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Higher hemoglobin A1C and atherogenic lipoprotein profiles in children and adolescents with type 2 diabetes mellitus

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ABSTRACT

Aim: Significant knowledge gaps exist regarding lipoprotein profiles in children with type 2 diabetes mellitus (T2DM). The primary objective was to analyze the type and nature of lipoprotein abnormalities present in children with T2DM and to identify determinants of adverse lipoprotein profiles. The secondary objective was to assess associations with elevated glycated hemoglobin (HbA1C), i.e., < 8% vs. ≥8.0% and pediatric dyslipidemias in the setting of T2DM.

Methods: This retrospective chart review included children with T2DM who had undergone lipoprotein analysis and were not on lipid lowering medications (n = 93).

Results: The participants (mean age 15.2 ± 2.7y) were 71% female and 78% African American (AA). Adjusted for age, sex, and race, BMI z-score was positively associated with LDL-pattern B (pro-atherogenic profile with small dense LDL particles) (P = 0.01), and negatively associated with total HDL-C (P = 0.0003). HbA1C was robustly positively associated with the LDL-C, apoB and LDL pattern B (all P < 0.001). Patients with an HbA1C > 8% had significantly higher total cholesterol (191.4 vs. 158.1 mg/dL, *P* = 0.0004), LDL-C (117.77 vs. 92.3 mg/dL, *P* = 0.002), apoB (99.5 vs. 80.9 mg/dL, *P* = 0.002), non-HDL-C (141.5 vs. 112.5, *P* = 0.002), and frequency of LDL pattern B (57% vs. 20%, *P* = 0.0008).

Conclusion: HbA1C and BMI were associated with adverse lipoprotein profiles, and may represent two major modifiable cardiovascular risk factors in the pediatric T2DM population. Patients with an HbA1C higher than 8.0% had significantly worse atherogenic lipid profile, i.e., higher LDL-C, non-HDL-C, apoB and LDL pattern B, suggesting adequate glycemia may improve adverse lipoprotein profiles.

Introduction

Alarmingly, there has been a significant increase in the incidence of type 2 diabetes mellitus (T2DM) in children [1,2], in parallel with increasing rates of childhood obesity, over the past three decades [3]. This increase has been even more dramatic among African Americans (AA) [4]. T2DM is associated with high morbidity and mortality secondary to cardiovascular disease (CVD). This association has significant pathologic implications in pediatrics where, earlier onset (exposure) and accelerated progression of atherosclerosis has a profound impact on mortality and quality of life [3]. The clustering of risk factors such as insulin resistance, increased body mass index (BMI), and physical inactivity are more prevalent in children with T2DM than in those with T1DM [5,6] and has generated significant information on the pathophysiologic link between T2D and CVD. Moreover, overweight/obese children with T2DM have a higher risk of adverse lipoprotein profiles compared to overweight/obese T1DM children [7].

Dyslipidemia associated with T2DM have been attributed to increased free fatty acid (FFA) flux from adipocytes secondary to insulin resistance and hepatic esterification of FFA to triglyceride (TG). This, in turn, augments very low density lipoprotein cholesterol (VLDL-C) and apolipoprotein B (apoB) 100 synthesis. VLDL-C hydrolysis produces intermediate density lipoprotein cholesterol (IDL-C) and low density lipoprotein cholesterol (LDL-C). Subsequently, VLDL triglyceride is exchanged for cholesteryl ester transported in HDL, leading to easily degradable HDL particles. This noxious cascade of reactions decreases the concentration of HDL-C, increases the concentration of small dense LDL-C, and increases plasma TG [8–10]. Alongside other researchers, our group has previously demonstrated that poor lipid profiles are influenced by glycemic control in a pediatric population [11,12].

