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Overweight adolescents with type 2 diabetes have significantly higher lipoprotein abnormalities than those with type 1 diabetes

Lynae J. Hanks, PhD, RDN^a, James Heath Pelham, MS^b, Shalini Vaid, MD^b, Krista Casazza, PhD, RDN^c, and Ambika P. Ashraf, MD^a

^aDepartment of Pediatrics/Division of Pediatric Endocrinology and Metabolism, Children's of Alabama, University of Alabama at Birmingham (UAB); CPPII M30, 1601 4th Ave S, Birmingham, Alabama 35233

^bUAB School of Medicine, University of Alabama at Birmingham; 1720 2nd Ave South, Birmingham, Alabama, 35294-0113

^cDepartment of Pediatrics/Division of General Pediatrics and Adolescent Medicine; CPP1 310, 1601 4th Ave S, Birmingham, Alabama, 35233-1711

Abstract

Aim—Diabetes-associated glucoregulatory derangements may precipitate atherogenesis in childhood and CVD risk, particularly with obesity. We aimed to delineate lipoprotein profile differences between children with type 1 and 2 diabetes who are overweight/obese.

Methods—Data were obtained from electronic medical records of patients 85th BMI percentile with type 1 (n=159) and type 2 (n=77) diabetes, ages 12–19y. Group differences were evaluated by correlations and general linear modeling analysis, adjusting for BMI, HbA1c, and diabetes duration.

Results—There were no group differences in TC, LDL, or non-HDL. Fewer subjects with type 1 diabetes had low HDL (17 vs. 30%; $P<0.05$). While no difference in HbA1c level was observed between groups, HbA1c was positively correlated with TC (P 0.0001), LDL (P 0.0001), non-HDL (P 0.0001), ApoB100 (P 0.0001), and LDL pattern B (P 0.0001). In adjusted models, apoB100 (85.4 vs. 91.3mg/dl; $P<0.05$) and incidence of LDL pattern B (21 vs. 42%; $P<0.01$) were lower in subjects with type 1 diabetes. BMI was inversely correlated with HDL, HDL-2 and HDL-3 (all P 0.0001). The correlation of BMI with HDL-2 and HDL-3 were attenuated when evaluating subjects by diabetes type.

Conclusions—Despite having no difference in absolute LDL levels, children with type 2 diabetes were more likely to have small, dense LDL particle pattern, higher apo B100 and lower total HDL, HDL-2, and HDL-3 fractions. Furthermore, poor glycemic control was associated with abnormal lipoprotein profiles in patients with both type 1 and 2 diabetes.

*Corresponding author: Ambika P. Ashraf, M.D., CPP 230, 1601, Fourth Ave S., Children's Hospital, UAB, Birmingham, AL 35233, Phone: 205 638-9107, Fax: 205 638-5257, AAshraf@peds.uab.edu.

Reprint requests: Ambika P. Ashraf, M.D.

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Keywords

type 1 diabetes; type 2 diabetes; lipoprotein profile; cardiovascular diseases; pediatric obesity

1.0 INTRODUCTION

Cardiovascular disease (CVD), the principal cause of mortality in the US population, has a 2–4% prevalence rate, but increases to 55% in the presence of diabetes [1–3]. Excess adiposity and abnormal lipid profile [e.g., elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL), and low high-density lipoprotein cholesterol (HDL) levels], common in patients with type 2 diabetes, are known major modifiable risk factors for CVD risk [4]. Although patients with type 1 diabetes have less advanced dyslipidemia and similar or better lipid profile relative to individuals without diabetes [5], CVD, especially myocardial infarction is considered a significant cause of death in these patients [6]. Even though the prevalence of both type 1 and type 2 diabetes among children and adolescents have increased, the incidence of type 2 diabetes has significantly increased due to the obesity epidemic [7]. This onset of diabetes at a relatively young age augments long-term CVD risks via accelerated atherosclerotic processes [8]. Tracking of many CVD risk factors is common from childhood to adulthood [9], raising particular concern for children with diabetes who are also overweight/obese.

The onset and progression to CVD appear to differ by diabetes type with underlying mechanisms leading to impaired lipid metabolism being a potential factor [10]. In pediatric patients with type 1 diabetes, glycemic control is directly related to TC and non-HDL [11]. Children with type 2 diabetes are known to have atherogenic dyslipidemia triad of elevated serum TG levels, decreased HDL and higher number of small, dense LDL even when glycemia is well-maintained [12,13], that has been generally attributed to chronic insulin resistance of obesity and intermittent hyperglycemia prior to overt disease onset [14].

