Pubertal lipid levels are significantly lower in youth with type 1 diabetes who experienced partial clinical remission

Benjamin U. Nwosu
University of Massachusetts Medical School

Let us know how access to this document benefits you.
Follow this and additional works at: https://escholarship.umassmed.edu/peds_endocrinology

Part of the Endocrine System Diseases Commons, Endocrinology, Diabetes, and Metabolism Commons, Lipids Commons, Pediatrics Commons, and the Reproductive and Urinary Physiology Commons

Repository Citation
Nwosu BU, Rupendu S, Zitek-Morrison E, Patel D, Villalobos-Ortiz TR, Jasmin G, Barton BA. (2019). Pubertal lipid levels are significantly lower in youth with type 1 diabetes who experienced partial clinical remission. Endocrinology/Diabetes. https://doi.org/10.1210/js.2019-00016. Retrieved from https://escholarship.umassmed.edu/peds_endocrinology/64

Creative Commons License
This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 4.0 License. This material is brought to you by eScholarship@UMassChan. It has been accepted for inclusion in Endocrinology/Diabetes by an authorized administrator of eScholarship@UMassChan. For more information, please contact Lisa.Palmer@umassmed.edu.
Pubertal lipid levels are significantly lower in youth with type 1 diabetes who experienced partial clinical remission

Benjamin Udoka Nwosu, MD, Shwetha Rupendu, MD, Emily Zitek-Morrison, Deepa Patel, MPH, Tony R. Villalobos-Ortiz B. S, Gabrielle Jasmin, MS, Bruce A. Barton PhD

Journal of the Endocrine Society
Endocrine Society

Submitted: January 13, 2019
Accepted: February 22, 2019
First Online: February 27, 2019

Advance Articles are PDF versions of manuscripts that have been peer reviewed and accepted but not yet copyedited. The manuscripts are published online as soon as possible after acceptance and before the copyedited, typeset articles are published. They are posted "as is" (i.e., as submitted by the authors at the modification stage), and do not reflect editorial changes. No corrections/changes to the PDF manuscripts are accepted. Accordingly, there likely will be differences between the Advance Article manuscripts and the final, typeset articles. The manuscripts remain listed on the Advance Article page until the final, typeset articles are posted. At that point, the manuscripts are removed from the Advance Article page.

DISCLAIMER: These manuscripts are provided "as is" without warranty of any kind, either express or particular purpose, or non-infringement. Changes will be made to these manuscripts before publication. Review and/or use or reliance on these materials is at the discretion and risk of the reader/user. In no event shall the Endocrine Society be liable for damages of any kind arising references to, products or publications do not imply endorsement of that product or publication.
Pubertal lipid patterns in type 1 diabetes

Pubertal lipid levels are significantly lower in youth with type 1 diabetes who experienced partial clinical remission

Benjamin Udoka Nwosu, MD¹, Shwetha Rupendu, MD¹, Emily Zitek-Morrison², Deepa Patel, MPH¹, Tony R. Villalobos-Ortiz B. S¹, Gabrielle Jasmin, MS¹, Bruce A. Barton PhD²

¹Division of Endocrinology, Department of Pediatrics, University of Massachusetts Medical School, Worcester, Massachusetts, USA.
²Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, Massachusetts, USA.

ORCID numbers:
0000-0003-2212-0276

Nwosu
Benjamin Udoka

**Keywords:** type 1 diabetes; children; partial clinical remission; honeymoon phase; cardiovascular disease risk; dyslipidemia

Received 13 January 2019. Accepted 22 February 2019.