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Notwithstanding the concern surrounding the impact of hyperglycemia on microvascular and macrovascular diabetic complications, there is a significant gap in knowledge regarding dyslipidemia in children with T2DM, in particular the more granular measures of lipids—e.g. LDL pattern, apoB, lipoprotein particle number and size. Current practice guidelines for the screening and clinical management of dyslipidemia in T2DM are based on standard lipid profile measurement, not lipoprotein measurements. The characterization of lipoprotein composition or components, i.e., apoB, LDL density patterns, HDL subtypes, or lipoprotein (a) [Lp (a)] is poorly defined in children with T2DM. ApoB has been shown in epidemiological studies to be significantly elevated in children with T2DM despite normal concentrations of LDL-C [13]. The number and size of LDL particles play a role in atherogenicity [8,14–16]. To our knowledge, few studies have reported on the lipoprotein profiles of children with T2DM [7,12,13].

The primary objective of this study was to describe the characteristics of lipoprotein abnormalities in a pediatric population with T2DM. Secondary aims included evaluating factors influencing lipoprotein variables and assessing whether lipoprotein profiles differ among subjects based on durable glycemic control (i.e., HbA1C < 8% vs. HbA1C ≥8.0%).

Methods

Subjects

This retrospective electronic medical record (EMR) review was conducted on children and adolescents with T2DM who were managed at the Department of Pediatric Endocrinology at Children's of Alabama, University of Alabama at Birmingham (UAB). After IRB approval, data was obtained from the EMR using the International Classification of Diseases (ICD-9-CM) diagnosis codes of 250.00 and 250.02 to identify all potentially eligible patients with physician-ascertained diagnosis of T2DM. Patient records over an eight-year period of time, 2007–2014, were abstracted. Inclusion criteria of patients with physician-ascertained diagnosis of T2DM were: 1) HbA1c ≥6.5% at the initial visit [17], 2) BMI ≥95th percentile for age and sex, and 3) availability of a lipoprotein analysis. Exclusion criteria included: 1) missing data on initial height or weight, 2) patients with T1DM, 3) an equivocal type of DM with characteristics of both T1DM and T2DM 4) with new onset hypothyroidism diagnosed at the time of lipid profile testing, and 5) use of lipid lowering (i.e., statins or fibrates) or blood pressure lowering medications, oral contraceptives or oral steroids. In addition, subjects with triglycerides > 400 mg/dL were also excluded as this value would interfere with the LDL calculation. Insulin dependent patients with diabetes were considered to have T1DM if they had a physician ascertained diagnosis of T1DM and presence of at least one positive autoimmune markers against islet cell, GAD-65, or IA-2 at diagnosis or at follow-up. Of the 216 patients with a diagnosis of T2DM, 93 patients met the inclusion and exclusion criteria. A total of 96 patients had vertical auto profile (VAP) lipoprotein analysis, 2 were excluded due to having serum TG > 400 mg/dL and one patient was excluded due to being on lipid lowering medication even prior to diagnosis of T2DM. Due to the demographics of patients attending the Children's Hospital, we lacked sufficient sample sizes of Hispanic (n = 2), Asian (n = 1) or other non-AA minority group children (n = 0) with T2DM who had a VAP lipoprotein analysis, and these children were also excluded. For patients who had multiple lipoprotein measurements, the initial lipoprotein measurement after the first year of T2DM diagnosis was collected.

All children and adolescents with T2DM received similar diabetes, nutrition, and physical activity counselling as per UAB Division of Endocrinology protocol. Insulin treatment was initiated according to the judgment of the attending physician and, was dependent on the levels of HbA1C. Briefly, the management in our center is summarized as follows: 1) metformin + a long acting insulin (glargine/determir 0.3–0.5 u/kg/day) along with meal bolus (0.3–0.5 u/kg/day) and correction factor with rapid acting analogue insulin (lispro or aspart) for patients with HbA1C > 9.0%, 2) metformin + a long acting insulin + correction doses of rapid acting insulin for hyperglycemia without prandial doses for those patients with HbA1C > 7.5% 3) metformin alone for patients with HbA1C < 7.5%.

BMI for age and sex was calculated according to the Centers for Disease Control and Prevention growth charts [18]. A systolic or diastolic blood pressure (SBP or DBP) ≥95th percentile for age, gender, and height was classified as hypertension according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents [19].