Although overweight and obesity in adolescents are associated with an increased TC, LDL, TG and lowered HDL, [15–17], it is unclear if overweight/obese status alone accounts for the atherogenic dyslipidemia that is more prevalent in patients with type 2 diabetes when compared to the lipid profile in youth with type 1 diabetes. The existing data [18–20] have not considered comparison by diabetes type in which both groups included subjects exclusively overweight or obese. In addition, comparisons between standard lipid profile (e.g. TC, HDL, LDL) may overlook atherogenic lipoprotein characteristics [21–24]. Characterization of lipoproteins [i.e., subclasses of HDL and LDL, and apolipoprotein B100 (apoB100) and lipoprotein(a); Lp(a)] may yield important information on the coalescence of dyslipidemia, diabetes and CVD risk. Therefore, the aim of the present study was to characterize the lipoprotein abnormalities in children with type 1 and type 2 diabetes who are also overweight/obese. We hypothesized that lipoprotein characteristics would be similar in both groups if all subjects are overweight or obese.

2.0 METHODS

2.1 Subjects

This was a cross-sectional retrospective chart review of pediatric patients ages 12–19y with type 1 or type 2 diabetes who were managed by the Division of Pediatric Endocrinology at Children's of Alabama, University of Alabama at Birmingham (UAB). Since the purpose of the study was to analyze the lipoprotein characteristics, only patients with type 1 and type 2 diabetes who had a vertical autoprofile (VAP), which is a density gradient rapid ultracentrifugation (Atherotech, Birmingham, AL), were included. VAP analysis provided information on TC, LDL, HDL, apoB100, LDL pattern, HDL subclasses and Lp(a). We reviewed electronic medical records from patients who were seen in the outpatient clinics of our institution over a seven-year period from 2007–2013. The International Classification of Diseases (ICD-9-CM) diagnosis codes of 250.01 and 250.03 were used to identify all eligible patients with type 1 diabetes and 250.00 and 250.02 codes to identify all eligible patients with type 2 diabetes. Inclusion criteria were the presence of overweight or obesity for age according to the United States Centers for Disease Control and Prevention growth charts, the availability of VAP profile, and race reported as black or white by the parent/guardian at the time of registration to the clinic. Each patient's data was collected only once for the study and all parameters were collected from a single clinic visit. In case of patients who had multiple VAP profiles, data at the time of their first VAP profile was included. Patients without clear characteristics for type 1 diabetes or type 2 diabetes were excluded. Patients were also excluded if medications such as cholesterol lowering pills, antihypertensive, or hormonal contraceptives listed in their medical records. Due to the demographics of the patients attending the Pediatric Endocrinology clinic, we had sufficient numbers for Black and White children only for inclusion into this the study. The research protocol was approved by the Institutional Review Board for Human Subjects at UAB.

All subjects received diabetes and nutritional education according to the UAB Endocrine Division policy and patients were given similar instructions to contact the pediatric endocrinologist frequently for medication adjustments to maintain euglycemia. Glycemic control was analyzed based on ISPAD (19) and ADA (20) criteria for optimal diabetes management, as HbA1c $\leq$ 7.5% (58 mmol/mol). Other cut-points were based on ADA and NHLBI [25] criteria: TC was considered elevated if $\geq$ 200 mg/dl, LDL was considered elevated if $\geq$ 130 mg/dl, and HDL was considered low if $\leq$ 40 mg/dl, and microalbuminuria was defined as urine albumin 30–299 mcg /mg of creatinine. As the fasting status could not be ascertained due to the retrospective nature of the study, we excluded triglycerides from analysis.

2.2 Statistics

Descriptive statistics were generated for the overall sample and stratified according to diabetes type. The Kolmogorov-Smirnov test and graphical inspections of data were used for evaluating distribution for normality. Microalbumin:creatinine ratio and Lp(a) were non-normally distributed, thus median and interquartile ranges are presented. Unpaired sample t-test (for normally distributed variables) and the Wilcoxon-Mann-Whitney test (for non-normally distributed data) were then used to identify differences between diabetes groups.

General linear models were evaluated to detect differences between diabetes groups, controlling for the potential confounding variables, age, sex, race, BMI, HbA1c, and diabetes duration. Pearson correlation analysis was performed to identify relationships of participant characteristics with lipid parameters. Statistical significance was accepted at P 0.05 for all tests using SAS software (version 9.4, SAS Institute Inc., Cary NC).

3.0 RESULTS

There were a total of 236 subjects, ages 12–19y with type 1 ($n=159$) or type 2 ($n=77$) diabetes, of which 60% were White and 40% were Black. Majority (93.8%) of patients with type 2 diabetes had a BMI >95th percentile; whereas, 42% of patients with type 1 diabetes had BMI >95th percentile and the rest were overweight. Table 1 illustrates descriptive and clinical characteristics of the subjects. On average, subjects with type 1 diabetes were younger (15.0 vs 15.6y; P 0.05), had lower BMI (27.6 vs. 36.5 kg/m²) and BMI percentile (93rd vs. 98th centile; $P < 0.0001$), had a lower frequency of Black individuals (19 vs. 83%; $P < 0.0001$) and greater frequency of males (44 vs 31%; P 0.01) compared to subjects with type 2 diabetes. Subjects with type 1 diabetes also had longer mean duration of diabetes (6.0y vs. 2.8y; $P < 0.0001$) and greater occurrence of suboptimal glycemic control [ie, HbA1c >7.5% (58 mmol/mol)] (86 vs. 76% ; $P < 0.0001$), although mean HbA1c was not significantly different between groups [9.1 vs. 8.6% (76 vs. 70 mmol/mol); $P = 0.11$]. Microalbumin:creatinine ratio was not different between diabetes types, and presence of microalbuminuria was lower among subjects with type 1 diabetes (17 vs. 30%; P 0.01).