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

**Aim:** To determine the effect of PCR on lipid changes during puberty in youth with T1D.

**Subjects and Methods:** A retrospective cross-sectional study of 194 subjects consisting of 71 controls of age 12.9±1.3y and 123 subjects with T1D stratified into remitters (n=44, age 13.0±0.8y) and non-remitters (n=79, age 11.2±0.6y). PCR 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 non-remitters compared to the remitters, 91.1±25.6mg/dL vs 77.2±25.8mg/dL, p=0.018; and the normal-weight controls, 91.1±25.6mg/dL vs 70.4±22.9mg/dL, p=0.009; but was similar between the overweight/obese controls and non-remitters, 89.7±28.9mg/dL vs 91.1±25.6mg/dL, p=0.81, and similarly between the normal-weight controls and remitters, 70.4±22.9mg/dL vs 77.2±25.8mg/dL, p=0.39. Total cholesterol was also significantly higher in the non-remitters compared to the remitters, 167.8±30.5 mg/dL vs 149.8±32.1mg/dL, p=0.012; and normal-weight controls, 167.8±30.5mg/dL vs 143.2±30.1mg/dL, p=0.011; but similar between the non-remitters and overweight/obese controls, p=0.098; and remitters and normal-weight controls, p=0.51. Non-HDL cholesterol was equally significantly higher in non-remitters compared to remitters, 111.3±30.1mg/dL vs 95.9±29.1mg/dL, p=0.028; and normal-weight controls, 111.3±30.1mg/dL vs 86.2±32.2mg/dL, p=0.028; but similar between non-remitters and overweight/obese controls, p=0.48; and remitters versus normal-weight controls, p=0.39.

**Conclusions:** Puberty-related reductions in LDL, TC, and non-HDL occur in remitters and normal-weight controls, but not in non-remitters and overweight/obese controls.
Introduction

There is no consensus on the changes in lipid parameters during puberty in youth with type 1 diabetes (T1D) as earlier studies did not stratify subjects based on partial clinical remission (PCR) 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 PCR which is characterized by an increased functional capacity of the surviving β-cells and associated increased endogenous insulin production(6, 7). PCR usually lasts for 3-12 months(8), but could last longer in some cases(9). PCR has significant 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 PCR is denoted by an insulin-dose adjusted hemoglobin A1c value of ≤9(8).

Classically, studies in healthy non-diabetic children and adolescents have reported a general improvement in lipid parameters during puberty as marked by reductions in lipid fractions, especially LDL cholesterol(13, 14). A longitudinal study of changes in fasting lipids during puberty in healthy, non-diabetic children reported a uniform decline in the levels of plasma TC, LDL-C, and non-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 to controls, Polak et al(1) reported that the T1D cohort had significantly higher TC than the controls, 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 non-diabetic 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 as PCR, denoted by residual β-cell function, has been reported by the Diabetes Complication and Control Trial (DCCT) 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 seven years of disease compared to non-remitters(10), while another found a significantly reduced LDL level in remitters compared to the non-remitters 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 controls during puberty. The hypothesis is that plasma TC, LDL-C, and non-HDL-C concentrations will be higher in the non-remitters and overweight/obese controls compared to the remitters and normal-weight controls during the pubertal years.

Subjects and Methods

Ethics Statement

Both 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 subjects’ data were anonymized and de-identified prior to analysis.

Subjects

The patient population consisted of 194 pediatric patients from the Children’s Medical Center Database of the UMassMemorial Medical Center, Worcester, Massachusetts, USA. In this retrospective cross-sectional study, we compared the anthropometric, pubertal, and biochemical
data of 71 controls of age 12.9±1.3y and 123 subjects with T1D stratified into remitters (n=44, age 13.0±0.8y) and non-remitters (n=79, age 11.2±0.6y). Subjects with T1D were included in the study if they were <21 years, of Tanner stages I-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 4-5 years; in addition to lipid data obtained at 4-5 years after the diagnosis of T1D. Twelve patients with T1D were excluded from analysis because of lack of data on Tanner staging. The control group consisted of healthy children and adolescents of <21 years appearing for routine evaluation. Subjects were excluded if they had a history of dyslipidemia, were receiving lipid-lowering medications, were on 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 PCR occurred at 6 months after the diagnosis of T1D(18). We have further published that additional anthropometric and biochemical data were collected at the 4th year or 5th 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 4-5 years after the diagnosis(17). PCR was defined by insulin dose-adjusted hemoglobin A1c (IDAA1c) of ≤9(8). The IDAA1c, which integrates HbA1c and TDD, is currently considered the gold standard clinical parameter for the detection of PCR(8). It has been validated in multiple cohort studies(6, 7, 19) and is useful for the characterization of PCR in clinical studies. The formula for IDAA1C is HbA1c (%) + [4 X total daily dose of insulin (units/kg/24h)](8).

