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## Glucose Control Predicts 2-Year Change in Lipid Profile in Youth with Type 1 Diabetes

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### Abstract

**Objective**—To test the hypothesis that a change in A1c over a follow-up interval of approximately 2 years would be associated with concomitant changes in fasting lipids in individuals with type 1 diabetes (T1D).

**Study design**—All subjects with T1D diagnosed 2002–2005 in the SEARCH for Diabetes in Youth study with at least two study visits approximately 12 and 24-months after an initial visit were included (age at initial visit=10.6±4.1 years, 48% female, diabetes duration=10±7 months, 76% non-Hispanic White, A1c=7.7±1.4%). Longitudinal mixed models were fit to examine the relationship between change in A1c and change in lipid levels (total cholesterol [TC], high-density lipoprotein-cholesterol [HDL-c], low-density lipoprotein-cholesterol [LDL-c], log triglycerides [TG], and non-high-density lipoprotein-cholesterol [non-HDL-c]) with adjustment for possible confounders.

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\*A list of members of the SEARCH for Diabetes in Youth Study and funding information are available at [www.jpeds.com](http://www.jpeds.com) (Appendix).

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**Results**—Change in A1c over time was significantly associated with changes in TC, HDL-c, LDL-c, TG, and non-HDL-c over the range of A1c values. For example, for a person with an A1c of 10% and then a 2% decrease in A1c 2-years later (to 8%), the model predicted concomitant changes in TC (−0.29 mmol/l, −11.4 mg/dl), HDL-c (0.03 mmol/l, 1.3 mg/dl), LDL-c (−0.23 mmol/l, −9.0 mg/dl), and non-HDL-c (−0.32 mmol/l, −12.4 mg/dl), and an 8.5% decrease in TG (mmol/l).

**Conclusions**—Improved glucose control over a 2-year follow-up was associated with a more favorable lipid profile, but may be insufficient to normalize lipids in dyslipidemic T1D youth needing to decrease lipids to goal.

### Key Terms

cholesterol; lipids; glycemic control; pediatrics; type 1 diabetes; cardiovascular disease risk factors; diabetes mellitus; epidemiology

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Hyperglycemia and dyslipidemia are metabolic abnormalities commonly found in individuals with type 1 diabetes (T1D). Both increase the risk of cardiovascular disease (CVD), the leading cause of mortality in individuals with T1D (1).

The antecedents of adult CVD, including dyslipidemia, are present in children and numerous studies demonstrate tracking of CVD risk factors into adulthood (2–4). Furthermore, CVD risk factors in childhood are associated with both surrogate markers of atherosclerosis (4) and atherosclerotic lesions at autopsy in adults (2;3). Due to these findings the American Diabetes Association (ADA) (5), the American Academy of Pediatrics (AAP) (6), the International Society of Pediatric and Adolescent Diabetes (ISPAD) (7), and the American Heart Association (AHA) (8) have all published guidelines for intervention in youth with diabetes and dyslipidemia. However, because there is a paucity of data on dyslipidemia in youth with T1D, these guidelines are based on extrapolation of data from adults and from youth without diabetes (1).

Each of these professional organizations recommends intensification of glucose control, a healthy diet, and exercise as the initial therapy for dyslipidemia in youth with T1D. However, it is unclear to what extent improved glucose control alters lipid measurements. Better understanding of the association of glucose control to dyslipidemia would inform current practice guidelines and clinical decision making about the treatment of dyslipidemia in youth with T1D (1). Therefore, we tested the hypothesis that a change in glycated hemoglobin (A1c) over a follow-up interval of approximately 2 years would be associated with concomitant changes in the lipid profile in youth with T1D participating in the SEARCH for Diabetes in Youth (SEARCH) study.

### Methods

SEARCH is an ongoing study that began in 2001 to conduct population-based case ascertainment of youth <20 years with diabetes (9). SEARCH has a defined protocol for incident cases to have 12- and 24-month follow-up visits after their initial study visit. This paper includes information for the participants in the 2002–2005 incident cohorts and the corresponding 12- and 24-month visits for participants with at least one follow-up visit after the initial study visit. The study was reviewed and approved by the local institutional review boards that had jurisdiction over the local study populations and all participants provided informed consent and/or assent.