Table 2 illustrates the differences in lipoprotein characteristics between subjects with type 1 and type 2 diabetes and with adjustment for potential confounders (age and sex; age, sex and race; and age, sex and race, separately adding BMI, HbA1c, and duration of diabetes). There were no significant differences in TC, LDL, and non-HDL between the two groups. Fewer subjects with type 1 diabetes had LDL pattern B, even after adjusting for potential confounders (21 vs. 42%, $P < 0.01$). Total HDL (55 vs. 48 mg/dl), HDL-2 (15 vs. 12mg/dl), and HDL-3 (40 vs. 36 mg/dl) were greater among subjects with type 1 diabetes (all $P < 0.01$), and these differences persisted when adjusting for all confounders. In addition, fewer subjects with type 1 diabetes had a low HDL (17 vs. 30%; $P < 0.05$). This difference persisted after inclusion of all potentially confounding variables except for BMI. In the adjusted models, apoB100 (85.4 vs. 91.3mg/dl; $P < 0.05$) and occurrence of LDL pattern B (21 vs. 42%; $P < 0.01$) were lower in subjects with type 1 diabetes relative to those with type 2 diabetes. There was no difference in the Lp(a) concentration between the two groups.

Pearson correlations between descriptive and clinical characteristics and lipid parameters are depicted in Table 3. BMI was inversely correlated with HDL, HDL-2 and HDL-3 (all P 0.0001). BMI was positively associated with apoB100 (P 0.01) and LDL pattern B (P 0.01) in the overall sample. The relationships between BMI and apoB100 (P 0.01) and between BMI and LDL pattern B (P 0.05) were only significant in subjects with type 1 diabetes. BMI was positively associated with LDL and non-HDL in subjects with type 1 diabetes (both P 0.05). Higher HbA1c level was correlated with TC (P 0.0001), LDL (P 0.0001), non-HDL (P 0.0001), ApoB100 (P 0.0001), LDL pattern B (P 0.0001), HDL (P 0.01), and HDL-3 (P 0.0001). The correlations between HbA1c with TC, LDL, non-

HDL, apoB100, and LDL pattern B persisted in both groups ($P = 0.05$); however, correlations between HbA1c with HDL and HDL-3 persisted among subjects with type 1 diabetes only ($P = 0.01$).

4.0 DISCUSSION

The atherogenic insult of dyslipidemia almost invariably present among patients with diabetes has been estimated to elevate CVD complications by 20–50% ([26]. This study of children with type 1 and type 2 diabetes, who are exclusively overweight or obese, demonstrates that subjects with type 2 diabetes display a more atherogenic lipoprotein profile when compared to those with type 1 diabetes. This study also illustrates that focusing on traditional lipid measures TC, LDL, non-HDL concentrations, or occurrence of elevated TC or LDL may overlook the significantly different lipoprotein abnormalities between diabetes type 2 and 1. Specifically, we found that despite having relatively better glycemic control, subjects with type 2 diabetes had greater occurrence of small, dense LDL particle pattern relative to subjects with type 1 diabetes. Further, subjects with type 2 diabetes had lower overall HDL, were more likely to meet the criteria for low HDL (i.e., <40 mg/dl), as well as lower HDL-2, and HDL-3 fractions.

This study indicates that although the mean values of traditional lipid measures were in the range of currently recommended cutpoints for both groups, subjects with type 2 diabetes were more likely to have low HDL and abnormalities in lipoprotein characteristics, highlighting a potential for acceleration of the atherogenic process in patients with type 2 diabetes that may be overlooked early on in the disease course. This is supported by the fact that type 2 diabetes is characterized by selective hepatic insulin resistance, VLDL overproduction, and hypertriglyceridemia, and subsequently smaller, cholesterol-depleted HDL particles and LDL particles [27].

Despite no difference in absolute LDL concentrations, patients with type 2 diabetes had higher occurrence of small, dense LDL particles, classified as LDL pattern B. This LDL pattern is characterized as more atherogenic, since these particles are more likely to form oxidized LDL, are less readily cleared, and have downstream effects on HDL particle size [28,29]. Our finding of greater frequency of LDL pattern B in subjects with type 2 diabetes is in concordance with that of a larger multiracial study inclusive of subjects with ages 3–20y and varying body weight classification, which reported that, as opposed to subjects with type 1 diabetes, elevated dense LDL were highly prevalent among subjects with type 2 diabetes [30].