In addition to standard lipid profile testing, the clinical laboratory at Children's of Alabama also offered VAP testing (through a commercial lab, Atherotech, Birmingham, AL) which is ordered based on the preference of the attending physician. VAP is a density gradient rapid ultracentrifugation method that yields additional lipoprotein characterization such as LDL density pattern (Pattern A, Pattern B, or Pattern A/B), HDL subclasses, apoB and Lp(a), in addition to TC, LDL-C and HDL-C present in the standard lipid profile. LDL cholesterol was directly measured. The VAP procedure has been described in detail previously [20,21]. The following correlation coefficients (r) were obtained by comparing VAP method with beta-quant method performed in an external laboratory: total cholesterol, 0.99; HDL cholesterol, 0.99; LDL cholesterol, 0.98; VLDL cholesterol, 0.98; IDL cholesterol, 0.78; Lp(a) cholesterol, 0.77; HDL_2 cholesterol, 0.94, and HDL_3 cholesterol, 0.91. The VAP results are also highly reproducible with the following typical between-days: coefficient of variation: total cholesterol, 2.0%; HDL cholesterol, 2.9%; LDL cholesterol, 2.1%; VLDL cholesterol, 2.8%; IDL cholesterol, 8.2%; Lp(a) cholesterol, 9.1%; HDL_2 cholesterol, 9.2%, and HDL_3 cholesterol, 2.5%. Based on density ultracentrifugation, LDL particles are classified into pattern A (large, buoyant LDL particles), pattern B (small, dense LDL particles) and AB (intermediate), and HDL particles to HDL 2 (large buoyant) and HDL3 (small dense). HDL2 is thought to be more cardio-protective. Atherogenic dyslipidemia is a triad of elevated serum TG levels, decreased HDL and higher number of small, dense LDL [10,22]. ApoB was calculated by the laboratory using separate equations for each LDL patterns A, A/B, and B (US patent no. 7521248; 2009). The modified equations were validated by comparing VAP apoB obtained using serum samples from 1517 patients with apoB measured by immunoturbidometric method (Abbott Architect Analyzer) using the same samples (correlation coefficient of 0.97 with a slope of 0.93, an intercept of 5.9 mg/dl, and a bias of 0.9%).

As the fasting status could not be guaranteed due to the retrospective nature of the study, we excluded triglycerides and IDL from analysis. LDL-C ≥130 mg/dL and non-HDL-C ≥145 mg/dL were deemed elevated [23]. HbA1C values measured by DCA Vantage analyzer were determined concurrently with the lipid profile measurements. The intra- and interassay coefficients of variation for the DCA Vantage assay was 3.0–4.0% and the multiple instrument comparisons was within the allowable error of ± 10%. The HbA1C cut off point of 8% was chosen to assess the differences in lipoprotein concentrations, based on durable glycemic control defined by the TODAY trial [24].

Statistics

Descriptive statistics were computed for the overall sample and stratified by race and sex. The Kolmogorov-Smirnov test and graphical inspections of data were conducted to evaluate normality of distributions. Unpaired independent sample t-tests were then used to identify differences between groups. Associations of BMI and HbA1C with lipid phenotypes were evaluated using generalized linear models, adjusted for race, age at diagnosis, and sex. Differences in lipoprotein parameters were also evaluated based on the HbA1c cutoff of 8% using t-tests for continuous variables and chi square tests for categorical variables. Occurrence of elevated non-HDL (≥145 mg/dl) was also compared to

Table 1
Descriptive Characteristics of Children with Type 2 Diabetes.