During the study visit, survey information, including medication use, was collected, an examination was performed to measure systolic and diastolic blood pressure, height, weight,

BMI, and waist circumference, as previously described (9) and blood samples were obtained under conditions of metabolic stability after at least eight hours of fasting. Specimens were processed locally at the sites and within 24 hours shipped to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle) where they were analyzed for measurement of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and triglycerides (TG). Measurements of TC, HDL-c, and TG were performed enzymatically using Roche reagent on a Hitachi Modular P autoanalyzer (Roche Diagnostics, Indianapolis, IN). Low-density lipoprotein cholesterol (LDL-c), levels were calculated by the Friedewald equation for individuals with TG levels less than 4.52 mmol/l and by Lipid Research Clinics Beta Quantification for those with triglyceride levels at least 4.52 mmol/l. Non-HDL-c concentration was computed as TC minus HDL-c. A1c levels were measured by ion-exchange high-performance liquid chromatography (TOSOH G7, TOSOH Biosciences Inc., South San Francisco, CA).

The diabetes type was categorized as type 1 and type 2, based on the health care provider diagnosis (9). Race/ethnicity was self-reported using the 2000 census questionnaire format. Five categories were created (Hispanic, American Indian, non-Hispanic Black, Asian/Pacific Islander, non-Hispanic White [NHW]).

The study population consisted of all SEARCH participants with T1D who were diagnosed from 2002 through 2005 and had at least two study visits where fasting lipids and A1c were measured simultaneously. Subjects reporting use of lipid-lowering medications ( $n=7$ ) were excluded. Of the 1,193 participants included in these analyses, fasting lipids were measured in all twice, and in 563 three times over an approximately 24-month period. Subjects were invited to a SEARCH visit only after diabetes has been diagnosed and no patients in DKA were included in the analyses.

### Statistical Analyses

The mean and SD (or median and Q1, Q3) for each variable of interest were calculated based on data collected at the initial visit. Longitudinal mixed models using all data from the initial and subsequent visits were fit to examine the relationship between A1c (initial value and time-varying values) and time-varying lipid levels (TC, HDL-c, LDL-c, TG, and non-HDL-c) included as the outcome in each model. As a marker of time for each participant, we included duration of diabetes (number of months since diabetes diagnosis) in these mixed models. Because this study is observational all assessments of the lipid measures (baseline and follow-up) are contained in our statistical models as part of the outcome.

Multivariable modeling focused on the effects of the initial A1c (measured at the first SEARCH study visit) and the time-varying effects of A1c measured at the 12- and/or 24-month follow-up visits. In addition we explored any interaction of the main effects. Each model also included several participant-level characteristics that were measured at the initial visit as covariates. These effects included participant age (included as age and age-squared to allow for non-linear relationships), race/ethnicity (NHW vs other groups), sex, site, season of the year when measurements were performed (autumn vs each other season), and baseline BMI z-score (BMI value represented as a z-score that adjusts for age and sex for each participant) Because Tanner Staging was not available for all participants due to IRB restrictions at some centers, we examined the correlation between Tanner Staging (where available) and participant age. We found these two measures were highly correlated ( $r=0.84$ ,  $p<0.0001$ ), thus the inclusion of age in the above models was also considered a surrogate for pubertal stage.

For multivariable models, the beta-coefficient and 95% confidence intervals (CI) for the association of time varying A1c (to determine the association of change in A1c with change

in lipid) adjusted for initial A1c and diabetes duration are reported (adjusted for age, age-squared, race/ethnicity, sex, site, season of the year, and baseline BMI z-score. Additionally, an interaction term (initial A1c by time varying A1c) was included in this model to determine whether the association of change in A1c with changes in lipids was different depending on the initial A1c value. All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

## Results

The clinical characteristics of 1,193 individuals at the initial visit are described in Table I (age=10.6±4.1 years, 48% female, T1D duration=10±7 months, 76% non-Hispanic White, A1c=7.7±1.4%). Mean and SD for fasting lipid measures at the initial visit were: TC 4.17±0.76 mmol/l or 161±29 mg/dl, HDL-c 1.39±0.33 mmol/l or 54±13 mg/dl, LDL-c 2.45±0.63 mmol/l or 95±24 mg/dl, TG [median (Q1,Q3)] 0.62 (0.50, 0.81) mmol/l or 55 (42, 72) mg/dl, and non-HDL-c 2.78±0.69 mmol/l or 108±27 mg/dl. Mean±SD annualized change in A1c was 0.45±0.89% and mean±SD annualized change in each fasting lipid measure were TC (0.08±0.41 mmol/L, 3.0±15.7 mg/dl), HDL-c (0.03±0.17 mmol/L, 1.2±6.5 mg/dl), LDL-c (0.02±0.30 mmol/L, 0.7±11.6 mg/dl), TG (0.07±0.36 mmol/L, 5.7±31.8 mg/dl) and non-HDL-c (0.05±0.35 mmol/L, 1.7±13.5 mg/dl). Using cut-points of TC 200 mg/dl, LDL-c 130 and 100 mg/dl, HDL-c 35 mg/dl, non-HDL-c 160 mg/dl, and TG 150mg/dl, then the rates of abnormalities at the initial visit for this analysis are 8.4%, 7.2% and 37.1%, 4.7%, 3.1% and 2.9%, respectively.