A substantial increase in elevated risk factors for CVD with poor glycemic control in children and adolescents both type 1 and type 2 diabetes groups has been reported [30]. In our cohort of subjects who were exclusively overweight or obese, HbA1c level was positively correlated with TC, LDL, non-HDL, ApoB100, and presence of LDL pattern B. In context of poor glycemic control, LDL pattern B may be more metabolically adverse than simple elevated LDL level [31]. Although contrast exists among studies, adequate glycemic control helped to normalize TG and HDL cholesterol levels in patients with diabetes [32–34]f. Conceivably, improvement of the glycemic control may have a greater impact for

mitigating atherogenesis among patients with type 2 diabetes by reducing the number of small, dense LDL particles and by increasing HDL.

The observed higher levels of HDL, as well as HDL-2 and HDL-3 subfractions among subjects with type 1 diabetes were independent of glucose control. Mean HbA1c level did not significantly differ between groups. However, poor glycemic control [HbA1c >7.5% (58 mmol/mol)] was more prevalent among subjects with type 1 diabetes. Type 1 diabetes represents a chronic hyperglycemic state and subjects with type 1 diabetes comprising this sample experienced a longer duration of diabetes. The chronic insulin-resistant state prior to overt type 2 diabetes development and the higher BMI could account for the low HDL in subjects with type 2 diabetes. Significant differences in baseline HDL concentrations among individuals with and without incident type 2 diabetes has been observed by Mackey et al. in a large multi-ethnic population of adults [12]. The Helsinki heart study has established a strong negative association between HDL and CVD risk even after adjusting for other risk factors [35].

In an effort to delineate a potential contribution due to patient demographic characteristics (i.e. race and sex), we evaluated the contribution of these variables. Historically Blacks have higher HDL concentrations compared to Whites [36]. Low HDL cholesterol is closely related to degree of insulin resistance [15]. We did not find any race differences in HDL between overweight and obese White and Black adolescents (data not shown). This is surprising given that only 19% of children with type 1 diabetes were Black when compared to 83% of children with type 2 diabetes in our study and may indicate that with increasing BMI the typically higher HDL concentrations attenuated in Blacks.

Relative to subjects with type 2 diabetes, those with type 1 diabetes displayed lower levels of apoB100, after adjusting for potential confounding factors, with the exception of inclusion of BMI. ApoB100 binds in a 1:1 ratio each circulating pro-atherogenic moiety, (LDL, VLDL, and IDL), and therefore, mirrors the total burden of the atherogenic cholesterol in the circulation. Increased serum apoB100 concentrations are established to be strong predictors for ischemic cardiovascular events [37]. Our findings coincide with that of a recent study reporting greater elevated apoB100 in children with type 2 diabetes relative to children with type 1 diabetes [30]. Obesity is also an established risk factor for cardiovascular disease, which may have accounted for the greater apo B100 levels in subjects with type 2 diabetes. Further research on the use of apoB100 in diabetes as biomarker for consideration of more aggressive lipid management in children with type 2 diabetes may be warranted.

We found no diabetes type-specific difference in lipoprotein (a) [Lp(a)], which is an LDL-like particle containing one molecule of apoB100 linked to apolipoprotein (a) [apo(a)]. Lp(a) levels are considered an independent risk factor for cardiovascular disease in the general population [38] and in individuals with both type 1 and type 2 diabetes [39,40]. Several meta-analyses have provided support for an association between Lp(a) and CVD [41–44]. It remains unclear as to whether Lp(a) causally affects increased CVD risk in patients with diabetes [45]. To our knowledge, this is the first study which has assessed information on Lp(a) in exclusively children with either type of diabetes who are also overweight or obese.

Obesity has been shown to have a particularly deleterious effect on concentration of lipoproteins in patients with type 2 diabetes [46]. We found that BMI was not only correlated with greater apoB100 concentration and LDL pattern B occurrence, but also lower HDL, and HDL subfractions. Obesity, and, circulating levels of the adipokines (i.e., high leptin and low adiponectin), may activate the inflammatory cascade, as well as contribute to decreased capacity for peripheral glucose uptake [47]. Patients with type 2 diabetes often have hyperinsulinemia, which is known to be associated with excess adiposity, and often as consequence, insulin resistance [48], as do Black relative to White and female relative to male adolescents [49][50]. The strengths of this study include the use of comprehensive lipoprotein cholesterol profile analysis, enabling attainment of information on lipoprotein heterogeneity in the two groups of patients. The standard lipid panel may overlook CVD risk lipid abnormalities since absolute values reflect a conglomeration of distinct particles that vary widely in size, protein composition and function. Our study subjects included patients who were exclusively overweight or obese, thus limiting confounding due to differences in weight status. However, there were limitations, major one being the retrospective and cross sectional nature of the study. We were unable to obtain information on socioeconomic status of the subjects. Patients with type 1 diabetes were relatively younger and included more Whites and males relative to patients with type 2 diabetes. Estimates of LDL become increasingly inaccurate as TG level increases, which is particularly problematic for patients with diabetes, who typically have an increase in atherogenic TG-rich lipoprotein levels. However, our clinical laboratory performs direct LDL measurements and the reported values would not be influenced by the concurrent TG value. TG concentration was not used in these analyses as the fasting status at the time of lab draw could not be determined due to the retrospective nature of the study. Insulin resistance is a key determinant of diabetic dyslipidemia especially in type 2 diabetes, and, hence future studies including more robust insulin resistance indices would provide more insight into the diabetic dyslipidemia seen in obese and overweight children. Further, due to the multiple comparisons performed in the study, it is prudent to point out a potential for false positive findings; thus, interpretation of the data should be with caution.

