDL _{3c}	10.0 (2.0)	8.2 (1.9) ^a
HDL _{3d}	9.7 (1.4)	10.2 (1.3)
IDL	5.6 (4.8)	9.9 (6.1) ^a
IDL ₁	1.0 (1.5)	3.5 (2.8) ^a
IDL ₂	4.7 (3.5)	6.4 (3.8)
VLDL	16.5 (3.3)	22.4 (7.6) ^a
VLDL _{1 and 2}	7.3 (1.5)	10.4 (4.1) ^a
VLDL ₃	9.2 (1.9)	12.1 (3.7) ^a
VLDL _{3a}	4.1 (0.9)	5.6 (1.9) ^a
VLDL _{3b}	5.2 (1.0)	6.4 (1.9) ^a
Lpa	7.5 (3.8)	5.2 (3.3) ^a
Lpa ₁	1.3 (2.3)	0.4 (1.4)
Lpa ₂	0.9 (1.8)	<0.1 (0.2) ^a
Lpa ₃	2.9 (2.7)	0.7 (1.6)
Lpa ₄	1.6 (2.6)	1.9 (2.3) ^a
Lpa ₅	0.8 (1.6)	2.2 (2.0) ^a
Non-HDL	119.8 (20.7)	139.7 (33.0) ^a
Non-HDL _c /HDL	2.4 (0.7)	3.5 (1.1)
Remnant ^b	14.9 (6.4)	21.9 (9.5) ^a

Lpa, lipoprotein(a).

^a $P \leq 0.05$ when comparing survivors with LDL pattern A and survivors with LDL pattern B; adjusted for age, gender, history of hypertension, and smoking history. Data presented as mean measured in mg/dl (SD).

^bRemnant lipoproteins = IDL + VLDL₃.

regression model, CRT accounted for only 5% of the variation in the LDL₃₊₄ levels ($R^2 = 0.05$). Survivors receiving CRT also had higher VAT volume compared with those who did not receive CRT (mean, 390.3 versus 228.5 cm³; adjusted $P = 0.002$). No difference was found in the prevalence of LDL pattern B based on prior exposure to anthracyclines, methotrexate, glucocorticoids, or any other chemotherapeutic agents. Age at diagnosis and interval since cancer diagnosis were not associated with the presence of LDL pattern B.

Atherogenic lipids and measures of body fat

In analyses that were adjusted for age, gender, history of smoking, and hypertension history, all measures of body fat, including increased BMI, waist circumference, and visceral pattern of obesity, were associated with atherogenic lipids: LDL pattern B and LDL₃₊₄ levels (Table 4 and Fig. 2). The highest prevalence of LDL pattern B was found among participants with a visceral pattern of obesity (73.7% versus 28.2% in participants without the visceral pattern of obesity; adjusted $P = 0.03$). This association was independent of other measures of body fat. Increased prevalence of LDL pattern B was observed in survivors with a visceral pattern of adiposity irrespective of therapy. Of survivors who received CRT and chemotherapy and had a visceral pattern of obesity, 80.0% (4/5) had LDL pattern B compared with 71.4% (10/14) of survivors who received only chemotherapy and had a visceral pattern of obesity (adjusted $P = 0.41$).

Atherogenic lipids and other cardiovascular risk factors

Insulin resistance was present in 67 of the 110 participants; 30 (45%) of the insulin-resistant survivors exhibited LDL pattern B compared with only 10 (23%) survivors without insulin resistance ($P = 0.03$, adjusted for age, gender, history of hypertension, and smoking history; Table 2). In a multivariate model adjusted for age, gender, history of hypertension, and smoking history, HOMA-IR was significantly associated with LDL₃₊₄ levels ($\beta = 2.63$; 95% CI, range 1.26–4.00; adjusted $P < 0.001$). However, this association was not significant after inclusion of VAT in the model. Metabolic syndrome was found in 14 participants, 13 (92.9%) of whom had LDL pattern B; 28% of participants without the metabolic syndrome had LDL pattern B (adjusted $P < 0.001$).

