Predictors of Dyslipidemia Over Time in Youth With Type 1 Diabetes: For the SEARCH for Diabetes in Youth Study

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OBJECTIVE

Understanding the risk factors associated with progression and regression of dyslipidemia in youth with type 1 diabetes may guide treatments.

RESEARCH DESIGN AND METHODS

We studied 1,478 youth with type 1 diabetes (age 10.8 ± 3.9 years, 50% male, 77% non-Hispanic white, not on lipid-lowering medications) at baseline and at a mean follow-up of 7.1 ± 1.9 years in the SEARCH for Diabetes in Youth (SEARCH) study. Progression to dyslipidemia was defined as normal lipid concentrations at baseline and abnormal at follow-up (non–HDL-cholesterol [C] >130 mg/dL or HDL-C <35 mg/dL). Regression was defined as abnormal lipids at baseline and normal at follow-up. Multivariable logistic regression was used to evaluate factors associated with progression and regression compared with stable normal and stable abnormal, respectively. An area under the curve (AUC) variable was used for the time-varying covariates A1C and waist-to-height ratio (WHtR).

RESULTS

Non–HDL-C progressed, regressed, was stable normal, and stable abnormal in 19%, 5%, 69%, and 7% of youth with type 1 diabetes, respectively. Corresponding percentages for HDL-C were 3%, 3%, 94%, and 1%, respectively. Factors associated with non–HDL-C progression were higher A1C AUC and higher WHtR AUC in males. Non–HDL-C regression was associated with lower WHtR AUC, and HDL-C progression was associated with male sex and higher WHtR AUC. HDL-C regression was not modeled due to small numbers.

CONCLUSIONS

A1C and WHtR are modifiable risk factors associated with change in dyslipidemia over time in youth with type 1 diabetes.

Cardiovascular disease is the leading cause of death in adults with type 1 diabetes (1,2). This process begins in youth (3,4), and dyslipidemia is a major contributing risk factor (4).

Dyslipidemia has been well documented among youth with type 1 diabetes (5–9). However, few longitudinal studies exist, and those that have been published are limited by their retrospective nature, small sample size, inclusion of nonfasting lipid measurements, and relatively short duration of follow-up (10–14).

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Thus, using 7 years of follow-up data in a large cohort of youth with type 1 diabetes, we examined *1*) how fasting lipid levels track over time and *2*) factors that are associated with progression or regression of dyslipidemia over time. Identifying risk factors that are associated with progression and regression of dyslipidemia in youth with type 1 diabetes may guide treatments.

RESEARCH DESIGN AND METHODS

Study Participants

Participants for this study were enrolled in the SEARCH for Diabetes in Youth (SEARCH) study, a multicenter study examining the prevalence, incidence, and complications for youth with all forms of diabetes. Extensive details of the SEARCH study have been published and are summarized in a recent publication by Hamman et al. (15). Youth included in this analysis were diagnosed with incident type 1 diabetes starting in 2002 (baseline study visit occurred 9.0 ± 6.1 months after diabetes diagnosis) and subsequently participated in a SEARCH study follow-up visit (all visits completed by 2015). At baseline all participants had type 1 diabetes, defined as diabetes autoantibody positivity (GAD, islet antigen 2 [IA2], or zinc transporter 8 [ZnT8]) or no diabetes autoantibodies with high insulin sensitivity, as previously described by Dabelea et al. (16).

There were 2,004 SEARCH participants who had a baseline and follow-up visit. We excluded participants if they did not have a fasting lipid profile at the baseline (n = 179) or follow-up (n = 205) visit, if they did not report being on insulin at the follow-up visit (n = 29), if they reported taking lipid-lowering drugs at either visit (n = 63) to evaluate change in lipids without the influence of medications, or if they were younger than 10 years old at the follow-up visit (n = 50). Therefore, this report includes 1,478 youth with type 1 diabetes. Of those, 1,356 had diabetes autoantibody positivity and 122 had a high insulin sensitivity score alone (16). The study was reviewed and approved by each of the local institutional review boards, and all participants and parents provided written informed assent and/or consent.