Change in A1c was associated with changes in TC, HDL-c, LDL-c, TG, and non-HDL-c over the range of A1c values in these data. The interaction term between initial A1c and time varying A1c was significant ( $p<0.01$ ) for TC, HDL-c, logTG, and non-HDL-c and  $p=0.0506$  for LDL-c, although because this was a test for an interaction rather than a main effect, this p-value is likely to also be clinically significant. This indicates that the effect of changing A1c on changes in lipid values over time differed based on the initial A1c values (Table II). For example, for a decrease in A1c from 10% at 6-months duration to 8% two years later (2% of subjects had a 2% change in A1c from first to last measure), the model predicted a change in TC (-8.5 mg/dL, -0.29 mmol/l, 95% CI: -0.37, -0.22 or -11.4, 95% CI: -14.3), HDL-c (2.5 mg/dL, 0.03 mmol/l, 95% CI: 0.00, 0.07 or 1.3, 95% CI: 0.03), LDL-c (-6.8 mg/dL, -0.23 mmol/l, 95% CI: -0.29, -0.17 or -9.0, 95% CI: -11.3), and non-HDL-c (-9.7 mg/dL, -0.32 mmol/l, 95% CI: -0.39, -0.25 or -12.4, 95% CI: -15.0), and a 8.46% (95% CI: 3.96%, 12.76%) decrease in TG. These associations were independent of initial age, race/ethnicity, sex, season of the year, diabetes duration, and BMI z-score. Of the 145 subjects with an initial LDL-c > 100 mg/dl who also had a decrease in A1c, 48 (33%) had an LDL-c < 100 mg/dl at the last measure.

The Figure illustrates the varying changes in lipid values over a 24 month interval (with a starting duration of 6 months) for a range of starting and ending A1c values. They are based on the results of the adjusted multivariate model (Table II) and display the predicted mean changes in lipid level associated with a 2% or 1% decrease or increase in A1c over 24-months (starting at 6-months duration) for a starting A1c level of 8% (in the first column) or 10% (in the second column). For example, for an initial A1c of 8%, a decrease in A1c of 2% and 1% would result in a predicted change in TC of  $-0.24\pm 0.03$  mmol/L ( $-3.9\pm 1.3$  mg/dl) and  $-0.10\pm 0.03$  mmol/L ( $-3.9\pm 1.0$  mg/dl), respectively, and an increase of 1% and 2% would result in a predicted change of  $0.18\pm 0.02$  mmol/L ( $6.9\pm 0.7$  mg/dl) and  $0.32\pm 0.02$  mmol/L ( $12.3\pm 0.9$  mg/dl), respectively.

We also found that the association of change in A1c to changes in lipids over time was non-symmetric. Thus, the models predict the following. First, change in A1c in subjects with a

higher initial A1c will have larger effects on change in TC, non-HDL-c, and TG (in either direction) compared with subjects with lower initial A1c. Second, the association of change in A1c to change in TC, HDL-c, and TG over 2-years is larger for those subjects who have an increasing A1c as compared with those who have a decreasing A1c (Figure).

Although the focus of this paper is on the association of change in A1c to changes in lipids, some initial visit covariates were independently associated with lipid outcomes. Higher BMI z-score was associated with lower HDL-c, and higher LDL-c, TG and non-HDL-c. Female sex was associated with higher TC, LDL-c, TG, and non-HDL-c. Non-Hispanic Black race/ethnicity (compared with NHW) was associated with higher HDL-c and lower TG and non-HDL-c. For LDL-c and non-HDL-c the quadratic term for age was significant and positive with a significant negative linear age effect, and estimates suggest a negative association between age and lipid for younger ages followed by a reversal to a positive association for older ages. In contrast, for HDL-c the quadratic term for age was significant and negative, with a significant positive linear effect, with estimates suggesting an initial positive relationship at younger ages with a reversal to a negative association at older ages.