Variable	Total (n = 93)	AA	EA	P-value	Males	Females	P-value
Age (years)	15.2 ± 2.7	15.3 ± 2.6	14.7 ± 3.2	0.35	**16.5 ± 1.9**	**14.7 ± 2.8**	**0.002**
Diabetes duration (years)	2.7 ± 1.7	2.7 ± 1.7	2.9 ± 2.1	0.69	2.8 ± 1.7	2.7 ± 1.7	0.81
Gender							
Females, n (%)	66 (71)	52 (56)	14 (15)	0.92	N/A	N/A	N/A
Males, n (%)	27 (29)	21 (23)	6 (6)				
Race							
EA, n (%)	20 (22)	N/A	N/A	N/A	22	21	0.92
AA, n (%)	73 (78)				78	79	
Weight (kg)	96.5 ± 26.8	101.7 ± 35.7	90.8 ± 38.7	0.27	113.7 ± 49.2	93.5 ± 28.1	**0.05**
Height (cm)	164.6 ± 10.2	165.4 ± 8.6	161.8 ± 14.5	0.17	**172.0 ± 7.1**	**161.5 ± 9.7**	**< 0.001**
BMI %	96.9 ± 4.8	97.3 ± 4.5	95.4 ± 5.4	0.12	96.6 ± 6.7	97.0 ± 3.7	0.76
BMI z-score	2.1 ± 0.5	2.2 ± 0.5	1.9 ± 0.6	0.12	2.2 ± 0.6	2.1 ± 0.5	0.67
Systolic blood pressure (mmHg)	124.9 ± 16.7	124.9 ± 16.4	124.9 ± 18.3	0.99	**134.0 ± 13.1**	**121.4 ± 16.7**	**0.001**
Diastolic blood pressure (mmHg)	68.9 ± 9.1	69.3 ± 9.1	67.4 ± 9.4	0.43	70.9 ± 9.7	68.1 ± 8.9	0.18
Total cholesterol (mg/dl)	173.1 ± 43.2	170.2 ± 42.8	184.0 ± 44.4	0.21	163.2 ± 35.9	177.2 ± 45.5	0.16
LDL-cholesterol (mg/dl)	103.8 ± 37.6	100.9 ± 37.6	114.4 ± 36.4	0.16	96.0 ± 28.6	107.0 ± 40.4	0.20
HDL-cholesterol (mg/dl)	47.5 ± 13.2	48.6 ± 13.3	43.9 ± 12.2	0.16	44.1 ± 64.1	49.0 ± 14.0	0.10
Non-HDL (mg/dl)	125.6 ± 41.9	121.6 ± 41.4	140.2 ± 41.7	0.08	119.1 ± 33.3	128.2 ± 45.0	0.34
Total Cholesterol/HDL-C	3.8 ± 1.2	**3.7 ± 1.1**	**4.4 ± 1.3**	**0.01**	3.8 ± 1.0	3.8 ± 1.3	0.96
Apo B 100 (mg/dl)	89.3 ± 26.9	**86.7 ± 26.6**	**98.7 ± 26.4**	**0.01**	85.9 ± 20.1	90.7 ± 29.3	0.43
Lp(a) (mg/dl)	9.5 ± 7.3	10.1 ± 7.9	7.4 ± 3.9	0.15	8.6 ± 5.6	9.8 ± 7.9	0.45
HDL 2 (mg/dl)	11.9 ± 5.6	12.3 ± 5.7	10.3 ± 5.0	0.15	10.6 ± 5.2	12.4 ± 5.7	0.16
HDL 3 (mg/dl)	35.7 ± 8.3	36.2 ± 8.4	33.6 ± 7.9	0.21	33.4 ± 6.2	36.6 ± 8.9	0.10
LDL Pattern, n (%)							
A	45 (48)	39 (42)	6 (6)		12 (13)	33 (35)	
B	34 (37)	24 (26)	10 (11)	0.08	14 (15)	20 (22)	0.20
A/B	14 (15)	10 (11)	4 (4)		1 (1)	13 (14)	
VLDL (mg/dl)	21.8 ± 10.0	**20.7 ± 10.1**	**25.9 ± 8.3**	**0.04**	23.3 ± 13.6	21.2 ± 8.1	0.37
VLDL-3 (mg/dl)	11.8 ± 3.9	**11.3 ± 4.0**	**13.5 ± 3.2**	**0.03**	12.1 ± 4.4	11.7 ± 3.9	0.66
HbA1c (%)	8.3 ± 2.6	8.4 ± 2.7	7.9 ± 2.3	0.48	8.8 ± 3.0	8.0 ± 2.4	0.19

Legend: Significant (P < 0.05) differences are in bold. Values are expressed as mean ± SD.
BMI: body mass index, HDL-C: high density lipoprotein cholesterol.

the standard cut-off for elevated LDL (≥130 mg/dl). All statistical tests were two-sided and performed using SAS software (version 9.3; SAS Institute, Inc., Cary, NC). An alpha of < 0.05 was considered significant.