**Anthropometry**

The approach for anthropometric assessments has been previously 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 gender. Sexual maturity rating was determined by Tanner staging, with Tanner I denoting prepubertal status, and Tanner II-V denoting pubertal status.

**Assays**

The assay methodologies have been previously 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-cholesterol level was measured by the beta quantification procedure(25). Serum concentrations of diabetes-associated autoantibodies were quantified by Quest Diagnostics, Chantilly, VA, USA.

**Statistical Analyses**

Means and standard deviations (SD) were calculated for the continuous descriptive summary statistics and biochemical parameters. Two-sided Student's t test was used to compare the two
groups, remitters and non-remitters, 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 were performed using Pearson's chi-squared test. P values for categorical variables were derived from chi-square statistics, while the p values for continuous variables were derived from ANOVA statistics. Non-parametric data were analyzed using Wilcoxon rank test. The 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).

Results

This retrospective cohort study analyzed the data of 194 subjects consisting of 71 controls and 123 subjects with T1D. The T1D subjects were further divided into remitters and non-remitters. Table 1 shows that the non-remitters were younger than the controls and remitters. The controls had significantly higher BMI than the T1D subjects. Systolic BP was lower in the remitters compared to the controls. Table 1 also shows that both the HbA1c and total daily dose (TDD) of insulin were significantly lower in the remitters at the time of peak PCR at 6 months; but were similar between the remitters and non-remitters at 4-5 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 the remitters, non-remitters, and controls. Because the controls had significantly higher BMI than the remitters and non-remitters (Table 1), we further subclassified the controls 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 as both the International Society for Pediatric and Adolescent Diabetes (ISPAD) (26) and the American Diabetes Association (ADA)(17) designate LDL as the primary marker of cardiovascular risk in children and adolescents with T1D while the 2011 Integrated Pediatric Guidelines for Cardiovascular Risk Reduction in Children and Adolescents(27, 28) recommend universal screening with non-fasting non-HDL-C at ages 9-11 and 17-21 years.

Stratification by Pubertal status

Low density lipoprotein cholesterol (LDL-C)

Serum LDL-C concentration was similar among the 4 groups for the prepubertal cohort. In contrast, among the pubertal cohort, LDL-C was significantly higher in the non-remitters compared to the remitters, 91.1 ± 25.6 mg/dL vs 77.2 ± 25.8 mg/dL, p = 0.018; and also significantly higher in the non-remitters compared to the normal-weight controls, 91.1 ± 25.6 mg/dL vs 70.4 ± 22.9 mg/dL, p = 0.009 (Figure 1a). Interestingly, though LDL-C was significantly higher in the overweight/obese controls compared to the normal-weight controls 89.7 ± 28.9 mg/dL vs 70.4 ± 22.9 mg/dL, p = 0.033, it was similar between the overweight/obese controls and non-remitters, 89.7 ± 28.9 mg/dL vs 91.1 ± 25.6 mg/dL, p = 0.81. LDL-C was equally similar between the normal-weight controls and remitters, 70.4 ± 22.9 mg/dL vs 77.2 ± 25.8 mg/dL, p = 0.39. Figure 1b shows lower LDL-C values in both the normal-weight control and remitters during puberty, but not in the overweight/obese controls and non-remitters.
Non-HDL Cholesterol