## Discussion

We demonstrate that change in glucose control is associated with changes in lipids over a period of approximately 2 years in youth with T1D. This relationship remains after controlling for the effects of initial age, race/ethnicity, sex, season of the year, T1D duration, and BMI z-score. These data suggest that improvement of glucose control in youth with T1D may have a limited (i.e. a decrease of 0.23 mmol/L in LDL-c associated with a decrease in A1c from 10% to 8% over 2 years), though beneficial effect on TC, HDL-c, TG, LDL-c and non-HDL-c. Thus, these data provide additional support for the current AHA, ADA, AAP, and ISPAD guidelines which recommend intensification of glucose control, in addition to a healthy diet and lifestyle, as the initial steps to treat dyslipidemia.

There are additional clinical implications of these findings. First, changes in A1c in patients with higher initial A1c will have larger effects on TC, non-HDL-c, and TG levels as compared with similar A1c changes in patients with lower initial A1c. Second, the associations of A1c change and changes in lipid levels is greater if A1c worsens than if A1c improves (for TC, HDL, and TG). These data are consistent with the concept of metabolic memory (10) such that increases in A1c could exert an atherogenic effect via the effect of hyperglycemia on lipids. Although some of these associations between A1c change and changes in lipid levels may be small clinically it is possible that even small changes in lipid levels may have negative health impact over time with prolonged duration of diabetes. It is also possible that for those patients with higher initial A1c additional healthy behaviors such as diet and exercise contributed to the larger effects on decrease in TC, non-HDL-c, and TG.

In these analyses, sex, age, race/ethnicity, and BMI z-score were also associated with change in lipids. Of these, only BMI is a modifiable risk factor for dyslipidemia. We found that a higher BMI z-score at baseline was associated with unfavorable changes in HDL-c, LDL-c, TG, and non-HDL-c, independent of glycemic control. This finding emphasizes the importance of weight control in youth with T1D. However, intensification of glucose control may also have an adverse effect on BMI and the lipid profile. Specifically, the Diabetes Control and Complications Trial (DCCT) study, which was predominantly a study of adults with T1D, reported that an increase in BMI was associated with a worsening in lipids in the intensive vs the conventionally treated groups (11), although a clinical trial in T1D adults has shown the feasibility of reducing A1c without increasing BMI (12). Furthermore, although improving glucose control is always one of the primary goals of care for persons with T1D and their diabetes care providers, based on these data improved glucose control

alone may not be sufficient to achieve lipids goals (i.e., a decrease of 0.23 mmol/L [9 mg/dl] in LDL-c associated with a decrease in A1c from 10% to 8% over 2 years). Similarly, in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study in adults with a longer duration of T1D, change in A1c was associated with significant changes in TC, LDL-c, TG, and non-HDL-c (but not HDL-c) over 6-years (13). However, in the CACTI study treatment with dyslipidemia medication eliminated statistical significance of the association of A1c to lipids as these medications had a stronger effect on lipids than did glycemic control. Understanding the complex interaction among A1c, BMI, and lipids and how these factors influence the development and progression of CVD in people with T1D requires further study.

These longitudinal data are consistent with previous smaller cross-sectional studies in youth with T1D in which a correlation between A1c and a more atherogenic lipid profile was found (14–17). The DCCT reported that TC, LDL-c, and TG increased with elevated A1c, but HDL-c was not correlated with A1c (18). In addition, a recent study from adolescents in the UK reported a significant positive association of glycemia to TC, TG, LDL-c, and non-HDL-c (19). However, a limitation of the UK study was that the participants were not fasting, calling into question the validity of the TG and LDL-c measures, although recent data suggest that the differences in fasting compared with non-fasting lipid profiles may not be clinically significant (20). Other longitudinal studies in youth reported similar results but in smaller samples (21;22) or using retrospective data (23). Further, pre-DCCT data (cohort of 212 subjects with T1D with a mean age 22 years) reported a 2.2% and 8% decrease in TC and TG, respectively, per 1% point decrease in A1c over an average interval of 3.7 years (24). Data on HDL-c, LDL-c, and non-HDL-c were not reported in that study. Another pre-DCCT study (mean A1c=14.2±2.1%) reported covariations in A1c and lipid levels (25). Thus, the literature supports concomitant changes in A1c and lipid measures and our data confirm and add additional dimensions to these previous findings.

In contrast to our findings, a previous SEARCH publication using cross-sectional analysis did not find an association between A1c and HDL-c (16) and a recent UK study of adolescents reported no association of glycemia and HDL-c (19). Purnell et al reported that intensive insulin therapy in the DCCT resulted in lower A1c and lower HDL-c associated with increased BMI (11) and suggest that concomitant changes in glucose control and HDL-c may be mediated by factors affecting insulin resistance (26). This possibility is supported by the association of insulin resistance (measured by a hyperinsulinemic-euglycemic clamp) with higher TG and TG/HDL-c in both adolescents and adults and lower HDL-c in adolescents with T1D(27). Similarly, in subjects with T1D, more insulin resistance was associated with a proatherogenic lipoprotein subfraction cholesterol distribution (28). Investigators have reported higher HDL-c concentrations in adults (29) and youth (17) with T1D than in non-diabetic controls. In a post-hoc analysis, units of insulin/kg/day was not significantly associated with changes in lipids. More research is needed to clarify the complex relationship between glucose control and HDL-c in T1D.

