Pubertal Lipid Levels Are Significantly Lower in Youth With Type 1 Diabetes Who Experienced Partial Clinical Remission

Benjamin Udoka Nwosu,[1] Shwetha Rupendu,[1] Emily Zitek-Morrison,[2] Deepa Patel,[1] Tony R. Villalobos-Ortiz,[1] Gabrielle Jasmin,[1] and Bruce A. Barton[2]

[1]Division of Endocrinology, Department of Pediatrics, University of Massachusetts Medical School, Worcester, Massachusetts 01655; and [2]Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, Massachusetts 01655

ORCiD numbers: 0000-0003-2212-0276 (B. U. Nwosu).

Importance: The physiologic changes in lipids during puberty in type 1 diabetes (T1D) are unclear because subjects in previous studies were not stratified by partial clinical remission status.

Aim: To determine the effect of partial clinical remission on lipid changes during puberty in youth with T1D.

Subjects and Methods: A retrospective cross-sectional study of 194 subjects consisting of 71 control subjects of age 12.9 ± 1.3 years and 123 subjects with T1D stratified into remitters (n = 44; age, 13.0 ± 0.8 years) and nonremitters (n = 79; age, 11.2 ± 0.6 years). Partial clinical remission was defined as insulin-dose adjusted HbA1c of ≤ 9. Pubertal status was determined by Tanner staging.

Results: Among the pubertal cohort, low-density lipoprotein cholesterol concentration was significantly higher in the nonremitters compared with remitters (91.1 ± 25.6 vs 77.2 ± 25.8 mg/dL, $P = 0.018$) and with normal-weight control subjects (91.1 ± 25.6 vs 70.4 ± 22.9 mg/dL, $P = 0.009$) but was similar between overweight/obese control subjects and nonremitters (89.7 ± 28.9 vs 91.1 ± 25.6 mg/dL, $P = 0.81$) and between normal-weight control subjects and remitters (70.4 ± 22.9 vs 77.2 ± 25.8 mg/dL, $P = 0.39$). Total cholesterol was also significantly higher in nonremitters compared with remitters (167.8 ± 30.5 vs 149.8 ± 32.1 mg/dL, $P = 0.012$) and with normal-weight control subjects (167.8 ± 30.5 vs 143.2 ± 30.1 mg/dL, $P = 0.011$) but was similar between nonremitters and overweight/obese control subjects ($P = 0.098$) and between remitters and normal-weight control subjects ($P = 0.51$). Non–high-density lipoprotein cholesterol was equally significantly higher in nonremitters compared with remitters (111.3 ± 30.1 vs 95.9 ± 29.1 mg/dL, $P = 0.028$) and normal-weight control subjects (111.3 ± 30.1 vs 86.2 ± 32.2 mg/dL, $P = 0.028$) but was similar between nonremitters and overweight/obese control subjects ($P = 0.48$) and between remitters vs normal-weight control subjects ($P = 0.39$).

Conclusions: Puberty-related reductions in low-density lipoprotein, total cholesterol, and non–high-density lipoprotein occur in remitters and normal-weight control subjects but not in nonremitters and overweight/obese control subjects.

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; IDAA1c, insulin dose–adjusted HbA1c; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; T1D, type 1 diabetes; TC, total cholesterol.

There is no consensus regarding the changes in lipid parameters during puberty in youth with type 1 diabetes (T1D) because earlier studies did not stratify subjects based on partial clinical remission history, also known as honeymoon status, as defined by a clinical marker of residual β-cell function [1–3].

T1D is a syndrome of persistent hyperglycemia due to autoimmune destruction of the pancreatic β-cells [4, 5]. The diagnosis of T1D is often followed by partial clinical remission, which is characterized by an increased functional capacity of the surviving β-cells and associated increased endogenous insulin production [6, 7]. Partial clinical remission usually lasts for 3 to 12 months [8] but could last longer in some cases [9]. Partial clinical remission has an important impact on both the near-term [10, 11] and long-term [12] lipid parameters and potential cardiovascular complications in patients with T1D. The presence of partial clinical remission is denoted by an insulin-dose adjusted hemoglobin A1c value of ≤9 [8].

Classically, studies in healthy nondiabetic children and adolescents have reported a general improvement in lipid parameters during puberty as marked by reductions in lipid fractions, especially low-density lipoprotein cholesterol (LDL-C) [13, 14]. A longitudinal study of changes in fasting lipids during puberty in healthy, nondiabetic children reported a uniform decline in the levels of plasma total cholesterol (TC), LDL-C, and non–high-density lipoprotein cholesterol (HDL-C) in both sexes during puberty [14].

In contrast, studies in children and adolescents with T1D have reached a different conclusion [1–3, 14]. In a study that compared the TC of children with T1D with control subjects, Polak *et al.* [1] reported that the T1D cohort had significantly higher TC than the control subjects and, more importantly, that the elevated TC in youth with T1D neither varied with the subjects' age nor with their stage of pubertal maturation, in contrast with the earlier report in healthy nondiabetic children and adolescents [14]. However, the studies that examined lipid profiles during puberty in youth with T1D did not take their subjects' remission status into consideration in the analyses [1–3, 14]. This is crucial because partial clinical remission, which is denoted by residual β-cell function, has been reported by the Diabetes Complication and Control Trial to reduce the risk for long-term cardiovascular disease in patients with T1D [12]. Furthermore, a recent study showed that remitters have significantly reduced risk for chronic microvascular complications of T1D in the first 7 years of disease compared with nonremitters [10], and another study found a significantly reduced low-density lipoprotein (LDL) level in remitters compared with the nonremitters in the first 5 years of diagnosis with T1D [11].