Results

Demographic and clinical characteristics of the sample population are presented in Table 1. The participants were 71% females and 29% males and 78% African American (AA) and 22% European American (EA). The mean age of the cohort was 15.2 ± 2.7 years, mean BMI percentile was 97% and mean BMI z-score was 2.1 ± 0.05. Males were older (17 vs. 15y, $P < 0.01$), heavier (113.7 kg vs. 93.5 kg, $P = 0.05$) and taller (172.0 vs. 161.5 cm, $P < 0.001$) than females, and had higher SBP (134.0 vs. 121.4 mmHg, $P < 0.01$). There were no sex differences in lipoprotein measures between males and females. AA had lower HDL:TC (3.7 vs. 4.4, P = 0.01), VLDL (20.7 vs. 25.9 mg/dl, $P = 0.04$), and VLDL-3 (11.3 vs. 13.5 mg/dl, $P = 0.03$).

The correlation between concentration of LDL-C and non-HDL-C was predictably high, 98%. Similarly, apoB concentration was correlated with both serum levels of LDL-C and non-HDL-C, also with over 96% correlation. Overall, 17 patients (18% of patients) had elevated LDL-C ≥130 mg/dL. Of those, 10 had LDL pattern B (4 had A, 3 had AB) and 10 had non-HDL-C ≥145 mg/dL. There were 24 patients (25.8%) who had non-HDL-C ≥145 mg/dL and 37 patients (39%) with LDL pattern B (Table 1).

Table 2 illustrates associations of lipoprotein variables with obesity (ascertained by BMI z-score) and HbA1C, adjusted for age, sex, and race. BMI z-scores were positively associated with frequency of LDL pattern B ($P = 0.01$), and negatively associated with total as well as subfractions of HDL-C (HDL-C $P = 0.0003$, HDL 2 $P = 0.0004$, HDL 3 $P = 0.0009$). HbA1C was robustly positively associated with total LDL-C ($P = < 0.0001$), apoB ($P = < 0.0001$) and LDL-pattern B ($P < 0.0001$).

Table 2
Associations of lipoprotein components with body mass index z-score and glycemic control in pediatric patients with T2DM, adjusted for age, sex, and race.

Lipoproteins	BMI Z-score		HbA1C	
	β (SE)	P-value	β (SE)	P-value
LDL-C	0.002 (0.002)	0.34	0.003 (0.0008)	**< 0.0001**
ApoB	0.004 (0.002)	0.07	0.005 (0.001)	**< 0.0001**
HDL-C	−0.02 (0.004)	**0.0003**	0.003 (0.002)	0.35
LDL (A, AB, or B)	0.16 (0.06)	**0.01**	0.165 (0.03)	**< 0.0001**
HDL2	−0.04 (0.01)	**0.0004**	−0.001 (0.006)	0.80
HDL3	−0.02 (0.007)	**0.0009**	0.007 (0.004)	0.09

Legend: Significant (P < 0.05) associations are in bold. Values are expressed as mean ± SE.
BMI: Body mass index, HbA1C: glycosylated hemoglobin, T2DM: type 2 diabetes.

Table 3 summarizes the differences in lipoproteins in patients with an HbA1C < 8% vs. > 8%. Patients with an HbA1C > 8% had a higher total serum cholesterol (191.4 vs. 158.1 mg/dL, $P = 0.0004$), LDL (91.7 vs. 92.3 mg/dL, $P = 0.002$), apoB (99.5 vs. 80.9 mg/dL, $P = 0.002$), non-HDL (141.5 vs. 112.5, $P = 0.002$), and frequency of LDL pattern B (57% vs. 20%, $P = 0.0008$). In addition, patients with HbA1C > 8% also had higher diastolic blood pressure ($P = 0.0008$).

