Influence of HbA\textsubscript{1c} and BMI on Lipid Trajectories in Youths and Young Adults With Type 1 Diabetes

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OBJECTIVE
To assess the influence of HbA\textsubscript{1c} and BMI (measured as BMI z score [zBMI]) on LDL, HDL, and non-HDL trajectories as youths with type 1 diabetes age into early adulthood.

RESEARCH DESIGN AND METHODS
Dynamic, retrospective cohort study examining changes in lipid values in 572 youths with type 1 diabetes followed longitudinally for a median of 9.3 years. Through longitudinal modeling, we describe the relationship of HbA\textsubscript{1c} and zBMI on lipid values as subjects age after adjusting for other relevant factors, including lipid-lowering medication use.

RESULTS
The median number of lipid assessments was 7 (range 2–39). Every 1% increase in HbA\textsubscript{1c} was associated with an \textasciitilde 2–6 mg/dL increase in LDL levels, with a greater increase in LDL levels as subjects progressed from prepubertal to postpubertal age ranges. A 1-SD increase in BMI was associated with a mean LDL increase of 2.1 mg/dL when subjects were 10 years old and increased to a mean of 8.2 mg/dL when subjects were 19 years old. The association between changes in HbA\textsubscript{1c} level and zBMI and changes in non-HDL levels as youths aged were similar to the associations found with LDL. The influence of HbA\textsubscript{1c} and zBMI on HDL levels was small and not dependent on age.

CONCLUSIONS
Changes in HbA\textsubscript{1c} level and zBMI modestly impact LDL and non-HDL cholesterol and have greater impacts as children age. Addressing elevations in HbA\textsubscript{1c} and zBMI as children enter into adolescence and beyond may lead to improvements in lipid levels.

Individuals with type 1 diabetes, and especially those with youth-onset disease, have significantly increased cardiovascular risk relative to the general population (1–3). Although much of this increased risk is attributed to diabetic nephropathy (4,5), cardiovascular disease (CVD) mortality remains elevated even in individuals with type 1 diabetes without renal disease (6,7). A study of the Swedish National Diabetes Register described an adjusted hazard ratio for death from CVD as over four times greater in individuals with type 1 diabetes than in individuals in the general population. Even in individuals with target glycemic control (HbA\textsubscript{1c} \lessapprox 6.9%), the risk of dying from CVD was twice that of the general population, suggesting the need to address nonglycemic CVD risk factors (7). Because of this increased risk,...
cardiovascular risk, the American Diabetes Association, American Heart Association, and National Heart, Lung, and Blood Institute guidelines recommend more aggressive management of elevated LDL cholesterol levels in youths with type 1 diabetes versus youths without type 1 diabetes (8–10).

Recent studies (11–13) have documented suboptimal management of dyslipidemia in youths with type 1 diabetes. Initial approaches for the treatment of dyslipidemia in youths with type 1 diabetes generally include improving glycemic control, dietary changes, and weight loss in overweight and obese youths. One study of a large cohort of youths with type 1 diabetes describes only modest reductions in LDL cholesterol levels with substantial improvements in HbA1c levels in youths over a 2-year period (14), documenting the challenge of targeting glycemic control in order to lower LDL levels.

Trajectories of lipid levels in youths with type 1 diabetes as they age from childhood into young adulthood warrant careful study in order to inform clinical guidelines and practice. Deepening the understanding of the influence of the modifiable risk factors HbA1c and weight status on lipid trajectories, and whether changes in HbA1c and weight status have differential effects on lipid levels at different stages of childhood and young adulthood could help to inform provider management recommendations for dyslipidemia in youths with type 1 diabetes.

In a dynamic cohort of youths observed for a median of 9.3 years (range 1.0–19.5 years), we aimed to describe the trajectories of LDL, HDL, and non-HDL cholesterol as youths with type 1 diabetes age into young adulthood. Further, we aimed to evaluate the effects of HbA1c and weight status (measured as BMI z score [zBMI]) on LDL, HDL, and non-HDL cholesterol levels as this cohort traverses childhood and adolescence and enters into young adulthood.