Our results indicate the children with type 2 diabetes have significantly more adverse lipoprotein characteristics when compared to children who are overweight or obese with type 1 diabetes, independent of confounding variables including BMI. Improved glycemic control may be particularly beneficial for patients with type 2 diabetes for mitigation of CVD risk. Overweight/obesity is an important harbinger of health, and adequate control of weight status (i.e., BMI) may improve the lower HDL seen in children with type 2 diabetes as previously reported in adults. These findings highlight the importance of assessment of lipoprotein measures and implementing stricter therapeutic goals in lipoprotein management strategies and HbA1C target for reducing CVD risk in patients with type 2 diabetes.

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A.A. and L.H. conceived the study. J.P. and S.V. collected the data from electronic medical records. L.H. researched data and wrote the manuscript. A.A. and K.C. reviewed/edited the manuscript. All authors were involved writing the paper and had final approval of the submitted and published versions. All authors take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript. None of the authors have any potential conflicts of interest to disclose.

References

1. Berry C, Tardif JC, Bourassa MG. Coronary heart disease in patients with diabetes: part I: recent advances in prevention and noninvasive management. *J Am Coll Cardiol.* 2007; 49:631–642. [PubMed: 17291928]
2. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, et al. Excess Mortality among Persons with Type 2 Diabetes. *N Engl J Med.* 2015; 373:1720–1732. [PubMed: 26510021]
3. Libby P, Nathan DM, Abraham K, Brunzell JD, Fradkin JE, et al. Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus. *Circulation.* 2005; 111:3489–3493. [PubMed: 15983263]
4. Winocour PH, Durrington PN, Ishola M, Anderson DC. Lipoprotein abnormalities in insulin-dependent diabetes mellitus. *Lancet.* 1986; 1:1176–1178. [PubMed: 2871420]
5. Verges B. Lipid disorders in type 1 diabetes. *Diabetes Metab.* 2009; 35:353–360. [PubMed: 19733492]
6. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, et al. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia.* 2003; 46:760–765. [PubMed: 12774166]
7. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA.* 2014; 311:1778–1786. [PubMed: 24794371]
8. Kwiterovich PO, Gidding SS. Universal screening of cholesterol in children. *Clin Cardiol.* 2012; 35:662–664. [PubMed: 22930527]
9. McMahan CA, Gidding SS, McGill HC Jr. Coronary heart disease risk factors and atherosclerosis in young people. *J Clin Lipidol.* 2008; 2:118–126. [PubMed: 21291730]
10. Gylling H, Tuominen JA, Koivisto VA, Miettinen TA. Cholesterol metabolism in type 1 diabetes. *Diabetes.* 2004; 53:2217–2222. [PubMed: 15331530]
11. Maahs DM, Maniatis AK, Nadeau K, Wadwa RP, McFann K, et al. Total cholesterol and high-density lipoprotein levels in pediatric subjects with type 1 diabetes mellitus. *J Pediatr.* 2005; 147:544–546. [PubMed: 16227045]
12. Mackey RH, Mora S, Bertoni AG, Wassel CL, Carnethon MR, et al. Lipoprotein particles and incident type 2 diabetes in the multi-ethnic study of atherosclerosis. *Diabetes Care.* 2015; 38:628–636. [PubMed: 25592196]
13. Ginsberg HN. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid trial: what we learn from subgroup analyses. *Diabetes Care.* 2011; 34(Suppl 2):S107–108. [PubMed: 21525439]
14. Burns SF, Lee S, Bacha F, Tfayli H, Hannon TS, et al. Pre-diabetes in overweight youth and early atherogenic risk. *Metabolism.* 2014; 63:1528–1535. [PubMed: 25240909]
15. Casavalle PL, Lifshitz F, Romano LS, Pandolfo M, Caamano A, et al. Prevalence of dyslipidemia and metabolic syndrome risk factor in overweight and obese children. *Pediatr Endocrinol Rev.* 2014; 12:213–223. [PubMed: 25581987]
16. Kit BK, Kuklina E, Carroll MD, Ostchega Y, Freedman DS, et al. Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999–2012. *JAMA Pediatr.* 2015; 169:272–279. [PubMed: 25599372]
17. Krochik AG, Botto M, Bravo M, Hepner M, Frontroth JP, et al. Association between insulin resistance and risk of complications in children and adolescents with type 1 diabetes. *Diabetes Metab Syndr.* 2015; 9:14–18. [PubMed: 25450815]
18. Hamman RF, Bell RA, Dabelea D, D'Agostino RB Jr, Dolan L, et al. The SEARCH for Diabetes in Youth study: rationale, findings, and future directions. *Diabetes Care.* 2014; 37:3336–3344. [PubMed: 25414389]
19. Maahs DM, Dabelea D, D'Agostino RB Jr, Andrews JS, Shah AS, et al. Glucose control predicts 2-year change in lipid profile in youth with type 1 diabetes. *J Pediatr.* 2013; 162:101–107. e101. [PubMed: 22795314]