Therefore, this study was designed to investigate differences in lipid concentration between children and adolescents with T1D and their age-matched control subjects during puberty. The hypothesis is that plasma TC, LDL-C, and non–HDL-C concentrations will be higher in the nonremitters and overweight/obese control subjects compared with remitters and normal-weight control subjects during the pubertal years.

1. Subjects and Methods

A. Ethics Statement

The study protocol and the waiver of authorization to review subjects' retrospective records were approved by the Institutional Review Board of the University of Massachusetts, Docket # H00015476. All subject data were anonymized and deidentified prior to analysis.

B. Subjects

The patient population consisted of 194 pediatric patients from the Children's Medical Center Database of the UMassMemorial Medical Center, Worcester, MA. In this retrospective cross-sectional study, we compared the anthropometric, pubertal, and biochemical data of 71 control subjects of age 12.9 ± 1.3 years and 123 subjects with T1D stratified into remitters (n = 44; age, 13.0 ± 0.8 years) and nonremitters (n = 79; age, 11.2 ± 0.6 years). Subjects with

T1D were included in the study if they were <21 years of age, of Tanner stages I to V, and had data on HbA1c and total daily dose of insulin obtained in the first 6 months of diagnosis of T1D and also at 4 to 5 years in addition to lipid data obtained at 4 to 5 years after the diagnosis of T1D. Twelve patients with T1D were excluded from analysis because of a lack of data on Tanner staging. The control group consisted of healthy children and adolescents of <21 years of age appearing for routine evaluation. Subjects were excluded if they had a history of dyslipidemia, were receiving lipid-lowering medications, were on the birth control pill, or had a documented family history of dyslipidemia. Twenty-three subjects were excluded from the control group based on these criteria. The methodology of the diagnosis of T1D has been previously described in detail [11, 15, 16] and was based on glycemic and antibody profiles as recommended by the American Diabetes Association (ADA) [17]. Individuals diagnosed with other forms of diabetes mellitus were excluded from the study.

For the T1D cohort, our group has previously published that data collection for anthropometric, biochemical clinical parameters were conducted at the time of diagnosis and then every 3 months for the first year and every 3 to 6 months until 36 months in patients with T1D [16, 18]. This study showed that the peak prevalence of partial clinical remission occurred at 6 months after the diagnosis of T1D [18]. We have further published that additional anthropometric and biochemical data were collected at the fourth year or fifth year visit, in line with the ADA recommendation for the initiation of screening for diabetes complication in children with T1D either at the inception of puberty or 4 to 5 years after diagnosis [17]. Partial clinical remission was defined by insulin dose–adjusted HbA1c (IDAA1c) of ≤9 [8]. IDAA1c, which integrates HbA1c and total daily dose, is currently considered the gold standard clinical parameter for the detection of partial clinical remission [8]. It has been validated in multiple cohort studies [6, 7, 19] and is useful for the characterization of partial clinical remission in clinical studies. The formula for IDAA1C is HbA1c (%) + [4 × total daily dose of insulin (units/kg/24 h)] [8].

C. Anthropometry

The approach for anthropometric assessments has been described in detail [11, 16, 18, 20]. Briefly, height and weight were measured by standard techniques, and body mass index (BMI) was calculated from the formula weight/height^2 (kg/m^2). These parameters were further expressed as z scores for age and sex based on National Center for Health Statistics data [21, 22]. Overweight was defined as BMI of ≥85th but <95th percentile, and obesity was defined as BMI of ≥95th percentile for age and sex. Sexual maturity rating was determined by Tanner staging, with Tanner I denoting prepubertal status and Tanner II, III, or V denoting pubertal status.

D. Assays

The assay methodologies have been described [11, 16, 20, 23]. The estimation of serum lipids was conducted at the University of Massachusetts Medical School Clinical Laboratory based on the Beckman Coulter AU system, which is certified to meet the National Cholesterol Education Program's criteria for accuracy [24]. In situations where triglycerides were ≥400 mg/dL, LDL-C level was measured by the β quantification procedure [25]. Serum concentrations of diabetes-associated autoantibodies were quantified by Quest Diagnostics (Chantilly, VA).

E. Statistical Analyses

Means and SD were calculated for the continuous descriptive summary statistics and biochemical parameters. A two-sided Student t test was used to compare the two groups (remitters and nonremitters) as defined by IDAA1c ≤9 criterion (Table 1). Proportions were calculated for the presence of overweight or obesity (BMI >85th percentile). Comparison of binary variables (sex, race, and Tanner stage) between the two groups was performed using Pearson χ^2 test. P values for categorical variables were derived from χ^2 statistics, whereas