**RESEARCH DESIGN AND METHODS**

To be included in this dynamic cohort study, participants must have been previously enrolled in one of five psychoeducational or observational studies (15–18) to allow careful phenotyping of participants with respect to type of diabetes, diabetes duration, and sociodemographic characteristics. For all of these studies, participants were required to be youth with type 1 diabetes and be without major untreated medical or psychiatric comorbidities. Other specific inclusion criteria have been published elsewhere (15–18) but were typical, non-restrictive criteria for youths participating in observational or family-focused interventions. Data were extracted from paper and electronic medical records for the time before and after formal study participation. The Joslin Diabetes Center institutional review board approved all studies, including separate institutional review board approval for the current study.

For the current study, further restrictions limited the initial observation to the availability of an LDL measurement between the ages of 6 and <18 years and a duration of type 1 diabetes of ≥0.5 years. The cohort was further restricted to include only youths with at least two LDL observations ≥1 year apart. Then, all calculated LDLs with triglycerides that were not reported or ≥400 mg/dL were excluded. Data were captured across 2 decades between January 1993 and March 2013.

**Outcome Definition and Covariates Included**

The primary study outcome was subject-specific longitudinal lipid levels. The covariates included in these analyses were age, sex, race/ethnicity, HbA1c, zBMI, cholesterol-lowering supplement usage, and cholesterol-lowering medication usage.

**Clinical Values**

Height was measured using a stadiometer until adulthood, and weight was obtained by clinical scale; medical assistants obtained both measurements as a part of routine clinical practice in a standardized manner. zBMI values were calculated from the Centers for Disease Control and Prevention normative values in children and National Health and Nutrition Examination Survey (NHANES) values in adults. The Centers for Disease Control and Prevention provide normative values for zBMI in children based on their age to the closest day (19), and the NHANES data provide normative values in adults based on their age to the closest decade such that all female or males 20–29 years of age have the same normative values (20). Because of this difference in precision for normative values for zBMI according to age, we treat zBMI before age 20 and at age 20 or after separately in our analyses. Because of the limited number of members of racial and ethnic minorities in our cohort, we categorize race/ethnicity as either white (excluding Hispanic) or nonwhite (including Hispanic).

**Lipid-Lowering Medications**

Data on medication or supplement use were obtained in a systematic manner by trained research staff by manual review of paper and electronic medical records for any participant with an LDL value ≥130 mg/dL at any point during follow-up. Although all medication-treated participants used hydroxymethylglutaryl-CoA reductase inhibitors at some point during follow-up, other medications (e.g., fibrates) were also used in either combination or isolation. Participants taking supplements that are known to affect lipid levels (e.g., plant stanol esters, flaxseed) were also noted in our analyses. We considered a lipid value to have been obtained while receiving treatment with a medication or supplement if the medication or supplement was prescribed before the LDL was obtained and if the chart did not indicate that the patient had stopped taking the medication or supplement.

**Laboratory Values**

The majority (>97%) of laboratory values were obtained at the diabetes center, but a few values were obtained from outside clinical laboratories and manually entered into the data set. The data set consisted of 4,440 laboratory and clinical observations from 572 subjects. LDL was missing for 141 observations, HDL was missing for 12 observations, non-HDL was missing for 19 observations, HbA1c was missing for 44 observations, and zBMI was missing for 57 observations (31 youth and 26 adult observations).

**Lipid Measurement**

In the Joslin Diabetes Center laboratory in Boston, MA, lipids were measured using a Beckman Synchron CX9 analyzer from 1993 until October 2007; using an Ortho Vitros Chemical System from October 2007 until August 2011; and using a Roche Cobas Integra 800 Chemistry Analyzer from August 2011 through
When the laboratory methodology changed, the clinical laboratory always performed quality checks to ensure consistency in lipid measurements. Standards (or calibrators) remained the same during the follow-up period. LDL values were calculated using the Friedewald formula, as follows: (total cholesterol-HDL) − (triglycerides × 0.20). Beginning in November 2007, a direct LDL was analyzed reflexively when HDL concentration was < 35 mg/dL and/or triglyceride concentration was > 200 mg/dL. Direct LDL was measured on the same platforms as the other lipid measurements (using the Ortho Vitros Chemical System Analyzer from November 2007 until August 2011, and using the Roche Cobas Integra 800 Chemistry Analyzer from August 2011 until 2013). Calculated LDL levels were excluded when LDL level was measured directly on the same day. For these analyses, LDL, HDL, and non-HDL could be fasting or nonfasting. The majority of the laboratory values are nonfasting because nonfasting lipid measurement is common practice within our department as they exhibit little variability with fasting status (21). The non-HDL level is calculated as total cholesterol − HDL.