In the prepubertal cohort, Non-HDL was similar among the 4 groups. In contrast, in the pubertal cohort, non-HDL cholesterol was significantly higher in the non-remitters compared to the remitters, 111.3 ± 30.1 mg/dL vs 95.9 ± 29.1 mg/dL, p=0.028; and also, significantly higher in the non-remitters compared to the normal-weight controls, 111.3 ± 30.1 mg/dL vs 86.2 ± 32.2 mg/dL, p=0.028 (Figure 2a). In line with the findings for the LDL-C and TC, non-HDL was similar between the non-remitters and overweight/obese controls on one hand, 111.3 ± 30.1 mg/dL vs 105.6 ± 37.6 mg/dL, p=0.48, and the remitters and normal-weight controls on the other, 95.9 ± 29.1 mg/dL vs 86.2 ± 32.2 mg/dL, p=0.39. Figure 2b shows that both the remitters and normal-weight controls demonstrated lower non-HDL cholesterol concentration during puberty, while the non-remitters and overweight/obese controls did not.

Because the comparisons for the TC, LDL, and non-HDL showed similar patterns of reduction in remitters, we chose to fully report the results of LDL and non-HDL in full, while the TC results are depicted in Figures 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.

Stratification by body mass index (BMI)

LDL

The overweight/obese controls had significantly higher LDL-C compared to the normal-weight controls, 86.3 ± 25.7 mg/dL 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 non-remitters.

Among the normal-weight cohort, LDL-C was significantly higher in the non-remitters compared to the normal-weight controls, 89.2 ± 27.4 mg/dL vs 71.2 ± 20.8 mg/dL, p=0.01, while LDL-C was similar between the normal-weight controls and remitters (p=0.40), as well as between the remitters and non-remitters, (p=0.13).

Among the overweight/obese cohort, LDL-C was significantly higher in the non-remitters compared to the remitters 96.7 ± 24.2 mg/dL vs 79.9 ± 21.2 mg/dL, p=0.031, but was similar between the controls and remitters, 86.3 ± 25.7 mg/dL vs 79.9 ± 21.2 mg/dL, p=0.37.

Non-HDL cholesterol

Among the normal-weight cohort, non-HDL was significantly higher in the non-remitters compared to the controls, 107.1 ± 29.3 mg/dL vs. 90.5 ± 30.1 mg/dL, p=0.024; as well as between the non-remitters and remitters, 107.1 ± 29.3 mg/dL vs. 88.4 ± 31.0 mg/dL, p=0.021. In contrast, non-HDL was similar between the controls and the remitters, 90.5 ± 30.1 mg/dL 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.

Stratification by sex

LDL-C

The intergroup comparison showed no significant difference among the female subjects. In contrast, among the male subjects, LDL was significantly higher in the overweight/obese controls compared to the normal-weight controls, 81.38 ± 23.3 mg/dL vs 65.6 ± 16.0 mg/dL, p=0.041. Furthermore, LDL was also significantly higher in the male non-remitters compared to the normal-weight controls, 92.6 ± 32.2 mg/dL vs 65.6 ± 16.0 mg/dL, p=0.0012; as well as male non-remitters compared to the male remitters, 92.6 ± 32.2 mg/dL vs 74.5 ± 24.3 mg/dL, p=0.034.
Non-HDL cholesterol
Non-HDL cholesterol was similar among the 4 groups for the female cohort. In contrast, the male cohort showed a significantly higher non-HDL cholesterol level in the overweight/obese controls compared to the normal-weight controls, 103.1 ± 24.3 mg/dL vs 83.5 ± 23.3 mg/dL, p=0.044; and significantly higher non-HDL in the non-remitters compared to the normal-weight controls, 110.9 ± 32.2 mg/dL vs 83.5 ± 23.3 mg/dL, p=0.019. Non-HDL was similar between the normal-weight controls and the remitters, 83.5 ± 23.3 mg/dL vs 93.5 ± 30.6 mg/dL, p=0.37, but non-significantly higher in the non-remitters compared to the remitters, 110.9 ± 32.2 mg/dL vs 93.5 ± 30.6 mg/dL, p=0.067.