Table 1. Anthropometric and Biochemical Characteristics of the Subjects

Parameters	Control Subjects (n = 71)	Nonremitters (n = 79)	Remitters (n = 44)	P Value
Age, y	12.9 ± 5.3	11.2 ± 2.9	13.0 ± 2.5	0.01
Sex				
Male, %	54	41	52	0.17
Female, %	46	59	48	
Race				
White, %	61	79	82	0.014
Nonwhite, %	39	21	18	
Pubertal status				
Tanner I, %	37	38	14	0.012
Tanner II–V, %	63	62	86	
BMI status in percentile				
Normal-weight (<85th), %	28	69	64	<0.0001
Overweight/obese (≥85th), %	72	31	36	
Height z score	0.3 ± 1.3	−0.01 ± 1.2	0.1 ± 0.9	0.29
Weight z score	1.7 ± 1.3	0.5 ± 1.0	0.7 ± 0.8	<0.0001
BMI z score	1.7 ± 1.1	0.7 ± 0.9	0.7 ± 0.8	<0.0001
Systolic blood pressure, mm Hg	111.8 ± 11.9	107.6 ± 11.8	111.3 ± 12.8	0.088
Diastolic blood pressure, mm Hg	69.9 ± 8.9	70.0 ± 7.0	70.6 ± 6.0	0.88
HDL-C, mg/dL	46.3 ± 9.7	57.8 ± 13.3	53.2 ± 11.7	<0.0001
LDL-C, mg/dL	82 ± 25.2	91.6 ± 26.5	78.8 ± 28.7	0.025
Triglycerides, mg/dL	105.8 ± 57	92.9 ± 57.4	99.1 ± 65.7	0.43
TC, mg/dL	150.1 ± 29.2	166.9 ± 29.7	151.5 ± 32.6	0.015
TC/HDL ratio	3.3 ± 0.8	3.0 ± 0.8	2.9 ± 0.7	0.012
HbA1c at the peak of remission at 6 mo, mmol/mol	N/A	70.4 ± 16.9	56.8 ± 14.6	0.0001
HbA1c at the peak of remission at 6 mo, %	N/A	8.6 ± 1.5	7.35 ± 1.3	0.0001
HbA1c at 4–5 y, mmol/mol	N/A	72.3 ± 13.5	70.4 ± 16.9	0.53
HbA1c at 4–5 y, %	N/A	8.8 ± 1.2	8.6 ± 1.5	0.53
Total daily dose of insulin at the peak of remission at 6 mo, U/kg/d	N/A	0.64 ± 0.6	0.22 ± 0.2	<0.001
Total daily dose of insulin at 4–5 y, U/kg/d	N/A	1.0 ± 0.4	0.9 ± 0.4	0.24
Duration of diabetes, y	N/A	4.8 ± 0.4	4.8 ± 0.4	1.00

P values for continuous variables were derived from ANOVA statistics. Nonparametric data were analyzed using the Wilcoxon rank test. Scatterplot trajectories were generated using Loess regression, a nonparametric smoothing technique using local weighted regression. Outlier analyses were performed, and extreme outliers were removed from the analyses. Boxplots are presented in the standard manner, with boxes and whiskers representing interquartile ranges. Symbols beyond the whiskers designate outliers determined to be valid data points. All analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC).

2. Results

This retrospective cohort study analyzed the data of 194 subjects (n = 71 control subjects; n = 123 subjects with T1D). The subjects with T1D were further divided into remitters and nonremitters. Table 1 shows that nonremitters were younger than the control subjects and remitters. Control subjects had significantly higher BMI than subjects with T1D. Systolic blood pressure was lower in remitters compared with control subjects. Table 1 shows that both the HbA1c and total daily dose of insulin were significantly lower in remitters at the time of peak partial clinical remission at 6 months but were similar between remitters and nonremitters at 4 to 5 years after the diagnosis of T1D.

    To accurately determine the influence of puberty or changes in lipid parameters, we stratified the subjects by prepubertal and pubertal status based on Tanner staging of sexual maturation. Comparisons were made between remitters, nonremitters, and control subjects.

Because the control subjects had significantly higher BMI than the remitters and non-remitters (Table 1), we further subclassified control subjects into normal weight (BMI <85th percentile) and overweight/obese (BMI ≥85th percentile) for the analysis.

We focused on changes in plasma TC, LDL-C, and non–HDL-C because both the International Society for Pediatric and Adolescent Diabetes [26] and the ADA [17] designate LDL as the primary marker of cardiovascular risk in children and adolescents with T1D and because the 2011 Integrated Pediatric Guidelines for Cardiovascular Risk Reduction in Children and Adolescents [27, 28] recommend universal screening with nonfasting non–HDL-C at ages 9 to 11 years and 17 to 21 years.

A. Stratification by Pubertal Status

A-1. LDL-C

Serum LDL-C concentration was similar among the four groups for the prepubertal cohort. In contrast, among the pubertal cohort, LDL-C was significantly higher in nonremitters compared with remitters (91.1 ± 25.6 vs 77.2 ± 25.8 mg/dL, $P = 0.018$) and was significantly higher in nonremitters compared with normal-weight control subjects (91.1 ± 25.6 vs 70.4 ± 22.9 mg/dL, $P = 0.009$) (Fig. 1a). Although LDL-C was significantly higher in overweight/obese control subjects compared with normal-weight control subjects (89.7 ± 28.9 vs 70.4 ± 22.9 mg/dL, $P = 0.033$), it was similar between overweight/obese control subjects and nonremitters (89.7 ± 28.9 vs 91.1 ± 25.6 mg/dL, $P = 0.81$). LDL-C was equally similar between normal-weight control subjects and remitters (70.4 ± 22.9 vs 77.2 ± 25.8 mg/dL, $P = 0.39$). Figure 1b shows lower LDL-C values in both normal-weight control subjects and remitters during puberty but not in overweight/obese control subjects and nonremitters.