20. Krishnan S, Copeland KC, Bright BC, Gardner AW, Blackett PR, et al. Impact of type 1 diabetes and body weight status on cardiovascular risk factors in adolescent children. *J Clin Hypertens* (Greenwich). 2011; 13:351–356. [PubMed: 21545396]
21. Braun LT, Rosenson RS. Assessing coronary heart disease risk and managing lipids. *Nurse Pract*. 2001; 26:30–32. 34, 37–41. quiz 42–33.
22. Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, et al. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. *Diabetes*. 2003; 52:453–462. [PubMed: 12540621]
23. Festa A, Williams K, Hanley AJ, Otvos JD, Goff DC, et al. Nuclear magnetic resonance lipoprotein abnormalities in prediabetic subjects in the Insulin Resistance Atherosclerosis Study. *Circulation*. 2005; 111:3465–3472. [PubMed: 15983261]
24. Lorenzo C, Hartnett S, Hanley AJ, Rewers MJ, Wagenknecht LE, et al. Impaired fasting glucose and impaired glucose tolerance have distinct lipoprotein and apolipoprotein changes: the insulin resistance atherosclerosis study. *J Clin Endocrinol Metab*. 2013; 98:1622–1630. [PubMed: 23450048]
25. Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents, National Heart L, Blood I. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011; 128(Suppl 5):S213–256. [PubMed: 22084329]
26. Jenkins, AJ., Toth, PP., Lyons, TJ. *Lipoproteins in Diabetes Mellitus*. Springer; New York: 2014.
27. Sparks JD, Sparks CE, Adeli K. Selective hepatic insulin resistance, VLDL overproduction, and hypertriglyceridemia. *Arterioscler Thromb Vasc Biol*. 2012; 32:2104–2112. [PubMed: 22796579]
28. Nesto RW. Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. *Am J Cardiovasc Drugs*. 2005; 5:379–387. [PubMed: 16259526]
29. Krauss RM. Triglycerides and atherogenic lipoproteins: rationale for lipid management. *Am J Med*. 1998; 105:58S–62S. [PubMed: 9707269]
30. Albers JJ, Marcovina SM, Imperatore G, Snively BM, Stafford J, et al. Prevalence and determinants of elevated apolipoprotein B and dense low-density lipoprotein in youths with type 1 and type 2 diabetes. *J Clin Endocrinol Metab*. 2008; 93:735–742. [PubMed: 18089692]
31. Jang EH, Park YM, Hur J, Kim MK, Ko SH, et al. Higher levels of small dense low-density lipoprotein (LDL) are associated with cardiac autonomic neuropathy in patients with type 2 diabetes. *Diabet Med*. 2013; 30:694–701. [PubMed: 23506430]
32. Shamir R, Kassis H, Kaplan M, Naveh T, Shehadeh N. Glycemic control in adolescents with type 1 diabetes mellitus improves lipid serum levels and oxidative stress. *Pediatr Diabetes*. 2008; 9:104–109. [PubMed: 18221422]
33. Dunn FL. Management of dyslipidemia in people with type 2 diabetes mellitus. *Rev Endocr Metab Disord*. 2010; 11:41–51. [PubMed: 20221703]
34. Joyce N, Wellenius GA, Dore DD, Newburger JW, Zachariah JP. Patterns of Lipid Lowering Therapy among Children Ages 8–20 Years. *J Pediatr*. 2015
35. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation*. 1992; 85:37–45. [PubMed: 1728471]
36. Bachorik PS, Lovejoy KL, Carroll MD, Johnson CL. Apolipoprotein B and AI distributions in the United States, 1988–1991: results of the National Health and Nutrition Examination Survey III (NHANES III). *Clin Chem*. 1997; 43:2364–2378. [PubMed: 9439456]
37. Stettler C, Suter Y, Allemann S, Zwahlen M, Christ ER, et al. Apolipoprotein B as a long-term predictor of mortality in type 1 diabetes mellitus: a 15-year follow up. *J Intern Med*. 2006; 260:272–280. [PubMed: 16918825]
38. McNeal CJ. Lipoprotein(a): Its relevance to the pediatric population. *J Clin Lipidol*. 2015; 9:S57–66. [PubMed: 26343213]
39. Mackey RH, McTigue KM, Chang YF, Barinas-Mitchell E, Evans RW, et al. Lipoprotein particles and size, total and high molecular weight adiponectin, and leptin in relation to incident coronary