Discussion

It is well known that atherogenic dyslipidemia of insulin resistance [25] is worsened by glucotoxicity and lipotoxicity of T2DM leading to accelerated CVD risk [9]. In this study, we found that BMI z-scores influenced atherogenic lipoprotein profiles, i.e., positive association

Table 3
Characteristics of patients by A1C ≤8% vs > 8%.

Variable	A1C ≤8% Mean ± SD (n = 51)	A1C > 8% Mean ± SD (n = 42)	P Value
Age (years)	14.7 ± 2.9	15.8 ± 2.3	**0.04**
Females, n (%)	38 (75)	28 (67)	0.41
AA, n (%)	39 (76)	34 (81)	0.60
Weight (Kg)	100.39 ± 43.2	98.1 ± 26.3	0.76
BMI z-score	2.2 ± 0.6	2.1 ± 0.5	0.62
BMI (kg/m^2)	35.0 ± 8.4	35.5 ± 8.7	0.79
Systolic BP (mmHg)	121.9 ± 18.4	128.7 ± 13.7	0.05
Diastolic BP (mmHg)	66.0 ± 8.5	72.5 ± 8.7	**0.0008**
Diastolic hypertension, n (%)	2 (4)	5 (12)	0.14
Systolic hypertension, n (%)	18 (35)	16 (39)	0.71
Total cholesterol (mg/dL)	158.1 ± 31.4	191.4 ± 48.7	**0.0004**
LDL-C (mg/dL)	92.3 ± 27.5	117.7 ± 43.4	**0.001**
LDL pattern A, n (%)	32 (63)	13 (31)	
LDL pattern AB, n (%)	9 (18)	5 (12)	
LDL pattern B, n (%)	10 (20)	24 (57)	**0.0008***
ApoB	80.9 ± 19.0	99.5 ± 31.5	**0.002**
Triglycerides (mg/dL)	121.5 ± 73.8	160.4 ± 112.6	0.06
HDL-C (mg/dL)	45.7 ± 13.1	49.8 ± 13.0	0.13
HDL2	11.5 ± 5.6	12.3 ± 5.6	0.50
HDL3	34.1 ± 8.2	37.6 ± 8.2	0.05
Non-HDL-C (mg/dL)	112.5 ± 30.0	141.5 ± 48.6	**0.002**
Lp(a)	9.1 ± 6.4	10.0 ± 8.3	0.59
TC/HDL-C	3.7 ± 1.1	4.0 ± 2.0	0.15

Legend: Significantly different variables are in bold. Values are expressed as mean ± SD.

* The value corresponds to the comparison of the overall lipoprotein pattern (A, AB, or B) across the two glycemic control groups.

with apoB and LDL pattern B and negative association with HDL-C subtractions in children with T2DM. HDL subfractions, HDL 2 and HDL 3 (smaller), are antiatherogenic, especially HDL 2. We also found that patients with HbA1C > 8% had more atherogenic lipoprotein profiles, i.e., higher LDL-C, apoB, non-HDL-C, LDL pattern B, when compared to those with HbA1C < 8%. Since children with T2DM have multiple CVD risk factors beyond hyperglycemia, it is essential to encourage tight management of blood glucose. Improved glycemic control and weight loss may be particularly beneficial for patients with T2DM who are obese, for mitigation of CVD risk. Our study also indicates that an LDL-C based treatment cutoff may not be sufficient for assessing dyslipidemia in children and adolescents with T2DM. Triglyceride-rich lipoproteins (chylomicrons and VLDL) are central to the dyslipidemia of type 2 diabetes. The ongoing transfer of triglycerides and cholesteryl ester between the circulating pool triglyceride rich lipoproteins, remnant lipoproteins, and LDL and HDL particles makes it difficult to accurately estimate the CV risk by LDL-C concentrations alone. Therefore, a 'normal' LDL concentration does not capture the atherogenic burden caused by the increased small dense LDL and increased apoB particles. There are emerging data on the benefits of targeting lipoproteins other than LDL-C in adult patients with T2DM and insulin resistance [26–28].