A-2. Non–HDL-C

In the prepubertal cohort, non– high-density lipoprotein (HDL) was similar among the four groups. In contrast, in the pubertal cohort, non–HDL-C was significantly higher in
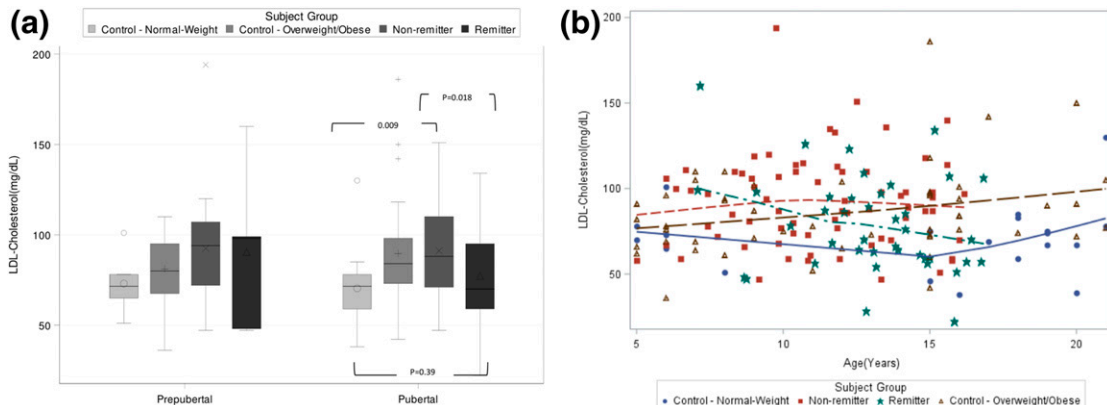

Figure 1. (a) Bar graphs of LDL-C concentration stratified by pubertal status in control subjects and subjects with T1D. There was no significant difference between the groups in the prepubertal cohort. In contrast, in the pubertal cohort, LDL was significantly higher in nonremitters compared with remitters ($P = 0.018$) and was significantly higher in nonremitters compared with normal-weight control subjects ($P = 0.009$). LDL was significantly higher in overweight/obese control subjects compared with normal-weight control subjects ($P = 0.033$) but was similar between normal-weight control subjects and remitters ($P = 0.39$). (b) A comparison of the patterns of LDL-C in control subjects and subjects with T1D. Remitters and normal-weight control subjects demonstrated lower LDL-C concentration during puberty, whereas overweight/obese control subjects and nonremitters did not.

nonremitters compared with remitters (111.3 ± 30.1 vs 95.9 ± 29.1 mg/dL, $P = 0.028$) and was significantly higher in nonremitters compared with normal-weight control subjects (111.3 ± 30.1 vs 86.2 ± 32.2 mg/dL, $P = 0.028$) (Fig. 2a). In line with the findings for LDL-C and TC, non-HDL was similar between nonremitters and overweight/obese control subjects (111.3 ± 30.1 vs 105.6 ± 37.6 mg/dL, $P = 0.48$) and between remitters and normal-weight control subjects (95.9 ± 29.1 vs 86.2 ± 32.2 mg/dL, $P = 0.39$). Figure 2b shows that remitters and normal-weight control subjects demonstrated lower non–HDL-C concentration during puberty, whereas nonremitters and overweight/obese control subjects did not.

Because the comparisons for the TC, LDL, and non-HDL showed similar patterns of reduction in remitters, we report the results of LDL and non-HDL in full. The TC results are depicted in Fig. 3a and 3b.

Next, we explored the effects of major covariates (BMI, sex, and race) on the differences in lipid parameters around the time of puberty in these subjects.

B. Stratification by BMI

B-1. LDL

Overweight/obese control subjects had significantly higher LDL-C compared with normal-weight control subjects (86.3 ± 25.7 vs 71.2 ± 20.8 mg/dL, $P = 0.022$), but there was no difference in LDL-C concentration between the normal-weight and overweight/obese groups for both the remitters and nonremitters.

Among the normal-weight cohort, LDL-C was significantly higher in nonremitters compared with normal-weight control subjects (89.2 ± 27.4 vs 71.2 ± 20.8 mg/dL, $P = 0.01$), whereas LDL-C was similar between normal-weight control subjects and remitters ($P = 0.40$) as well as between remitters and nonremitters ($P = 0.13$).