Anthropometric and Metabolic Measurements

Race/ethnicity was self-reported, and participants were categorized as non-Hispanic white (NHW), non-Hispanic black, Hispanic, or other racial/ethnic group (Asian, Pacific Islander, American Indian, or other). Participants completed standardized questionnaires for medical history and medications. BMI was calculated as weight (kg)/height (m^2), and age- and sex-specific BMI z scores were derived (17). Waist circumference was measured using the National Health and Nutrition Examination Survey (NHANES) protocol (18) and divided by height in centimeters to calculate the waist-to-height ratio (WHtR). Measurements of hemoglobin A_{1c} (A1C), total cholesterol (TC), triglycerides (TGs), and HDL-cholesterol (C) were performed as previously described (19). LDL-C was calculated by the Friedewald equation or measured by the beta quantification procedure if TGs were ≥400 mg/dL.

Definitions of Abnormal Lipids

The major outcomes for this analysis were changes in dyslipidemia status for non–HDL-C (computed as TC − HDL-C) and HDL-C over time. Non–HDL-C was selected because it accounts for the cholesterol carried by all particles containing apolipoprotein B and outperforms the individual lipid parameters (TC, TGs, and LDL-C) in predicting subclinical atherosclerosis and cardiovascular disease (20–22). Abnormal non–HDL-C was defined as >130 mg/dL, and abnormal HDL-C was defined as <35 mg/dL, thresholds based on current recommendations in adults and children with diabetes (23,24). For each of these two measures, we defined progression of dyslipidemia as normal lipid concentrations at baseline (non–HDL-C ≤130 mg/dL or HDL-C ≥35 mg/dL) and abnormal at final follow-up, and regression was defined as abnormal at baseline and normal at final follow-up. Stable normal was defined as normal at baseline and follow-up and stable abnormal as abnormal at both baseline and follow-up.

Statistical Analysis

Data are presented as mean ± SD or median (interquartile range) for continuous variables, or frequencies (and percentages) for categorical variables. Demographics, anthropometrics, and cardiovascular risk factors were compared across the four groups (stable normal, stable abnormal, progression, and regression) by one-way ANOVA for continuous variables and χ^2 tests for categorical variables.

We used separate multivariable logistic regression models to examine factors associated with non–HDL-C and HDL-C progression compared with stable normal and those associated with non–HDL-C regression compared with stable abnormal. HDL-C regression was not modeled because of small numbers in the regression and stable abnormal groups. Model covariates included age at baseline visit (in years), race/ethnicity (NHW vs. other), sex (female vs. male), and duration of type 1 diabetes at baseline (in years).

A derived area under the curve (AUC) summary statistic (a continuous variable) for WHtR and A1C was also included in the models. AUC summarizes the longitudinal measures collected over time adjusting for the interval between each measure. WHtR was chosen over other measures of adiposity (BMI z score or waist circumference) because the former has been shown to be more strongly associated with adverse cardiovascular risk factors in children and adults (25,26). We also evaluated interaction terms (race/ethnicity or sex by WHtR) to determine whether the associations between WHtR and lipid progression and regression were different by race/ethnic group or sex. All models were also adjusted for clinic site, time interval between the visits, and season of the baseline visit. Variables with P values of <0.05 were considered statistically significant. Statistical analyses were performed using SAS 9.4 software (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of SEARCH participants with type 1 diabetes included in this analysis at baseline and follow-up are presented in Table 1. At baseline, the cohort was a mean age of 10.8 ± 3.9 years, the average disease duration was 0.75 ± 0.5 years, and mean A1C was 7.6 ± 1.5%. NHW comprised 77% of the cohort, and 50% were male.