**HbA1c Measurement**

HbA1c level was measured using high-performance liquid chromatography from 1993 until November 2010 (Bio-Rad Variant Hemoglobin Testing System, Tosoh 2+2 Analyzer, and Tosoh G7 HPLC Analyzer). Beginning in November 2010, a turbidimetric inhibition immunoassay using the Roche Cobas Integra 800 Analyzer was used. Reference ranges remained constant at 4.0–6.0% and were consistently calibrated to the Diabetes Control and Complications Trial. Similar to the lipid measurements above, when the HbA1c assay changed, the clinical laboratory performed quality checks and ensured the calibration of methodologies.

**Proximate Data Capture**

For these analyses, each observation was captured according to the date of the lipid measurements. For some observations, if additional clinical or laboratory data were not available on the date that lipids were measured, the data closest temporally to the date of the lipid measurement were used. For missing HbA1c data, the closest HbA1c measurement within 3 months of a lipid measurement was used. For missing height or weight data, the closest measurements within 1 year of the lipid measurement were used.

**Statistical Analysis**

Descriptive statistics are given for subject level and measurement level characteristics using frequencies (percentages) for discrete variables and mean (SD) or median (25th to 75th percentiles) for continuous variables, as appropriate for the distribution. Longitudinal mixed models were fit separately for LDL, HDL, and non-HDL as the dependent variable. Each model adjusted for sex and race/ethnicity. Due to nonlinear effects, age at the time of the measurement was modeled as a cubic polynomial. No deviations from linearity were detected for HbA1c or zBMI. Type 1 diabetes duration or age at onset was not included in the models because of collinearity with age. Random subject-level intercepts and HbA1c slopes were included in the LDL and non-HDL models. The HDL model included random subject intercepts and age slopes because the HbA1c slope did not vary significantly by subject. No other factor was identified with a slope that varied significantly by subject in any of the three models. Models also accounted for autocorrelated errors within each subject.

Modifiable risk factors HbA1c, zBMI, and the use of medications and/or supplements were considered as independent variables and included in the model if \( P < 0.05 \) or if there was substantial clinical significance. Since \( z \) scores for BMI were calculated using different methods for children and young adults (see above), separate zBMI slopes were modeled for age (at measurement) of < 20 years versus > 20 years. To mitigate selection bias for the use of medications, indicator variables were included as independent variables for whether the subject ever used medications during the observation period and for whether the subject was currently using medication at the time of the measurement (time-varying indicator). Similar indicator variables were fit for the use of supplements. Interaction terms were included in the model if they were statistically significant (\( P < 0.05 \)). For models where there was a significant interaction of age with HbA1c and/or zBMI, slope estimates were given for various ages. We also tested whether the interaction between age and/or zBMI differed by sex.

Separate between-subject and within-subject slopes were modeled for HbA1c by including the cluster-averaged value in the model as a covariate (22). Since the objective of this study was to assess modifiable risk factors, the within-subject slope was reported in the regression results. No other factor had significantly different between-subject and within-subject slopes.

Residual values from each model were verified to have an approximately normal distribution. All reported \( P \) values are two sided. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

**RESULTS**

**Cohort Characteristics at First Observation**

A total of 572 subjects of the 645 in the data set fulfilled the inclusion criteria for these analyses. At the initial observation, subjects were 54% female and had a mean age of 11.9 ± 2.9 years, with a mean age at type 1 diabetes onset of 7.1 ± 3.4 years, and 34% were overweight or obese. The mean LDL concentration was 95 ± 29 mg/dL, the mean HDL concentration was 55 ± 13 mg/dL, and the mean non-HDL concentration was 115 ± 30 mg/dL (Table 1). At the initial observation, 41% of subjects had an LDL concentration of ≥ 100 mg/dL, 23% had an HDL concentration of < 45 mg/dL, and 40% had a non-HDL concentration of ≥ 120 mg/dL. The initial HbA1c level was 8.9 ± 1.5% (74 ± 16.4 mmol/mol).