Among the overweight/obese cohort, LDL-C was significantly higher in nonremitters compared with remitters (96.7 ± 24.2 vs 79.9 ± 21.2 mg/dL, $P = 0.031$) but was similar between control subjects and remitters (86.3 ± 25.7 vs 79.9 ± 21.2 mg/dL, $P = 0.37$).
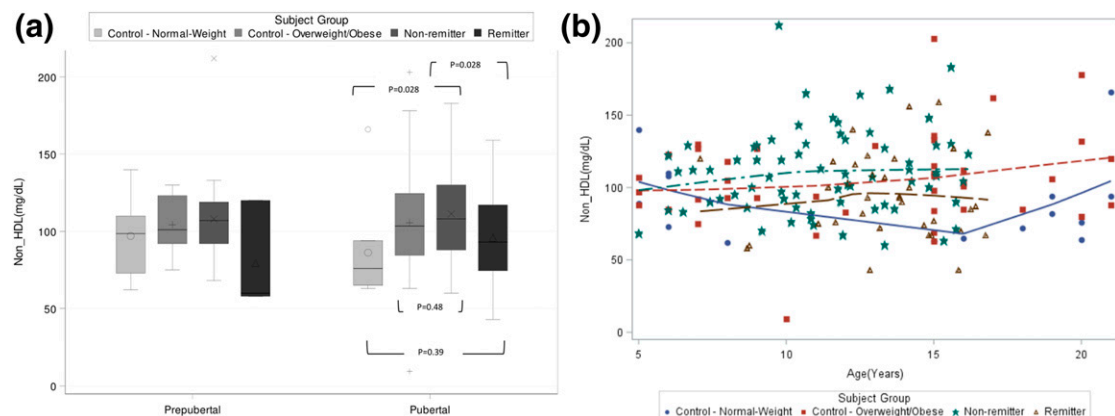

Figure 2. (a) Bar graphs of non–HDL-C concentration stratified by pubertal status in control subjects and subjects with T1D. In the prepubertal cohort, non-HDL was similar between groups. However, in the pubertal cohort, non-HDL was significantly higher in nonremitters compared with control subjects ($P = 0.028$) and remitters ($P = 0.028$) but was similar between normal-weight control subjects and remitters ($P = 0.39$) and between overweight/obese control subjects and nonremitters ($P = 0.48$). (b) A comparison of the patterns of non–HDL-C in control subjects and subjects with T1D. Remitters and normal-weight control subjects demonstrated lower non-HDL concentration during puberty, whereas overweight/obese control subjects and nonremitters did not.
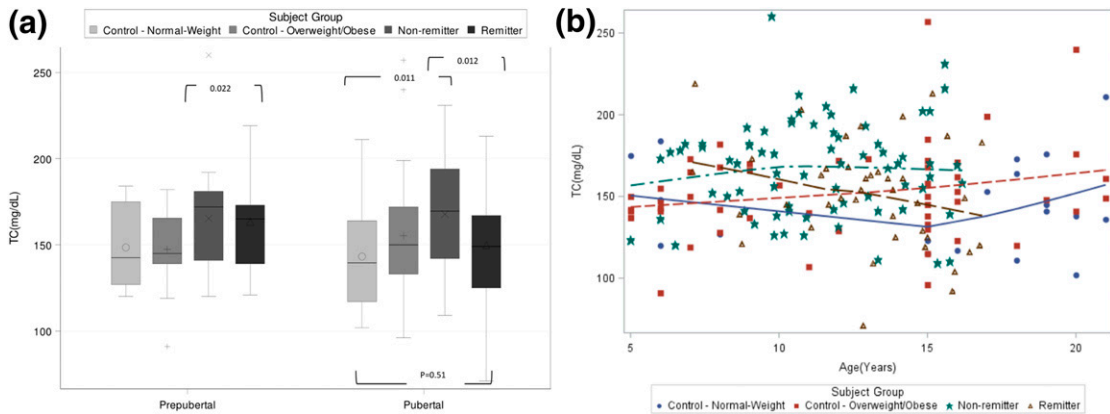
Figure 3. (a) Bar graphs of TC concentration stratified by pubertal status in control subjects and subjects with T1D. In the prepubertal cohort, LDL was significantly higher in nonremitters compared with control subjects ($P = 0.022$). However, in the pubertal cohort, LDL was significantly higher in nonremitters compared with normal-weight control subjects ($P = 0.011$) and remitters ($P = 0.012$) but was similar between overweight/obese control subjects and nonremitters ($P = 0.09$) and between normal-weight control subjects and remitters ($P = 0.51$). (b) A comparison of the patterns of TC in control subjects and subjects with T1D. Remitters and normal-weight control subjects demonstrated lower TC concentration during puberty, whereas overweight/obese control subjects and nonremitters did not.

B-2. Non–HDL-C

Among the normal-weight cohort, non-HDL was significantly higher in nonremitters compared with control subjects (107.1 ± 29.3 vs 90.5 ± 30.1 mg/dL, $P = 0.024$) as well as between nonremitters and remitters (107.1 ± 29.3 vs 88.4 ± 31.0 mg/dL, $P = 0.021$). In contrast, non-HDL was similar between control subjects and remitters (90.5 ± 30.1 vs 88.4 ± 31.0 mg/dL, $P = 0.88$). Among the overweight/obese cohort, the differences in non-HDL did not reach statistical significance.

C. Stratification by Sex

C-1. LDL-C

The intergroup comparison showed no significant difference among female subjects. In contrast, among male subjects, LDL was significantly higher in overweight/obese control subjects compared with normal-weight control subjects (81.38 ± 23.3 vs 65.6 ± 16.0 mg/dL, $P = 0.041$). LDL was also significantly higher in male nonremitters compared with normal-weight control subjects (92.6 ± 32.2 vs 65.6 ± 16.0 mg/dL, $P = 0.0012$) and higher in male nonremitters compared with male remitters (92.6 ± 32.2 vs 74.5 ± 24.3 mg/dL, $P = 0.034$).