Follow-up data were obtained an average of 7.1 ± 1.9 years later, when participants were an average age of 17.9 ± 4.1 years and had an average disease duration of 7.8 ± 1.9 years. The mean A1C at follow-up was 9.2 ± 1.8%. Non–HDL-C progressed in 19%, regressed in 5%, and remained stable abnormal in 7%

Table 1—Study cohort at baseline and follow-up

	Baseline		Follow-up	
	n	Mean ± SD or *n* (%)	*n*	Mean ± SD or *n* (%)
Age (years)	1,478	10.8 ± 3.9	1,478	17.9 ± 4.1
Race/ethnicity	1,477			
Non-Hispanic				
White		1,141 (77.3)		–
Black		140 (9.5)		–
Hispanic		170 (11.5)		–
Other		26 (1.8)		
Male sex	1,478	743 (50.3)		–
BMI *z* score	1,457	0.48 ± 1.04	1,473	0.59 ± 0.96
WHtR	1,358	0.48 ± 0.06	1,472	0.51 ± 0.08
Type 1 diabetes duration (years)	1,478	0.7 ± 0.5	1,478	7.8 ± 1.9
A1C (%)	1,472	7.6 ± 1.5	1,474	9.2 ± 1.8
A1C (mmol/mol)	1,472	59.8 ± 16.1	1,474	76.6 ± 19.9
TC (mg/dL)	1,478	159 ± 27	1,478	169 ± 34
LDL-C (mg/dL)	1,478	91 ± 22	1,478	96 ± 28
HDL-C (mg/dL)	1,478	56 ± 13	1,478	55 ± 13
Non–HDL-C (mg/dL)	1,478	103 ± 25	1,478	114 ± 35
TGs (mg/dL), median (Q1, Q3)	1,478	55 (42, 71)	1,478	75 (56, 105)
Systolic blood pressure (mmHg)	1,438	99 ± 12	1,475	106 ± 11
Diastolic blood pressure (mmHg)	1,436	63 ± 10	1,475	69 ± 9

Mean interval between visits 7.1 ± 1.9 years. Q, quartile.

and stable normal in 69%. HDL-C progressed in 3%, regressed in 3%, and remained stable abnormal in 1% and stable normal in 94%.

Participants who had progression of non–HDL-C levels compared with those who remained stable normal (Table 2) were older, more likely to be female, had greater adiposity (measured by BMI *z* score or WHtR), a longer duration of type 1 diabetes, a higher A1C, and higher diastolic blood pressure (all $P < 0.05$). Participants who remained stable abnormal were more likely to be non–Hispanic black, Hispanic, or other race/ethnicity, female, have more adiposity, and have higher A1C than youth who were stable normal (all $P < 0.05$).

We constructed multivariable logistic regression models to examine factors associated with progression and regression of dyslipidemia compared with stable normal and stable abnormal, respectively, after adjusting for covariates (Table 3). Factors associated with non–HDL-C progression were higher A1C AUC and higher WHtR AUC. Non–HDL-C regression was associated with lower WHtR AUC. HDL-C progression was associated with male sex and higher WHtR AUC. HDL-C regression was not modeled because of small numbers in the regression (3%) and stable abnormal (1%) groups.

We evaluated the interactions between race or sex and WHtR for each of the outcomes. We found a significant sex-by-WHtR interaction ($P = 0.0071$) for non–HDL-C progression such that the association between WHtR and non–HDL-C progression was stronger for males (2.63; 95% CI 1.83, 3.77) than for females (1.38; 95% CI 1.02, 1.87).

CONCLUSIONS

We report the natural evolution of dyslipidemia over 7 years in a large cohort of youth with type 1 diabetes. After adjusting for covariates, we identified two modifiable risk factors, WHtR and A1C burden over time, that were independent predictors of unfavorable changes in lipids or of stable abnormal levels over time.