**Cohort Characteristics at Last Observation**

At the final observation, subjects were 21.7 ± 4.1 years old. The mean LDL concentration was 98 ± 35 mg/dL, the mean HDL concentration was 60 ± 18 mg/dL, and the mean non-HDL concentration was 118 ± 45 mg/dL. At the last observation, 41% of subjects had an LDL concentration of ≥ 100 mg/dL, 17% had an HDL concentration of < 45 mg/dL, and 40% had a non-HDL concentration of ≥ 120 mg/dL. The last HbA1c level was 8.9 ± 1.7% (74 ± 18.6 mmol/mol). Fifty-five of the 572 (10%) subjects were exposed to...
lipid-modifying medications or supplements over the course of follow-up.

Supplementary Table 1 describes the measurement level characteristics for the study.

**Relationship Between Unadjusted Lipid Levels and HbA1c or Weight Status**

Figure 1A and B describes the unadjusted associations between LDL and HbA1c or weight status, respectively, as subjects age. Both figures demonstrate a stronger impact of the covariate of interest (HbA1c or weight status) and LDL in older subjects than in younger subjects. Figure 1C and D describe the unadjusted associations between HDL and HbA1c or weight status, respectively, as subjects age. Supplementary Fig. 1 describes the unadjusted associations between non-HDL and HbA1c or weight status as subjects age.

**Relationship Between Adjusted Lipid Levels and HbA1c or zBMI**

Table 2 reports the adjusted associations of HbA1c and zBMI with LDL. After adjusting for sex and race/ethnicity, both HbA1c and zBMI have age-dependent effects on LDL trajectories. For every 1% increase in HbA1c, LDL levels increase by ~2.6 mg/dL, with a greater increase in LDL levels as subjects progressed into adulthood. Similarly, for a 1-SD increase in BMI related to age- and sex-specific

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**Table 1—Subject demographics and characteristics (N = 572)**

|                          | Initial | Last | Initial | Last |
|--------------------------|---------|------|---------|------|
| Female sex               | 54      |      |         |      |
| Nonwhite                 | 9       |      |         |      |
| Age at T1D onset (years) | 7.1 ± 3.4 | 0.2–15.0 | 21.7 ± 4.1 | 6.1–17.9 |
| Age (years)              | 11.9 ± 2.9 | 10.4–32.1 | 14.6 ± 4.8 | 2.4–27.5 |
| Diabetes duration        | 4.8 ± 3.1 | 0.5–13.8 | 98 ± 35 | 12–255 |
| Neither medication/supplement usage | 90 | | 60 ± 18 | 9–140 |
| Medications usage only   | 6       |      |         |      |
| Supplements usage only   | 2       |      |         |      |
| Both medication/supplement usage | 2 | | 22–103 | 17–611 |
| LDL value (mg/dL)*       | 95 ± 29 | 18–247 | 98 ± 35 | 12–255 |
| HDL value (mg/dL)        | 55 ± 13 | 22–103 | 60 ± 18 | 9–140 |
| Non-HDL value (mg/dL)    | 115 ± 31 | 45–303 | 118 ± 45 | 17–611 |
| Triglycerides (mg/dL)    | 89 (60, 133) | 19–1,331 | 94 (65, 136) | 23–1,167 |
| Hba1c (%)                | 8.9 ± 1.5 | 5.5–14.6 | 8.9 ± 1.7 | 5.6–16.1 |
| Hba1c (mmol/mol)         | 74 ± 16.4 | 37–136 | 74 ± 18.6 | 38–152 |

T1D, type 1 diabetes; *LDL values were available for only 571 subjects.