C-2. Non–HDL-C

Non–HDL-C was similar among the four groups for the female cohort. In contrast, the male cohort showed a significantly higher non–HDL-C level in overweight/obese control subjects compared with normal-weight control subjects (103.1 ± 24.3 vs 83.5 ± 23.3 mg/dL, $P = 0.044$) and significantly higher non-HDL in nonremitters compared with normal-weight control subjects (110.9 ± 32.2 vs 83.5 ± 23.3 mg/dL, $P = 0.019$). Non-HDL was similar between normal-weight control subjects and remitters (83.5 ± 23.3 vs 93.5 ± 30.6 mg/dL, $P = 0.37$) but was not significantly higher in nonremitters compared with remitters (110.9 ± 32.2 vs 93.5 ± 30.6 mg/dL, $P = 0.067$).

D. Stratification by Race

D-1. LDL

Serum LDL-C was similar among the groups for the nonwhite cohort. In contrast, among the white cohort, LDL-C was significantly higher in overweight/obese control subjects compared with normal-weight control subjects (85.1 ± 23.5 vs 66.8 ± 13.2 mg/dL, $P = 0.0022$). Equally, nonremitters had significantly higher LDL-C compared with normal-weight control subjects (93.6 ± 26.6 vs 66.8 ± 13.2 mg/dL, $P < 0.001$) and compared with remitters (93.6 ± 26.6 vs 78.3 ± 29.4 mg/dL, $P = 0.013$). In contrast, LDL-C was similar between normal-weight control subjects and remitters (66.8 ± 13.2 vs 78.3 ± 29.4 mg/dL, $P = 0.07$) and between overweight/obese control subjects and nonremitters ($P = 0.15$).

D-2. Non-HDL

Significant findings for this analysis were seen in the white cohort where non-HDL was significantly higher in nonremitters compared with normal-weight control subjects (110.7 ± 28.1 vs 85.9 ± 24.7 mg/dL, $P = 0.011$) and also significantly higher in nonremitters compared with remitters (110.7 ± 28.1 vs 92.8 ± 29.3 mg/dL, $P = 0.0075$). Non–HDL-C was similar between normal-weight control subjects and remitters ($P = 0.51$) and between overweight/obese control subjects and remitters ($P = 0.19$).

D-3. Triglycerides

The comprehensive analysis of changes in serum triglycerides did not show any appreciable differences between male and female subjects, between white and nonwhite subjects, or between prepubertal and pubertal subjects.

3. Discussion

The origins of the dichotomy in cardiovascular disease risk in adults with T1D are rooted in childhood [10–12], but the exact mechanism and point of divergence from normal in cardiovascular risk are not known. This study was designed to support or disprove the current thinking that children with T1D do not experience a reduction in TC, LDL, and non-HDL during puberty [1], as has been reported for healthy children without T1D [13, 14]. This study characterizes the natural pattern of lipid profiles in children and adolescents with T1D as they traverse through puberty based on stratification by remission status and compared with their healthy peers.

Our results show that remission status at least partially determines the pattern of lipid concentrations in youth with T1D during pubertal maturation: children with T1D who experienced the honeymoon phase or partial clinical remission showed reductions in LDL-C, TC, and non–HDL-C similar to those seen in normal-weight, healthy children without T1D [14], whereas nonremitters did not. The stratification of the subjects into remitters and nonremitters is crucial for this investigation because the lack of consensus from earlier studies on the patterns of lipid profile in children and adolescents with T1D may have resulted from the lack of stratification of subjects by partial clinical remission history [2, 29–31].

The second important finding is that remitters have an intrinsic protection against adiposity-driven dyslipidemia, and this protection is absent in nonremitters, as demonstrated by the significantly elevated LDL-C in overweight/obese nonremitters compared with overweight/obese remitters during puberty. This is in line with the finding that residual C-peptide has vascular protective function [12] and could protect remitters from early-phase anatomic changes in vasculature caused by dyslipidemia.

The third important finding is that overweight/obese children without T1D do not experience the classic reduction in LDL, TC, and non-HDL that was described by Eissa *et al.* [14] in healthy children during puberty. This is important because Eissa *et al.* [14] did not stratify their subjects by normal-weight and overweight/obese status.

The peripubertal lipid patterns were further explored in relation to major covariates: BMI, sex, and race. When subjects were stratified by BMI status into normal-weight and overweight/obese groups, analysis of the normal-weight cohort showed that LDL-C was significantly higher in nonremitters than in control subjects but was similar between nonremitters and remitters. Similarly, in the overweight/obese cohort, LDL-C was significantly higher in nonremitters compared with remitters ($P = 0.031$) but was similar between control subjects and remitters ($P = 0.37$).

When the subjects were stratified by sex, LDL and TC were significantly higher in male nonremitters, which is in contrast to the report that male subjects without diabetes display robust declines in LDL, TC, and non-HDL compared with female subjects during puberty [14]. This suggests that nonremission may diminish this robust decline in TC, LDL, and non-HDL in male subjects with T1D.

When the subjects were stratified by race, the results show that among the white subjects, LDL, TC, and non-HDL concentrations were significantly higher in nonremitters compared with control subjects and remitters, suggesting that white subjects could be at a higher risk for early-phase dyslipidemia in subjects with T1D [28]. Nonremission appears to worsen this trend toward dyslipidemia.

Even among control subjects, overweight/obese subjects did not undergo a robust decrease in TC, LDL, and non-HDL during puberty (Figs. 1b, 2b, and 3b). Instead, only normal-weight control subjects and remitters exhibited this phenomenon. This is important because it argues against the notion [14] that healthy children without T1D experience reductions in TC, LDL, and non-HDL during puberty.