- heart disease among severely obese postmenopausal women: The Women's Health Initiative Observational Study. *BBA Clin.* 2015; 3:243–250. [PubMed: 25825692]
40. Koschinsky ML, Marcovina SM. The relationship between lipoprotein(a) and the complications of diabetes mellitus. *Acta Diabetol.* 2003; 40:65–76. [PubMed: 12861403]
41. Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, et al. Emerging Risk Factors C. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA.* 2009; 302:412–423. [PubMed: 19622820]
42. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA.* 2009; 301:2331–2339. [PubMed: 19509380]
43. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med.* 2009; 361:2518–2528. [PubMed: 20032323]
44. Erqou S, Thompson A, Di Angelantonio E, Saleheen D, Kaptoge S, et al. Apolipoprotein(a) isoforms and the risk of vascular disease: systematic review of 40 studies involving 58,000 participants. *J Am Coll Cardiol.* 2010; 55:2160–2167. [PubMed: 20447543]
45. Qi Q, Qi L. Lipoprotein(a) and cardiovascular disease in diabetic patients. *Clin Lipidol.* 2012; 7:397–407. [PubMed: 23136583]
46. Laakso M, Pyorala K. Adverse effects of obesity on lipid and lipoprotein levels in insulin-dependent and non-insulin-dependent diabetes. *Metabolism.* 1990; 39:117–122. [PubMed: 2299984]
47. Ahima RS. Adipose tissue as an endocrine organ. *Obesity (Silver Spring).* 2006; 14(Suppl 5): 242S–249S. [PubMed: 17021375]
48. Vestergaard P, Jorgensen NR, Schwarz P, Mosekilde L. Effects of treatment with fluoride on bone mineral density and fracture risk--a meta-analysis. *Osteoporos Int.* 2008; 19:257–268. [PubMed: 17701094]
49. Sumner AE, Cowie CC. Ethnic differences in the ability of triglyceride levels to identify insulin resistance. *Atherosclerosis.* 2008; 196:696–703. [PubMed: 17254586]
50. Chen W, Bao W, Begum S, Elkasabany A, Srinivasan SR, et al. Age-related patterns of the clustering of cardiovascular risk variables of syndrome X from childhood to young adulthood in a population made up of black and white subjects: the Bogalusa Heart Study. *Diabetes.* 2000; 49:1042–1048. [PubMed: 10866058]

Table 1

Descriptive and clinical characteristics of children with type 1 and type 2 diabetes *

	Overall (n=236)	Type 1 (n=159)	Type 2 (n=77)	P-value
Age (12–19y)	15.2 (2.1)	15.0 (2.1)	15.6 (2.0)	0.0461
Male	39.8	44.0	31.2	0.0025
Black	40.3	19.2	83.1	<0.0001
Diabetes Duration (y)	5.0 (3.4)	6.0 (3.6)	2.8 (1.7)	<0.0001
BMI	30.5 (6.8)	27.6 (3.4)	36.5 (8.0)	<0.0001
%BMI	94.6 (4.3)	93.1 (4.1)	97.6 (3.1)	<0.0001
HbA1C (%)	8.9 (2.1)	9.1 (1.8)	8.6 (2.7)	0.1096
HbA1C (mmol/mol)	74 (46)	76 (40)	70 (59)	0.1096
Elevated HbA1C (≥ 7.5%)	76.1	86.1	55.3	<0.0001
Microalbumin:creatinine	10.9 (5.7, 22.0)	9.5 (5.3, 18.2)	11.6 (7.3, 34.7)	0.0659
Microalbuminuria (%)	20.7	16.9	30.4	0.0108

* All subjects were ≥ 85th BMI percentile.

Data are presented as frequency, mean (SD), or median (interquartile range).

Significant differences between groups were considered at $P \leq 0.05$.

Table 2

Differences in lipoprotein characteristics between children with type 1 and type 2 diabetes.

	Overall	Type 1 (n=159)	Type 2 (n=77)	Crude P-value	Adjusted P-value *	Adjusted P-value †	Adjusted P-value ‡	Adjusted P-value §
Total cholesterol (mg/dl)	178.2 (42.9)	179.2 (42.0)	176.1 (44.9)	0.6009	0.4405	0.5500	0.4962	0.7464
Elevated total (>200 mg/dl)	24.6	25.8	22.1	0.5370	0.4658	0.2626	0.3311	0.3227
LDL cholesterol (mg/dl)	104.1 (35.8)	103.1 (34.5)	106.2 (38.5)	0.5356	0.7339	0.4986	0.9907	0.3478
Elevated LDL (>130)	19.1	18.9	22.1	0.9110	0.9556	0.9678	0.8451	0.7324
Non-HDL cholesterol (mg/dl)	125.8 (40.9)	124.6 (40.0)	127.4 (42.9)	0.5014	0.6562	0.2801	0.8107	0.1579
ApoB100 (mg/dl)	87.5 (25.3)	85.7 (24.0)	91.3 (27.5)	0.1079	0.1555	0.0413	0.9660	0.0229
LDL pattern B (%)	28.0	21.4	41.6	0.0011	0.0018	0.0003	0.0112	0.0001
HDL cholesterol (mg/dl)	52.4 (14.6)	54.7 (14.5)	47.7 (13.7)	0.0005	0.0003	<0.0001	0.0041	<0.0001
Low HDL (<40)	21.2	17.0	29.9	0.0231	0.0200	0.0038	0.2906	0.0043
HDL-2 cholesterol (mg/dl)	13.7 (6.3)	14.6 (6.4)	11.9 (5.7)	0.0022	0.0029	<0.0001	0.0074	<0.0001
HDL-3 cholesterol (mg/dl)	38.6 (9.1)	40.4 (9.0)	35.8 (8.7)	0.0006	0.0002	<0.0001	0.0071	<0.0001
Lipoprotein (a) (mg/dl)	7 (5, 11)	7 (5, 11)	8 (5, 13)	0.7073	0.1195	0.9045	0.4777	0.8158