DISCUSSION

In this study of 110 young adult survivors of childhood ALL, we have shown that a substantial proportion (over one third) have an atherogenic LDL profile despite mean LDL-c levels within the normal range. To our knowledge, this study is the first to describe these lipid abnormalities in long-term ALL survivors, and it may lead to a better understanding of the cardiovascular risk in this population. Although we saw a modest relationship between CRT and atherogenic lipid profile, nearly one third (32.5%) of survivors without a history of CRT had an atherogenic pattern. Importantly, visceral adiposity was associated with small

TABLE 3. Lipid subfractions among 110 survivors of childhood leukemia, by history of treatment with cranial radiotherapy

	All (n = 110)	CRT (n = 33)	No CRT (n = 77)
Total cholesterol	175.6 (29.1)	183.8 (29.3)	172.1 (28.5) ^a
Triglycerides	108.4 (70.0)	131.0 (95.3)	98.7 (53.8) ^a
LDL	108.7 (26.8)	115.9 (28.7)	105.7 (25.5) ^a
LDL ₁	15.3 (5.4)	15.3 (5.4)	15.4 (5.5)
LDL ₂	28.6 (15.6)	27.3 (17.1)	29.2 (15.0)
LDL ₃	41.8 (15.3)	46.8 (16.4)	39.7 (14.3) ^a
LDL ₄	9.1 (8.4)	10.8 (9.0)	8.3 (8.0) ^a
LDLR	94.9 (23.9)	100.3 (26.8)	92.6 (22.4)
HDL	48.3 (10.3)	47.5 (9.2)	48.6 (10.8)
HDL ₂	10.9 (4.4)	10.4 (3.8)	11.1 (4.7)
HDL _{2a}	8.0 (3.3)	7.5 (2.9)	8.2 (3.5)
HDL _{2b}	2.1 (1.2)	2.1 (1.3)	2.1 (1.2)
HDL _{2c}	0.8 (1.4)	0.8 (1.3)	0.7 (1.4)
HDL ₃	37.4 (6.5)	37.1 (6.1)	37.6 (6.7)
HDL _{3a}	11.3 (4.1)	10.6 (3.3)	11.7 (4.4) ^a
HDL _{3b}	6.8 (1.6)	7.1 (1.7)	6.6 (1.6)
HDL _{3c}	9.4 (2.1)	9.1 (1.9)	9.5 (2.2)
HDL _{3d}	9.9 (1.4)	10.2 (1.3)	9.7 (1.4) ^a
IDL	7.2 (5.7)	8.7 (6.7)	6.5 (5.1)
IDL ₁	1.9 (2.4)	2.7 (3.2)	1.6 (1.9) ^a
IDL ₂	5.3 (3.7)	6.0 (4.0)	5.0 (3.5)
VLDL	18.6 (6.0)	20.5 (7.6)	17.8 (5.0) ^a
VLDL _{1 and 2}	8.5 (3.1)	9.4 (4.0)	8.1 (2.5) ^a
VLDL ₃	10.3 (3.0)	11.2 (3.7)	9.8 (2.6) ^a
VLDL _{3a}	4.6 (1.5)	5.0 (1.9)	4.4 (1.3)
VLDL _{3b}	5.6 (1.5)	6.1 (1.9)	5.4 (1.3) ^a
Lpa	6.7 (3.8)	6.9 (4.2)	6.6 (3.6)
Lpa ₁	1.0 (2.1)	1.3 (2.6)	0.9 (1.8)
Lpa ₂	0.6 (1.5)	0.4 (1.1)	0.6 (1.6)
Lpa ₃	2.1 (2.6)	2.4 (2.9)	1.9 (2.4)
Lpa ₄	1.7 (2.5)	1.5 (2.4)	1.8 (2.5)
Lpa ₅	1.3 (1.9)	1.3 (1.8)	1.3 (1.9)
Non-HDL	129.4 (28.8)	128.1 (30.3)	129.9 (28.5)
Non-HDL/HDL	2.9 (1.0)	2.9 (1.0)	2.9 (1.1)
Remnant ^b	17.4 (8.3)	19.9 (10.0)	16.4 (7.4)
LDL pattern			
A	70 (63.6%)	18 (54.5%)	52 (67.5%) ^a
B	40 (36.4%)	15 (45.5%)	25 (32.5%)

Lpa, lipoprotein(a).

^a $P \leq 0.05$ when comparing survivors who received CRT and survivors who did not receive CRT; adjusted for age, gender, history of hypertension, and smoking history. Data presented as mean measured in mg/dl (SD) or number (%).