The findings from this study are important because they provide the much-needed data on the timing of the onset of the divergence in lipid profiles, and consequent cardiovascular disease risk, in youth with T1D. According to our data, this occurs between ages 11 and 12 years for LDL-C, TC, and non–HDL-C; this finding is consistent with the timing of the onset of reduction in LDL-C, TC, and non-HDL during puberty in children without diabetes mellitus [28].

The reduction in LDL-C, TC, and non-HDL during puberty is likely due to the effect of sex hormones on lipoprotein metabolism, specifically changes in α and β lipoproteins [28]. We believe that this reduction in the concentrations of LDL-C, TC, and non-HDL could be attenuated or abolished by increased insulin-resistant state [32] as reported in our overweight/obese cohort. In contrast, partial clinical remission appears to facilitate this reduction in LDL-C, TC, and non-HDL in youth with T1D.

Some of the limitations of this study include its retrospective design, which precludes causality among the parameters studied. The lack of data on stimulated serum C-peptide limited our ability to confirm the reliability of IDAA1c as a definition for partial clinical remission. Furthermore, the lack of data on insulin resistance limited our ability to explore the association between TC/HDL and insulin resistance. The strengths of this study include the use of a representative sample of control subjects to compare the pubertal patterns of lipid parameters in children and adolescents with T1D and the definition of partial clinical remission using the IDAA1c criterion. These measures allowed for meaningful comparison of core parameters among control subjects, remitters, and nonremitters.

4. Conclusions

Remission status is the key determinant of lipid concentration in youth with T1D during puberty: subjects with a history of remission show reductions in TC, LDL, and non-HDL similar to those seen in normal-weight healthy children, whereas nonremitters and overweight/obese control subjects fail to show this distinctive lipid pattern in youth. This

principal finding clarifies the pattern of the early changes in lipid profiles in youth with T1D and suggests that the differences in cardiovascular disease risk stemming from early-phase dyslipidemia in children and adolescents with T1D might arise at puberty. This clarification of the timing of the divergence in lipid profile in youth with T1D suggests that early lipid-lowering interventions may be necessary in nonremitters during puberty to reduce the prevalence of cardiovascular complications in adulthood.

Acknowledgments

Correspondence: Benjamin Udoka Nwosu, MD, FAAP, Division of Endocrinology, Department of Pediatrics, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, Massachusetts 01655. E-mail: Benjamin.Nwosu@umassmemorial.org.

Disclosure Summary: The authors have nothing to disclose.

References and Notes

1. Polak M, Souchon PF, Benali K, Tubiana-Rufi N, Czernichow P. Type 1 diabetic children have abnormal lipid profiles during pubertal years. *Pediatr Diabetes*. 2000;**1**(2):74–81.
2. Katz ML, Kollman CR, Dougher CE, Mubasher M, Laffel LM. Influence of HbA1c and BMI on lipid trajectories in youths and young adults with type 1 diabetes. *Diabetes Care*. 2017;**40**(1):30–37.
3. Kobbah M, Proos L, Tuvemo T, Vessby B. Serum lipoproteins and apolipoproteins in children during the first five years of diabetes. *Acta Paediatr Suppl*. 1997;**418**(S418):11–14.
4. American Diabetes Association. Standards of medical care in diabetes-2016: Summary of revisions. *Diabetes Care*. 2016;**39**(Suppl 1):S4–S5.
5. Chmelova H, Cohrs CM, Chouinard JA, Petzold C, Kuhn M, Chen C, Roeder I, Kretschmer K, Speier S. Distinct roles of β-cell mass and function during type 1 diabetes onset and remission. *Diabetes*. 2015; **64**(6):2148–2160.
6. Nagl K, Hermann JM, Plamper M, Schröder C, Dost A, Kordonouri O, Rami-Merhar B, Holl RW. Factors contributing to partial remission in type 1 diabetes: analysis based on the insulin dose-adjusted HbA1c in 3657 children and adolescents from Germany and Austria. *Pediatr Diabetes*. 2017;**18**(6): 428–434.
7. Max Andersen ML, Hougaard P, Pörksen S, Nielsen LB, Fredheim S, Svensson J, Thomsen J, Vikre-Jørgensen J, Hertel T, Petersen JS, Hansen L, Mortensen HB. Partial remission definition: validation based on the insulin dose-adjusted HbA1c (IDAA1C) in 129 Danish children with new-onset type 1 diabetes. *Pediatr Diabetes*. 2014;**15**(7):469–476.
8. Mortensen HB, Hougaard P, Swift P, Hansen L, Holl RW, Hoey H, Bjoerndalen H, de Beaufort C, Chiarelli F, Danne T, Schoenle EJ, Aman J; Hvidoere Study Group on Childhood Diabetes. New definition for the partial remission period in children and adolescents with type 1 diabetes. *Diabetes Care*. 2009;**32**(8):1384–1390.
9. Shields BM, McDonald TJ, Oram R, Hill A, Hudson M, Leete P, Pearson ER, Richardson SJ, Morgan NG, Hattersley AT, Consortium T; TIGI Consortium. C-peptide decline in type 1 diabetes has two phases: an initial exponential fall and a subsequent stable phase. *Diabetes Care*. 2018;**41**(7):1486–1492.
10. Niedzwiecki P, Pilacinski S, Uruska A, Adamska A, Naskret D, Zozulinska-Ziolkiewicz D. Influence of remission and its duration on development of early microvascular complications in young adults with type 1 diabetes. *J Diabetes Complications*. 2015;**29**(8):1105–1111.
11. Nwosu BU, Zhang B, Ayyoub SS, Choi S, Villalobos-Ortiz TR, Alonso LC, Barton BA. Children with type 1 diabetes who experienced a honeymoon phase had significantly lower LDL cholesterol 5 years after diagnosis. *PLoS One*. 2018;**13**(5):e0196912.
12. Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care*. 2003;**26**(3): 832–836.
13. Dai S, Fulton JE, Harrist RB, Grunbaum JA, Steffen LM, Labarthe DR. Blood lipids in children: age-related patterns and association with body-fat indices: Project HeartBeat! *Am J Prev Med*. 2009;**37**(1, Suppl):S56–S64.