Stratification by race

LDL
Serum LDL-C was similar among the groups for the non-white cohort. In contrast, among the white cohort, LDL-C was significantly higher in the overweight/obese controls compared to the normal-weight controls, 85.1 ± 23.5 mg/dL vs 66.8 ± 13.2 mg/dL, p=0.0022. Equally, non-remitters had significantly higher LDL-C compared to the normal-weight controls, 93.6 ± 26.6 vs 66.8 ± 13.2 mg/dL, p<0.001; and also compared to the remitters, 93.6 ± 26.6 vs 78.3 ± 29.4 mg/dL, p=0.013. In contrast, LDL-C was similar between the normal-weight controls and remitters, 66.8 ± 13.2 mg/dL vs 78.3 ± 29.4 mg/dL, p=0.07; and overweight/obese controls and non-remitters (p=0.15).

Non-HDL
Significant findings for this analysis were seen in the White cohort where non-HDL was significantly higher in the non-remitters compared to the normal-weight controls, 110.7 ± 28.1 mg/dL vs 85.9 ± 24.7 mg/dL, p=0.011; and also significantly higher in the non-remitters compared to the remitters, 110.7 ± 28.1 mg/dL vs 92.8 ± 29.3 mg/dL, p=0.0075. Non-HDL cholesterol was similar between the normal-weight controls and the remitters (p=0.51), as well as overweight/obese controls and remitters (p=0.19).

Triglycerides (TG)
The comprehensive analysis of changes in serum triglycerides did not show any appreciable differences between the male and female subjects; the white- and non-white subjects; and the prepubertal and the pubertal subjects.

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 is the first study to characterize 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 to their healthy peers.

The first novel finding is 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 PCR showed similar reductions in LDL-C, TC, and non-HDL-C as do normal-weight, healthy children without T1D(14), while non-remitters did not. The stratification of the subjects into remitters and non-remitters is crucial for this investigation.
as 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 PCR history(2, 29-31).

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

The third novel 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 as 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 stratified by BMI status into normal-weight and overweight/obese groups, an analysis of the normal-weight cohort showed that LDL-C was significantly higher in the non-remitters than the controls, but similar between the non-remitters and remitters. Similarly, in the overweight/obese cohort, LDL-C was significantly higher in the non-remitters compared to the remitters (p=0.031), but was similar between the controls and remitters (p=0.37).

When the subjects were stratified by sex, LDL, and TC were significantly higher in male non-remitters, which is in contrast to the report that male subjects without diabetes display robust declines in LDL, TC, and non-HDL - than female subjects during puberty(14). This suggests that non-remission 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 the non-remitters compared to the controls, and remitters; suggesting that White subjects could be at a higher risk for early-phase dyslipidemia in subjects with T1D(28). Non-remission appears to worsen this trend toward dyslipidemia.

Figures 1b, 2b, and 3b show that even among the controls, the overweight/obese subjects do not undergo a robust decrease in TC, LDL, and non-HDL during puberty. Instead, only the normal-weight controls and remitters exhibit this phenomenon. This is important as 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 11-12 years for LDL-C, TC, and non-HDL cholesterol; a finding that 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 mechanism of 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 alpha and beta 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, PCR 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 any 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 PCR. Furthermore, 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 PCR using the IDAA1c criterion. These measures allowed for meaningful comparison of core parameters among the controls, remitters, and non-remitters.

**Conclusions**

Remission status is the key determinant of lipid concentration in youth with T1D during puberty: subject with a history of remission show similar reductions in TC, LDL, non-HDL, as in normal-weight healthy children; while both non-remitters and overweight/obese controls 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 non-remitters during puberty to reduce the prevalence of cardiovascular complications in adulthood.

**Acknowledgments**

We thank Professor Alan D. Rogol for his scientific review of this manuscript.