Group differences in models sequentially adjusting for:

1 age, sex,

2 age, sex,

3 age, sex, race,

4 age, sex, race, BMI,

5 age, sex, race, HbA1C,

6 age, sex, race, diabetes duration.

Significant differences between groups were considered at $P = 0.05$.

Table 3

Pearson correlations (r-value) of lipoprotein parameters with covariates of interest in the overall group (n=236) and by diabetes type.

Type	Duration	Age	Male sex	Black race	BMI	%BMI	HbA1c	Microalbuminuria
Total cholesterol								
Overall	0.03	0.06	-0.03	-0.15 [*]	-0.03	0.01	-0.004	0.38 [‡] 0.10
Type 1	0.05	0.04	-0.15	0.06	0.10	0.07	0.36 [‡]	0.11
Type 2	0.09	-0.15	-0.17	-0.15	-0.01	-0.12	0.42 [‡]	0.11
LDL cholesterol								
Overall	0.04	0.05	0.02	-0.14 [*]	-0.02	0.10	0.08	0.34 [‡] 0.10
Type 1	0.08	0.10	-0.12	-0.01	0.17 [*]	-0.13	0.30 [‡]	0.09
Type 2	0.09	-0.16	0.09	-0.15	0.04	-0.08	0.40 [‡]	0.11
Non-HDL cholesterol								
Overall	0.04	0.06	0.02	-0.11	-0.05	0.11	0.10	0.34 [‡] 0.08
Type 1	0.09	0.09	-0.10	-0.04	0.17 [*]	0.10	0.30 [‡]	0.07
Type 2	0.09	-0.15	0.09	-0.20	0.06	-0.01	0.42 [‡]	0.10
ApoB100								
Overall	0.11	0.03	0.02	-0.09	-0.03	0.17 [‡]	0.17 [*]	0.35 [‡] 0.10
Type 1	0.09	0.09	-0.07	-0.06	0.20 [‡]	0.18 [*]	0.31 [‡]	0.09
Type 2	0.09	-0.14	0.09	-0.20	0.09	0.04	0.43 [‡]	0.08
LDL pattern B								
Overall	0.21 [‡]	0.003	0.13 [*]	0.03	0.03	0.20 [‡]	0.27 [‡]	0.25 [‡] 0.08
Type 1	0.12	0.14	-0.03	-0.06	0.19 [*]	0.17 [*]	0.15 [*]	0.04
Type 2	0.11	0.04	0.23 [*]	-0.25 [*]	0.03	0.25 [*]	0.43 [‡]	0.04
HDL cholesterol								
Overall	-0.22 [‡]	0.01	-0.12	-0.14 [*]	0.04	-0.29 [‡]	-0.30 [‡]	0.17 [‡] 0.05
Type 1	-0.12	-0.14	-0.15 [*]	0.27 [‡]	-0.18 [*]	-0.17 [*]	0.22 [‡]	0.12
Type 2	-0.004	-0.001	-0.22 [*]	0.14	-0.24 [*]	-0.36 [‡]	0.06	0.05
HDL-2 cholesterol								

Type	Duration	Age	Male sex	Black race	BMI	%BMI	HbA1c	Microalbuminuria
Overall	-0.20 [†]	-0.16 [†]	-0.08	0.07	-0.27 [‡]	-0.28 [‡]	0.05	0.05
Type 1	-0.14 [#]	-0.20 [†]	-0.07	0.29 [†]	-0.23 [†]	-0.16 [*]	0.08	0.10
Type 2	-0.003	0.02	-0.21	0.13	-0.21	-0.37 [†]	-0.06	0.04
HDL-3 cholesterol								
Overall	-0.22 [‡]	0.03	-0.09	0.02	-0.27 [‡]	-0.28 [‡]	0.24 [‡]	0.06
Type 1	-0.09	-0.09	-0.20 [†]	0.23 [†]	-0.14	-0.16 [*]	0.29 [‡]	0.12
Type 2	-0.003	-0.02	-0.22	0.13	-0.24 [*]	-0.32 [†]	0.14	0.06

Children with type 1 (n=159) and type 2 (n=77) diabetes (all BMI 85th percentile).

^{*} *P* 0.05,

[†] *P* 0.01,

[‡] *P* 0.0001

Significance was considered at *P* 0.05.