The prevalence of dyslipidemia in youth with type 1 diabetes has been well documented in two large multicenter cross-sectional studies, the SEARCH for Diabetes in Youth study and the German prospective documentation and quality management system (DPV) study (5–7), as well several smaller cross-sectional studies (8,9,27). Although a few longitudinal studies exist, these studies are retrospective, have small sample sizes, include nonfasting lipid measurements, and are of relatively short follow-up duration (10–14). In 2007, Maahs et al. (11) retrospectively examined lipids over time in 360 youth with type 1 diabetes (age range 2–21 years) with a mean follow-up of 2.9 years. Using the thresholds for non–HDL-C and HDL-C of ≥130 mg/dL and <35 mg/dL as abnormal, they reported 27.8 and 3.3%, respectively, of youth with type 1 diabetes had sustained dyslipidemia over time. In addition, they found that higher A1C was positively associated with non–HDL-C levels and that a higher BMI *z* score was inversely related to HDL-C levels (11). Using similar criteria, Edge et al. (10) reported the frequency of dyslipidemia in 229 youth with type 1 diabetes in the U.K. as 4.3% for non–HDL-C and 0% for HDL-C. Furthermore, they showed that a higher non–HDL-C concentration was associated with higher A1C and longer duration of type 1 diabetes but lacked measures of adiposity to evaluate associations with lipids over time. Marcovecchio et al. (12) did find that sustained non–HDL-C abnormalities were related to older age, longer duration of type 1 diabetes, and higher BMI and A1C levels. However, with loss of greater than 75% of their cohort at the end of 2.3 years, this precluded definitive conclusions. In contrast, Reh et al. (13) reported longitudinal lipid levels in a cohort of 46 adolescents and young adults with type 1 diabetes in the U.S. (age range 12–25 years) during 3 years of follow-up and found that 0% of the cohort had sustained abnormal HDL-C (defined as <40 mg/dL) over time; non–HDL-C was not reported.

Here, we report prospective lipid data in youth with type 1 diabetes over a mean follow-up of ~7 years, the longest follow-up published in this population to date. We show that 19% of the cohort progressed to abnormal non–HDL-C concentrations during this time. Also concerning is that 7% of youth had sustained abnormal non–HDL-C over time, but only 5% had regressed. This stable abnormal frequency is somewhat lower than previously reported by Maahs et al. (11), where 27.8% of their adolescent cohort with type 1 diabetes had sustained elevation in non–HDL-C. The lower frequency of dyslipidemia reported here may be explained by our exclusion of those on lipid-lowering medication. Differences

Table 2—Characteristics of participants at follow-up visit: comparisons using non–HDL-C*