^bRemnant lipoproteins = IDL + VLDL₃.

dense LDL regardless of therapy. An atherogenic pattern was present in 71.4% of survivors without a history of CRT but with a visceral pattern of obesity. Further, small dense LDL was strongly associated with other cardiovascular risk factors, including insulin resistance and metabolic syndrome. As observed in the general population (30), male ALL survivors in our study were more likely than females to have LDL pattern B.

In a previously reported analysis from ALLIFE, we found no difference in mean LDL-c and HDL-c levels in ALLIFE compared with 782 noncancer controls from the Dallas Heart Study (15). Furthermore, no significant difference in mean LDL-c levels was found among subjects with a history of CRT compared with those who had no history of CRT. A separate study by Geenen et al. compared 79 ALL survivors (16.5–21 years from time of diagnosis) to noncancer sibling controls and found no significant difference in mean LDL-c or HDL-c (19). Of note, mean LDL-c levels in the 48 patients in that study who received CRT were not different from those who did not receive CRT. Link et al.

reported increased LDL-c and decreased HDL-c levels in 44 ALL survivors, on average 19 years from treatment (31). However, this study included only patients who received CRT doses of more than 18 Gy. None of these studies reported lipid subfraction data.

Despite normal mean LDL-c, HDL-c, and triglyceride levels, more than one third of our patients exhibited the atherogenic LDL pattern B; this finding suggests that an atherogenic LDL pattern might contribute to the increased cardiovascular risk observed in ALL survivors (2, 3). Importantly, measurement of LDL-c alone might not be sufficient for cardiovascular risk stratification in this patient population. Prior studies in noncancer populations have shown that routine lipid profile with normal LDL-c might underestimate the atherogenic risk (10) and that the presence of LDL pattern B is more predictive of CAD than is elevated LDL-c (11). Our findings suggest that the same may be true of the survivor population.

Studies in similarly aged noncancer populations have demonstrated a much lower prevalence of LDL pattern B

TABLE 4. Prevalence of LDL pattern B by measures of body fat and insulin resistance/metabolic syndrome among 110 survivors of childhood leukemia

	N	Pattern A	Pattern B	P
BMI				
< 25 kg/m ²	36	32 (88.9%)	4 (11.1%)	<0.001
≥ 25 kg/m ²	74	38 (51.4%)	36 (48.6%)	
Waist circumference ^a				
Normal	62	42 (67.7%)	20 (32.3%)	0.01
Increased	48	28 (58.3%)	20 (41.7%)	
Visceral pattern of obesity ^b				
VAT/SAT < 0.4	85	61 (71.8%)	24 (28.2%)	0.03
VAT/SAT ≥ 0.4	19	5 (26.3%)	14 (73.7%)	
Insulin resistance				
HOMA-IR < 2.86	43	33 (76.7%)	10 (23.3%)	0.03
HOMA-IR ≥ 2.86	67	37 (55.2%)	30 (44.8%)	
Metabolic syndrome				
No	96	69 (71.9%)	27 (28.1%)	<0.001
Yes	14	1 (7.1%)	13 (92.9%)	

All analyses adjusted for age, gender, history of hypertension, and smoking history.

^aWaist circumference increased if ≥ 102 cm in males or ≥ 88 cm in females.

^bVAT/SAT reported for 106 survivors; data missing for 4 survivors.

than that reported in our study. Watson et al. found the prevalence of LDL pattern B in young adults (mean age 31.7 years) to be 18.5% (22.6% in males and 12.4% in females) (13). The Bogalusa Heart Study included young adults between ages 20 and 37; 131 out of 449 participants (29.2%) had an atherogenic LDL pattern (14), in contrast to 36.4% in our report. Of note, the average age of participants in our study was 8 years younger than those in these two studies.

ALL survivors have significantly increased long-term risk for cardiovascular morbidity and mortality (2, 3). A study of 5,030 ALL survivors (>20 years from the time of diagnosis) from the CCSS found a significantly increased risk for cardiac-related deaths compared with unaffected siblings (age- and sex-adjusted standardized mortality ratio, 4.2; 95% CI, range 2.3–6.9; $P < 0.01$) (3). In addition, leukemia survivors are at a 6-fold greater risk of late-occurring stroke than their noncancer siblings (32). Therefore, due to the cardiovascular and cerebrovascular risk in childhood ALL survivors, it is imperative to identify and treat risk factors related to accelerated atherosclerosis in this group. Our study shows a high prevalence of atherogenic

LDL phenotype in ALL survivors that may help explain the observed increase in cardiovascular risk in this population. Some interventions that have been documented to reduce small dense LDL in noncancer populations include the use of statins (33) and fibrates (34), as well as diet and exercise to reduce weight (35).