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**Figure 1**—A: The distribution of LDL levels according to age-group stratified by Hba1c. B: The distribution of LDL levels according to age-group stratified by weight status. C: The distribution of HDL levels according to age-group stratified by Hba1c. D: The distribution of HDL levels according to age-group stratified by weight status. The horizontal line inside each box indicates the median; the bottom and top of the box indicate the 25th and 75th percentiles, respectively; and the dots indicate the mean. The number of measurements denotes the number where at least one lipid value (LDL, HDL, or non-HDL) is available. The actual number of measurements may be fewer for a particular lipid type. For LDL: Hba1c at <8.0% 25 fewer measurements; at 8.0% to <9.0% 38 fewer measurements; ≥9.0% 71 fewer measurements; weight status normal, 67 fewer measurements; overweight, 50 fewer measurements; obese, 15 fewer measurements than given in the legend. For HDL: Hba1c at <8.0% 2 fewer measurements; at 8.0% to <9.0% 0 fewer measurements; ≥9.0% 4 fewer measurements; weight status normal, 6 fewer measurements; overweight, 0 fewer measurements; obese, 0 fewer measurements than given in the legend.
normative values (an increase of 1 in zBMI), LDL increased significantly more as subjects aged from 2 mg/dL to >10 mg/dL. A 1-SD increase in BMI (an increase of 1 in zBMI) was associated with a mean LDL increase of only 2.1 mg/dL when subjects were 10 years old, but increased to a mean of 8.2 mg/dL when subjects were 19 years old. The modification effect of age on HbA1c or zBMI did not differ by a subject’s sex.

As expected, medication use was associated with the largest decrement in LDL (19.1 mg/dL). There was no significant effect of prescription of supplements, sex, or ethnicity on LDL.

Table 2 also reports the adjusted associations of HbA1c and zBMI with HDL. Increases in zBMI were associated with significant but modest decreases in HDL (a 1.6 mg/dL decrease in HDL in youths and a 3.4 mg/dL decrease in adults for every 1-SD increase in BMI) (Table 2). Increases in HbA1c level were associated with very small increases in HDL level (a 0.4 mg/dL increase in HDL for every 1% increase in HbA1c). The impact of HbA1c and zBMI on changes in HDL was linear and constant as subjects aged (i.e., no interaction between HbA1c or zBMI and age). Medication or supplement prescription did not impact HDL. Females had significantly greater HDL levels than males, and race/ethnicity did not significantly influence HDL levels.

Table 2 also reports the unadjusted associations of HbA1c and zBMI with non-HDL. HbA1c and zBMI similarly related to LDL and non-HDL. After adjusting for sex and race/ethnicity, our models demonstrated that age modified the relationship between changes in HbA1c, and zBMI and changes in non-HDL level (Table 2) with a magnitude similar to that of LDL levels. Our models estimated that medication use led to an ~12 mg/dL drop in non-HDL level. There was no significant effect of supplement use, sex, or ethnicity on non-HDL level.

Figure 2A shows the modeled influence of HbA1c on LDL levels as subjects age, and Fig. 2B shows the modeled influence of zBMI on LDL levels as subjects age. Both figures demonstrate the greater dispersion in LDL levels according to HbA1c level or zBMI as subjects progress from childhood into adulthood. Because the relationship between HbA1c, or zBMI and HDL was predicted to be constant as subjects aged, we do not include a graphic illustration of this relationship as a part of Fig. 2, but it is included in Supplementary Fig. 2. Figure 2C and D show the modeled influence of HbA1c, and zBMI, respectively, on non-HDL levels as subjects age. As for LDL, these figures demonstrate the greater dispersion in LDL levels according to HbA1c level and zBMI as subjects progress from childhood to adulthood.

**Sensitivity Analyses**

Regression results were similar when the total number of measurements for a subject was included as a covariate (data not shown). Results from a sensitivity analysis restricting each subject to one value per year (data not shown) were also similar. For the model predicting change in LDL, results were unchanged when calculated LDL values were only analyzed if triglyceride concentrations were <200 mg/dL.

**CONCLUSIONS**

In summary, this article describes the trajectories of LDL, HDL, and non-HDL cholesterol levels in a cohort of youths with type 1 diabetes as they age from childhood into young adulthood. Our
data demonstrate modest increases in LDL and non-HDL cholesterol with increases in HbA1c and zBMI across all ages studied. Notably, increases in HbA1c and zBMI have a greater effect on LDL and non-HDL cholesterol as subjects age. We demonstrate that HDL level decreases with increasing zBMI and that changes in HbA1c have a limited effect on HDL levels.

The negative effects of elevations in childhood lipid levels have been well established. Large cohort studies (23,24) of youths and young adults without type 1 diabetes demonstrate the strong tracking of childhood cholesterol values into young adulthood. Previous research also demonstrates that childhood cholesterol levels impact adult atherosclerosis because childhood LDL levels have significantly predicted adult carotid intima media thickness (25,26). Further, cardiovascular risk factors, including LDL levels, assessed in young adults correspond with coronary artery calcification 15 years later as well or better than contemporaneous assessments of cardiovascular risk (27), demonstrating the importance of addressing cardiovascular risk factor management in youths and young adults.