Grant support: None

**Corresponding Author:** Benjamin Udoka Nwosu, MD, FAAP., Professor, Division of Endocrinology, Department of Pediatrics, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA., Phone: 774-441-7784; Fax: 774-441-8055, Email: Benjamin.Nwosu@umassmemorial.org

**Reprint Requests:** Benjamin Udoka Nwosu, MD, FAAP. Address – same as for the corresponding author

Disclosure statement: The authors have nothing to disclose

**References**

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; 1:74-81.
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; 40:30-37.
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; 418:11-14.
4. Standards of Medical Care in Diabetes-2016: Summary of Revisions. *Diabetes Care*. 2016; 39 Suppl 1:S4-5.
5. Chmelova H, Cohrs CM, Chouinard JA, Petzold C, Kuhn M, Chen C, Roeder I, Kretschmer K, Speier S. Distinct roles of beta-cell mass and function during type 1 diabetes onset and remission. *Diabetes*. 2015; 64:2148-2160.
6. Nagl K, Hermann JM, Plamper M, Schroder 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; 18:428-434.

7. Max Andersen ML, Hougaard P, Porksen S, Nielsen LB, Fredheim S, Svensson J, Thomsen J, Vikre-Jorgensen 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; 15:469-476.

8. Mortensen HB, Hougaard P, Swift P, Hansen L, Holl RW, Hoey H, Bjoernsdal H, de Beaufort C, Chiarelli F, Danne T, Schoenle EJ, Aman J, Hvidoere Study Group on Childhood D. New definition for the partial remission period in children and adolescents with type 1 diabetes. *Diabetes Care*. 2009; 32:1384-1390.

9. Shields BM, McDonald TJ, Oram R, Hill A, Hudson M, Leete P, Pearson ER, Richardson SJ, Morgan NG, Hattersley AT, Consortium T. C-Peptide Decline in Type 1 Diabetes Has Two Phases: An Initial Exponential Fall and a Subsequent Stable Phase. *Diabetes Care*. 2018; 41:1486-1492.

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; 29:1105-1111.

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: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; 26:832-836.

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:S56-64.

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: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; 30:823-830.

17. American Diabetes A. Standards of Medical Care in Diabetes-2017 Abridged for Primary Care Providers. *Clin Diabetes*. 2017; 35:5-26.

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:e0176860.

19. Neylon OM, White M, MA OC, Cameron FJ. Insulin-dose-adjusted HbA1c-defined partial remission phase in a paediatric population--when is the honeymoon over? *Diabet Med*. 2013; 30:627-628.
20. Veit LE, Maranda L, Fong J, Nwosu BU. The vitamin D status in inflammatory bowel disease. *PLoS One*. 2014; 9:e101583.

21. Kuczynski 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*. 2002:1-190.

22. National Center for Health Statistics: https://www.cdc.gov/growthcharts/zscore.htm. In: 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*. 2002:1-190.

23. Veit LE, Maranda, L., Nwosu, B. U. The non-dietary determinants of vitamin D status in pediatric inflammatory bowel disease. *Nutrition*. 2015; in press

24. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomfield 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 Complete Appendix to Guidelines available at http://journals.aace.com. *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; 36:15-19.

26. Donaghue KC, Wadwa RP, Dimiglio LA, Wong TY, Chiarelli F, Marcovecchio ML, Salem M, Raza J, Hofman PL, Craig ME, International Society for P, Adolescent D. 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 Adolescents, National 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:S213-256.

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; 113:157-170.

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; 40:607-613.

30. Obermannova B, Petruzeltkova 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; 18:304-310.

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; 30:181-187.

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

**Figure 1a**. Bar graphs of low-density lipoprotein (LDL) cholesterol concentration stratified by pubertal status in controls and subjects with type 1 diabetes. There was no significant difference between the groups in the prepubertal cohort. In contrast, in the pubertal cohort, LDL was significantly higher in the non-remitters compared to the remitters (p=0.018), significantly higher in the non-remitters compared to the normal-weight controls (p=0.009). LDL was significantly
higher in the overweight/obese controls compared to the normal-weight controls (p=0.033), but similar between the normal-weight controls and remitters (p=0.39).