	Stable normal n = 1,020	Stable abnormal n = 105	Progression n = 285	Regression n = 68	P value*	P value*	P value*	P value*
	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	Overall among four groups	Progression vs. stable normal	Stable abnormal vs. stable normal	Regression vs. stable normal
Age (years)	17.68 ± 4.14	17.88 ± 4.15	18.53 ± 3.73	18.49 ± 4.58	0.0111	0.0019	0.6198	0.1121
Race/ethnicity					0.0225	0.0530	0.0224	0.5495
Non-Hispanic								
White	806 (79.1)	71 (67.6)	206 (72.3)	58 (85.3)				
Black	88 (8.6)	18 (17.1)	30 (10.5)	4 (5.9)				
Hispanic	110 (10.8)	14 (13.3)	40 (14.0)	6 (8.8)				
Other	15 (1.5)	2 (1.9)	9 (3.2)	0 (0)				
Male sex	535 (52.5)	42 (40.0)	130 (45.6)	36 (52.9)	0.0288	0.0412	0.0151	0.9375
BMI z score	0.52 ± 0.93	1.01 ± 0.99	0.77 ± 0.92	0.32 ± 1.11	<0.0001	<0.0001	<0.0001	0.0924
WHtR	0.49 ± 0.07	0.55 ± 0.10	0.53 ± 0.08	0.49 ± 0.08	<0.0001	<0.0001	<0.0001	0.7894
Type 1 diabetes duration (years)	7.73 ± 1.85	7.97 ± 1.91	8.07 ± 1.93	8.14 ± 1.97	0.0184	0.0069	0.2082	0.0792
A1C (%)	8.90 ± 1.66	9.80 ± 1.96	9.92 ± 2.02	8.78 ± 1.97	<0.0001	<0.0001	<0.0001	0.5943
TC (mg/dL)	153.54 ± 21.23	211.56 ± 29.96	209.54 ± 30.67	166.13 ± 18.94	<0.0001	<0.0001	<0.0001	<0.0001
LDL-C (mg/dL)	82.57 ± 17.08	136.57 ± 26.32	128.26 ± 22.63	95.74 ± 12.09	<0.0001	<0.0001	<0.0001	<0.0001
HDL-C (mg/dL)	56.32 ± 13.56	49.67 ± 13.64	52.36 ± 12.46	53.72 ± 12.68	<0.0001	<0.0001	<0.0001	0.1198
Non–HDL-C (mg/dL)	97.22 ± 18.68	161.90 ± 29.54	157.18 ± 29.57	112.41 ± 12.15	<0.0001	<0.0001	<0.0001	<0.0001
TGs† (mg/dL), median (Q1, Q3)	65.0 (51, 86)	107.0 (76, 157)	115.0 (89, 167)	74.5 (57.5, 94.5)	<0.0001	<0.0001	<0.0001	0.0259
Blood pressure								
Systolic (mmHg)	106.02 ± 10.77	106.84 ± 9.84	106.32 ± 11.01	105.95 ± 12.39	0.8801	^	^	^
Diastolic (mmHg)	68.31 ± 8.55	69.93 ± 8.53	70.28 ± 9.29	67.49 ± 9.50	0.0022	0.0008	0.0707	0.4512

Q, quartile. *Comparisons among groups evaluated using one-way ANOVA (continuous) or χ^2 tests (categorical); ^pairwise tests are not reported where the overall test across four groups is not statistically significant ($P > 0.05$); †tested using log (TGs).

Table 3—Multivariable logistic regression models for dyslipidemia progression and regression

	Non–HDL-C progression compared with stable normal *n* = 1,288 (281 events)		Non–HDL-C regression compared with stable abnormal *n* = 170 (67 events)		HDL progression compared with stable normal *n* = 1,405 (38 events)	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age at initial visit: 1 year increase	1.03 (0.99, 1.07)	0.1815	1.07 (0.98, 1.18)	0.1205	1.02 (0.94, 1.11)	0.6354
Race/ethnicity: other vs. NHW	1.22 (0.85, 1.75)	0.2726	0.48 (0.19, 1.23)	0.1274	1.10 (0.48, 2.53)	0.8172
Sex: female vs. male	1.03 (0.77, 1.38)	0.8199	0.71 (0.32, 1.54)	0.3815	**0.44 (0.22, 0.91)**	**0.0257**
Type 1 diabetes duration at initial visit: 1 year increase	0.98 (0.74, 1.31)	0.8985	1.77 (0.93, 3.33)	0.0800	1.48 (0.79, 2.76)	0.2183
A1C (AUC): 1% unit increase	**1.39 (1.25, 1.55)**	**<0.0001**	0.84 (0.65, 1.08)	0.1734	1.07 (0.83, 1.37)	0.5894
WHtR (AUC): 0.1 unit increase	**1.81 (1.42, 2.29)**	**<0.0001**	**0.49 (0.29, 0.84)**	**0.0089**	**1.64 (1.03, 2.59)**	**0.0353**

Variables included in the models: age and type 1 diabetes duration at initial visit, race/ethnicity, sex, A1C AUC, and WHtR AUC. Each model also adjusted for clinical site, the time interval between the baseline and follow-up visit, and season at the baseline visit. Statistically significant covariates appear in boldface type. OR, odds ratio.

may also be explained by lower baseline BMI and A1C in our cohort (11). Progression to abnormal HDL-C was 3% and sustained abnormal HDL-C was 1% in this study, consistent with previous reports (10,11,13).