Our study illustrates significant differences in LDL pattern B (representing small, dense LDL particles) and other lipoproteins based on HbA1C. Those with HbA1C > 8% had adverse lipoprotein abnormalities, i.e. higher total cholesterol, LDL-C, apoB, non-HDL-C, and frequency of LDL pattern B compared to patients with lower HbA1C, representing a need for strict glycemic control for CV risk reduction in that population. Moreover, patients with elevated HbA1C also had higher diastolic blood pressure, yet another cardiovascular risk factor.

Our group has previously demonstrated that overweight and obese children with T2DM have significantly more atherogenic lipoprotein profiles even when compared to overweight and obese children with T1DM [7], suggesting an inherently increased risk for atherogenicity in children with T2DM. This has been also supported by a larger multicenter trial [12]. Along with other studies, this study supports the indication of aggressive glycemic control in children with T2DM, a high risk population for CVD. More prospective studies are needed to demonstrate whether altered lipoprotein profiles improve solely by achieving normoglycemia in patients with uncontrolled T2DM.

Conventional clinical management of dyslipidemia in pediatrics primarily involves an evaluation of LDL-C and TG. Lack of a detailed lipoprotein analysis, including apoB measurements, may underestimate the severity of dyslipidemia in children and adolescents with T2DM. In a sample population of Canadian First Nation youth with T2DM, apoB was significantly elevated [29], while serum concentrations of LDL-C were normal. In our study, even though only 18% of patients had elevated LDL-C > 130 mg/dL and 26% of patients had non-HDL-C ≥145 mg/dL, 37 patients (39%) had LDL pattern B. Therefore, an LDL-C based treatment cutoff may not be sufficient for assessing dyslipidemia. It is important to establish data on longitudinal analysis of lipoprotein profiles in children with T2DM and to determine whether improved glycemic control can ameliorate the atherogenic dyslipidemia.

Notable limitations of this study included limited sample size, lack of generalizability due to the relatively small sample size and the exclusion of other ethnic groups (Hispanic, Asian, and other non-AA minority groups), retrospective and cross-sectional nature, which prevented us from ascertaining causality. Serum TG concentration was not included in our analyses because fasting status of subjects could not be determined. Moreover, metformin that is commonly prescribed to children with T2DM can influence insulin resistance and thus lipid outcomes. Due to the retrospective nature of the study we do not have the information on medication adherence, dietary habits and physical activity. Retrospective nature of the study also precluded the use of insulin resistance indices and ability to identify patients with familial hyperlipidemias. The main inclusion criteria, i.e., availability of VAP testing, was based on the preference of attending physician and therefore a selection bias is possible as to which patient had lipoprotein profile vs. standard lipid profile. We have excluded patients who were on lipid lowering agents prior to their diagnosis of T2DM. For the study purpose we have included the HbA1C at the time of lipoprotein analysis which may not reflect the true glycemic control, since fluctuating blood sugars prior to the lipoprotein measurement might have influenced the results.

Multiple determinants contribute to the suboptimal outcomes in the pediatric T2DM diabetes. Specifically, compliance with treatment and lifestyle adherence may be challenging due to socioeconomic challenges including inadequate access to healthcare, unsafe neighborhoods and insufficient psychosocial support [3,30,31]. Addressing these systemic barriers should be complemented by clinical attention to glycemic control to improve outcomes in this pediatric population.

Conclusion

HbA1C and BMI were associated with adverse lipoprotein profiles in children and adolescents with T2DM. Therefore, poor glycemic control and obesity represent two major modifiable factors to reduce CV risk in children with T2DM. Elevated HbA1C is associated with adverse lipoprotein abnormalities, especially elevated apoB, and higher frequency of LDL pattern B relative to patients with normal HbA1C, representing a need for optimal glycemic control strategies in CV risk reduction. Since elevated HbA1c is associated with pro-atherogenic lipid profiles, improvements in HbA1c may mitigate that CV risk.

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Declarations of interest

None.

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A.A. and H.P conceived the study. H.P collected the data from electronic medical records. L.H. and S.A. performed statistical analysis. A.A., H.P. and S.D. were involved in manuscript preparation. All authors were involved writing and editing 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2018.11.006.

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