14. Eissa MA, Mihalopoulos NL, Holubkov R, Dai S, Labarthe DR. Changes in fasting lipids during puberty. *J Pediatr*. 2016;**170**:199–205.

15. Nwosu BU, Maranda L. The effects of vitamin D supplementation on hepatic dysfunction, vitamin D status, and glycemic control in children and adolescents with vitamin D deficiency and either type 1 or type 2 diabetes mellitus. *PLoS One*. 2014;**9**(6):e99646.

16. Lundberg RL, Marino KR, Jasrotia A, Maranda LS, Barton BA, Alonso LC, Nwosu BU. Partial clinical remission in type 1 diabetes: a comparison of the accuracy of total daily dose of insulin of <0.3 units/kg/day to the gold standard insulin-dose adjusted hemoglobin A1c of ≤9 for the detection of partial clinical remission. *J Pediatr Endocrinol Metab*. 2017;**30**(8):823–830.

17. American Diabetes Association. Standards of medical care in diabetes-2017: abridged for primary care providers. *Clin Diabetes*. 2017;**35**(1):5–26.

18. Marino KR, Lundberg RL, Jasrotia A, Maranda LS, Thompson MJ, Barton BA, Alonso LC, Nwosu BU. A predictive model for lack of partial clinical remission in new-onset pediatric type 1 diabetes. *PLoS One*. 2017;**12**(5):e0176860.

19. Neylon OM, White M, O Connell MA, Cameron FJ. Insulin-dose-adjusted HbA1c-defined partial remission phase in a paediatric population: when is the honeymoon over? *Diabet Med*. 2013;**30**(5):627–628.

20. Veit LE, Maranda L, Fong J, Nwosu BU. The vitamin D status in inflammatory bowel disease. *PLoS One*. 2014;**9**(7):e101583.

21. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL. 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat 11*. 2002;**2002**(246):1–190.

22. Centers for Disease Control and Prevention. National Center for Health Statistics. Accessed on 1 January 2019. Available at: https://www.cdc.gov/growthcharts/zscore.htm.

23. Veit LE, Maranda L, Nwosu BU. The nondietary determinants of vitamin D status in pediatric inflammatory bowel disease. *Nutrition*. 2015;**31**(7-8):994–999.

24. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, Pessah-Pollack R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M, Zangeneh F, Bush MA. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease: executive summary. *Endocr Pract*. 2017;**23**:479–497.

25. Warnick GR, Knopp RH, Fitzpatrick V, Branson L. Estimating low-density lipoprotein cholesterol by the Friedewald equation is adequate for classifying patients on the basis of nationally recommended cutpoints. *Clin Chem*. 1990;**36**(1):15–19.

26. Donaghue KC, Wadwa RP, Dimeglio LA, Wong TY, Chiarelli F, Marcovecchio ML, Salem M, Raza J, Hofman PL, Craig ME; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014: microvascular and macrovascular complications in children and adolescents. *Pediatr Diabetes*. 2014;**15**(Suppl 20):257–269.

27. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and AdolescentsNational Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;**128**(Suppl 5):S213–S256.

28. Berenson GS, Srinivasan SR, Cresanta JL, Foster TA, Webber LS. Dynamic changes of serum lipoproteins in children during adolescence and sexual maturation. *Am J Epidemiol*. 1981;**113**(2):157–170.

29. Shah AS, Maahs DM, Stafford JM, Dolan LM, Lang W, Imperatore G, Bell RA, Liese AD, Reynolds K, Pihoker C, Marcovina S, D'Agostino RB Jr, Dabelea D. Predictors of dyslipidemia over time in youth with type 1 diabetes: for the Search for Diabetes in Youth Study. *Diabetes Care*. 2017;**40**(4):607–613.

30. Obermannova B, Petruzelkova L, Sulakova T, Sumnik Z. HbA1c but not diabetes duration predicts increased arterial stiffness in adolescents with poorly controlled type 1 diabetes. *Pediatr Diabetes*. 2017;**18**(4):304–310.

31. Bulut T, Demirel F, Metin A. The prevalence of dyslipidemia and associated factors in children and adolescents with type 1 diabetes. *J Pediatr Endocrinol Metab*. 2017;**30**(2):181–187.

32. Chait A, Bierman EL, Albers JJ. Low-density lipoprotein receptor activity in cultured human skin fibroblasts: mechanism of insulin-induced stimulation. *J Clin Invest*. 1979;**64**(5):1309–1319.