We used the WHtR AUC to explore the association between burden of adiposity over time and dyslipidemia, which has not been assessed in longitudinal studies of youth with type 1 diabetes to date. We show that although a higher WHtR AUC is independently associated with non–HDL-C and HDL-C progression, a lower WHtR AUC ratio is associated with higher odds of non–HDL-C regression. Furthermore, we show that the association between WHtR AUC and non–HDL-C progression is stronger for males compared with females. These data suggest that similar to youth without diabetes (28), adiposity is an important independent risk factor for dyslipidemia among youth with type 1 diabetes. Future work is needed to determine whether reductions in abdominal adiposity improve lipid levels over time in youth with type 1 diabetes and whether these effects are more pronounced in males.

We show that glycemic control over time is another important modifiable risk factor that is associated with higher odds of non–HDL-C progression. These findings are consistent with prior cross-sectional and longitudinal studies in youth with type 1 diabetes (5,7,8,11) as well as data from adults who participated in the Diabetes Control and Complications Trial (DCCT) (29). Although worse glycemic control over time appears to adversely affect lipid levels, lowering of A1C through intensive insulin therapy has been shown to negatively affect weight (30), although not in all studies (31). These results point to a delicate balance between achieving glycemic control and maintaining body weight that affects lipids and remains to be elucidated.

One potential mechanism linking adiposity, glycemic control, and dyslipidemia in type 1 diabetes may be insulin resistance. Although insulin resistance among those with type 1 diabetes appears counterintuitive, because they are by definition insulin deficient, prior work has shown that youth with type 1 diabetes exhibit insulin resistance (32,33). The etiology of insulin resistance in type 1 diabetes is not clear, but adiposity, physical inactivity, and/or chronic exogenous insulin use may all play a role. Therefore, determining the optimal level of insulin needed to achieve glycemic control while avoiding weight gain appears critical to decreasing the progression of dyslipidemia in youth with type 1 diabetes. Unfortunately, we were not able to assess or estimate insulin resistance or sensitivity in this study. Prior SEARCH studies have used an equation that incorporates A1C, waist circumference, and TGs (32) to estimate insulin sensitivity, but the current study used insulin sensitivity to define the cohort, included A1C and WHtR AUC in the models, and TGs are included in the outcome non–HDL-C.

We found that male sex was associated with higher odds of HDL-C progression. Longitudinal data in healthy children, including work from the Bogalusa Heart Study, have shown that HDL-C levels, particularly for NHW males, decline at age 14 years and continue to drop until age 26 years, unlike NHW females, who have little decrease in HDL-C (34). Therefore, it is unclear whether the higher odds of HDL-C progression observed in this cohort of predominantly NHW males is a result of type 1 diabetes or normal tracking of lipids through adolescence.

Strengths of this study include a large cohort of youth with type 1 diabetes, standardized lipid measurements, follow-up data over 7 years, and the ability to evaluate the associations between burden of risk factors and lipids over time. Limitations of the study include a lack of more frequent lipid assessments during the 7 years of follow-up, relatively small numbers of participants in each category that limited our ability to explore HDL-C regression, and lack of some variables, including thyroid status, family history of hyper/dyslipidemia, and pubertal status, each of which is known to influence lipids. In addition, physical activity, diet history, and smoking status were not obtained on all participants at the baseline visit and thus could not be included as covariates to evaluate change in lipids overtime, although it is possible physical activity and diet may be reflected by changes in adiposity. Future studies should include these variables.

In conclusion, we demonstrate approximately one-quarter of youth with type 1 diabetes has progression of dyslipidemia or abnormal lipids that persists over time. Risk factors that influence progression include both increased abdominal adiposity and worse glycemic control over time. Until the complex interplay

between adiposity and glycemic control on lipids is elucidated, our data suggest both risk factors are important and influence lipids in youth with type 1 diabetes and are potential opportunities for intervention.

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