**Figure 1b**. A comparison of the patterns of LDL cholesterol in controls and subjects with type 1 diabetes. Both the remitters and normal-weight controls demonstrated lower LDL cholesterol concentration during puberty, while the overweight/obese controls and the non-remitters did not.

**Figure 2a**. Bar graphs of non-HDL cholesterol concentration stratified by pubertal status in controls and subjects with type 1 diabetes. In the prepubertal cohort, non-HDL was similar between the groups. However, in the pubertal cohort, non-HDL was significantly higher in the non-remitters compared to the controls (p=0.028), and the remitters (p=0.028), but similar between the normal-weight controls and remitters (p=0.39); and between the overweight/obese controls and the non-remitters (p=0.48).

**Figure 2b**. A comparison of the patterns of non-HDL cholesterol in controls and subjects with type 1 diabetes. Both the remitters and normal-weight controls demonstrated lower non-HDL concentration during puberty, while the overweight/obese controls and the non-remitters did not.

**Figure 3a**. Bar graphs of total cholesterol (TC) concentration stratified by pubertal status in controls and subjects with type 1 diabetes. In the prepubertal cohort, LDL was significantly higher in the non-remitters compared to the controls (p=0.022). However, in the pubertal cohort, LDL was significantly higher in the non-remitters compared to the normal-weight controls (p=0.011), and the remitters (p=0.012), but similar between the overweight/obese controls and non-remitters (p=0.09), and the normal-weight controls and remitters (p=0.51).

**Figure 3b**. A comparison of the patterns of total cholesterol (TC) in controls and subjects with type 1 diabetes. Both the remitters and normal-weight controls demonstrated lower TC concentration during puberty, while the overweight/obese controls and the non-remitters did not.

**Table 1. Anthropometric and Biochemical Characteristics of the subjects**

| Parameters                        | Controls (n=71) | Non-Remitters (n=79) | Remitters (n=44) | p value |
|-----------------------------------|----------------|----------------------|------------------|---------|
| Age (years)                       | 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   |
| Non-white (%)                     | 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      | -0.1 ± 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 |
| Body mass index (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- cholesterol (mg/dL)          | 46.1 ± 9.7     | 57.8 ± 13.3          | 53.2 ± 11.7      | <0.0001 |
| LDL- cholesterol (mg/dL)          | 82 ± 25.2      | 91.6 ± 26.5          | 78.8 ± 28.7      | 0.025   |
| Measure                                      | N/A | 105.8 ± 57 | 92.9 ± 57.4 | 99.1 ± 65.7 | 0.43 |
|----------------------------------------------|-----|------------|-------------|-------------|------|
| Triglycerides (mg/dL)                        |     |            |             |             |      |
| Total cholesterol (TC) (mg/dL)               |     | 150.1 ± 29.2 | 166.9 ± 29.7 | 151.5 ± 32.6 | 0.015 |
| Total cholesterol/HDL ratio                  |     | 3.3 ± 0.8   | 3.0 ± 8     | 2.9 ± 0.7   | 0.012 |
| HbA1c (mmol/mol) at the peak of remission at 6 months | N/A | 70.4 ± 16.9 | 56.8 ± 14.6 | 0.0001 |
| HbA1c (%) at the peak of remission at 6 months | N/A | 8.6 ± 1.5   | 7.35 ± 1.3  | 0.0001 |
| HbA1c (mmol/mol) at 4-5 years                 |     | 72.3 ± 13.5 | 70.4 ± 16.9 | 0.53 |
| HbA1c (%) at 4-5 years                       | N/A | 8.8 ± 1.2   | 8.6 ± 1.5   | 0.53 |
| Total daily dose of insulin (units/kg/day) at the peak of remission at 6 months | N/A | 0.64 ± 0.6 | 0.22 ± 0.2 | <0.001 |
| Total daily dose of insulin (units/kg/day) at 4-5 years | N/A | 1.0 ± 0.4  | 0.9 ± 0.4  | 0.24 |
| Duration of diabetes (years)                 | N/A | 4.8 ± 0.4   | 4.8 ± 0.4   | 1.00 |