LDL cholesterol levels have been previously shown to relate to HbA1c and zBMI in youths with type 1 diabetes (28,29). In a 2-year study (14) of youths with type 1 diabetes, longitudinal models predicted improvements in LDL cholesterol levels with improvements in HbA1c levels that were more pronounced in youths with a higher HbA1c level. Another study (29) of 46 youths with type 1 diabetes who were observed over at least 3 years demonstrated increasing LDL levels with increasing zBMI and HbA1c level. Non-HDL level has also been previously shown to relate to HbA1c level and zBMI in youths with type 1 diabetes in cross-sectional analyses (30), and only to HbA1c level in a longitudinal analysis (31). We have added to this literature by examining these associations in a large cohort of youths as they age into adolescence and young adulthood. Additionally, we have included lipid-lowering medication and supplement use in our models.

Our models demonstrate that large changes in HbA1c levels and zBMI values are needed to influence cholesterol levels and that, in childhood, the same decrement in HbA1c or zBMI yields significantly smaller improvement in LDL and non-HDL cholesterol levels than it would in young adulthood. Guidelines often recommend lifestyle change, including weight loss in overweight or obese youths (8) and improvements in glycemic control (9), in addition to specific nutritional changes, such as limiting saturated fat intake, as the initial management of elevated LDL levels in youths with type 1 diabetes. However, our results suggest the degree of improvement in HbA1c levels or zBMI values needed to substantially influence LDL cholesterol levels may not be achievable for many youths and may be especially difficult to achieve for the youngest pediatric patients.

Our study does have limitations. As an observational study, there is the risk of confounders that were not accounted for in our models.
for in our analyses. The racial diversity in our cohort was limited. The laboratory values that we assessed were obtained as a part of clinical care at irregular intervals, and individuals with higher LDL levels had values obtained more frequently. We accounted for this by adjusting for the number of laboratory values in our models in a sensitivity analysis. Additionally, we completed a sensitivity analysis limited to annual cholesterol measurements in order to create more regular spacing of lipid values, and the results were unchanged. Although pediatric guidelines continue to recommend fasting lipid measurement, lipid panels were also often obtained as nonfasting samples, which may have impacted our analyses. However, the results for non-HDL cholesterol and LDL cholesterol levels were quite similar, and non-HDL level is not influenced by fasting status. Further, epidemiologic studies in youths and adults suggest that LDL cholesterol is affected only minimally by fasting status. We do not analyze triglyceride levels because of concerns over the impact of fasting status on these levels. Theoretically, as these lipid values were obtained as a part of clinical care, clinical lifestyle recommendations could have influenced lipid trajectories but a careful analysis of the effectiveness of such counseling demonstrates that this was not the case. Although the laboratory methods for HbA1c measurement were calibrated to agree with each other, the methodology for HbA1c measurement changed during the study, and this could potentially influence our model results.

In summary, LDL and non-HDL cholesterol levels relate similarly to HbA1c and zBMI in our population of youths and young adults with type 1 diabetes. Increases in HbA1c levels and zBMI values are associated with modest increases in LDL and non-HDL cholesterol levels. There are greater effects of HbA1c levels and zBMI values on LDL and non-HDL cholesterol levels as subjects age, but the influence of HbA1c level and zBMI values on HDL level are constant as subjects age. As an observational study, our study is limited by changes in laboratory methodology, differences in laboratory measurement intervals between subjects, differences in fasting status, and unmeasured confounding. Although this study provides needed context to the management of dyslipidemia in childhood, it cannot answer the important, unanswered questions related to the degree to which dyslipidemia influences later cardiovascular risk in youths and young adults with type 1 diabetes, or to the optimal timing, method, and effectiveness of management for dyslipidemia in pediatric diabetes. Interventional research, such as the currently ongoing AdDiT study, that treats select youths with type 1 diabetes with statins is promising, but more research on dyslipidemia management in pediatrics in general and pediatric diabetes in particular is needed so that providers can progress from measuring and tracking lipid levels in youths with type 1 diabetes to effectively providing evidence-based management for dyslipidemia when it occurs.

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