The increased prevalence of LDL pattern B seen in ALL survivors could be related to increased visceral adiposity in this group. It is well established that ALL survivors have a higher BMI, increased visceral adiposity, and increased waist-to-height ratio; possible mechanisms include growth hormone deficiency (GHD), leptin dysregulation, poor dietary choices, and reduced physical activity (15–17, 19, 36). We found a strong independent association of visceral adiposity with small dense LDL levels. This finding is consistent with previous studies in noncancer populations that have demonstrated that visceral adiposity is independently associated with smaller LDL particle size (37) and increased prevalence of the small dense LDL phenotype (38). Intra-abdominal adipocytes are more lipolytically active, resulting in increased influx of free fatty acids into the liver via the portal circulation. This leads to an unfavorable lipid profile, as well as a reduction in hepatic insulin sensitivity and dysregulation of glucose metabolism (39). As visceral adiposity can increase both small dense LDL prevalence and insulin resistance through this mechanism, excess visceral adiposity may explain our finding of an association between insulin resistance and small dense LDL levels that was not independent of visceral adiposity. Visceral adiposity may also be mediating the higher prevalence of LDL pattern B observed among those who were treated with CRT. Cancer survivors who receive CRT are at increased risk for obesity, especially if they received more than 18 Gy, were less than 5 years of age at the time of diagnosis, or developed GHD (16, 17). The association between CRT and small dense LDL in our study was attenuated by statistical adjustment for visceral adiposity.

LDL pattern B is associated with increased triglycerides and lower HDL-c levels and together form the triad of atherogenic dyslipidemia (24). Fasting plasma triglycerides

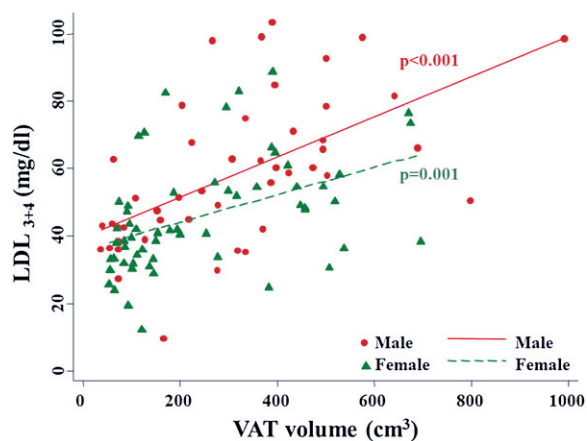



Fig. 2. Association of small dense LDL (LDL₃₊₄) levels with visceral adiposity volume by gender, among 110 survivors of childhood leukemia.

have been shown to be the strongest independent correlate of LDL peak particle size (40). In fact, triglycerides/HDL-c ratio is the best predictor of the presence of LDL pattern B phenotype (41). It has been reported that more than 80% of patients with triglyceride/HDL-c ratio ≥ 3.8 will have LDL pattern B (42). In our study, 88% of participants with triglyceride/HDL-c ratio ≥ 3.8 had LDL pattern B, implying that the ratio of triglycerides/HDL-c can be used as a surrogate measure of small dense LDL phenotype if lipid subfraction analysis is not available in the clinical setting.

A limitation of our study was that it was a cross-sectional analysis; therefore, causal inferences cannot be derived. Future longitudinal studies are needed to delineate underlying mechanisms associated with development of visceral adiposity and small dense LDL in ALL survivors. Additionally, this study did not include a noncancer population for comparison. Nonetheless, as described above, previous studies in young adults without a history of cancer have described a lower prevalence of LDL pattern B than that reported here (13, 14).

In conclusion, this study of 110 adult survivors of childhood ALL found a high prevalence of atherogenic LDL pattern B, even in the setting of normal range LDL-c levels. Because atherogenic small dense LDL may contribute to increased cardiovascular morbidity and mortality, further study in this area is warranted. 

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