Our study has some limitations. First, the data are observational and not the result of a randomized clinical trial nor can we comment on the duration of A1c change to changes in lipids. We also do not have follow-up data or Tanner stage data on all participants. However, minimal differences existed between those who did and did not participate in the follow-up assessment. Also, the study was conducted on a cohort of youth recently diagnosed with T1D (diabetes duration 10±7 months at baseline) of whom many likely had residual beta-cell function, which may limit A1c variability. Finally, although the SEARCH study population includes an ethnic representation that is consistent with the ethnic diversity in the United States, SEARCH does not represent all of the geographic areas in the United States nor does it account for regional ethnic diversity and does not focus on racial-ethnic

differences in lipids (30). Thus, these findings may not apply to all populations in the United States or other populations worldwide.

In conclusion, improved glucose control in youth with T1D was associated with more favorable TC, HDL-c, TG, LDL-c, and non-HDL-c levels over a 2-year follow-up. However, reduction in A1c may be insufficient to normalize lipids in dyslipidemic T1D youth needing to decrease lipids to goal. Although longitudinal studies of lipids in youth with T1D (21;23) have been published, we investigated the relationship between the change in glucose control and changes in fasting lipids in a large cohort of youth with T1D. We also report that the association of change in A1c to changes in lipids is more pronounced with higher initial A1c values and for increases as compared with decreases in A1c. Further research is needed to establish the roles of glucose control, diet, exercise, and dyslipidemia medications to improve the cardiovascular health of youth with T1D.

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## Appendix

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Figure 1a

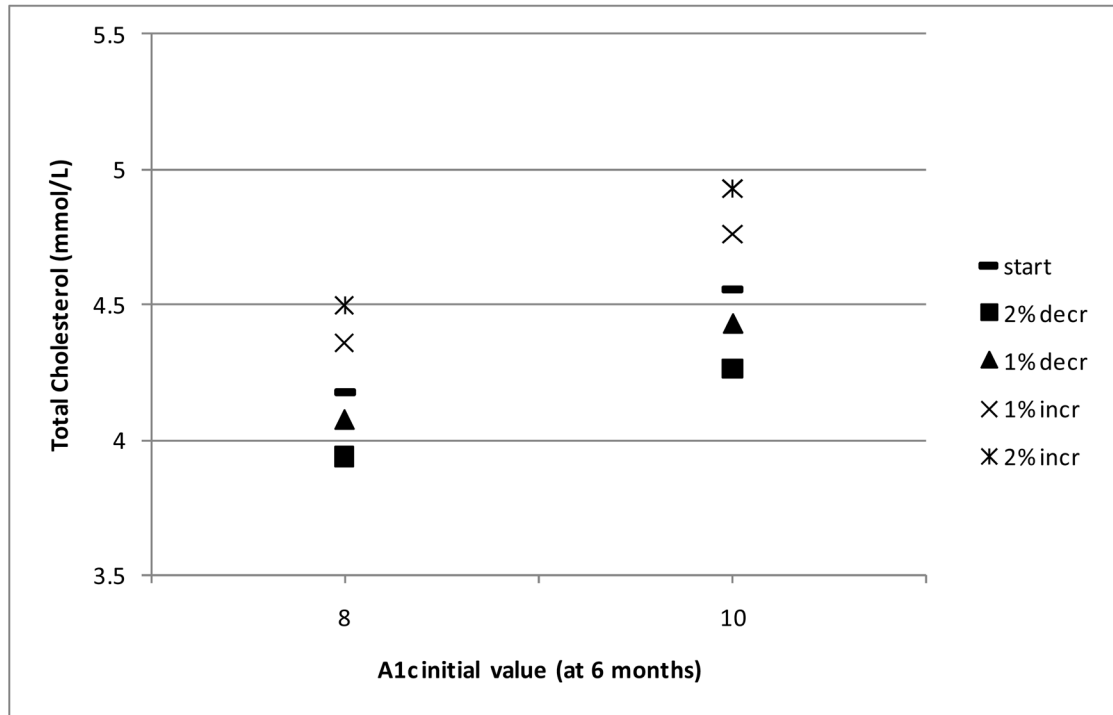


Figure 1b

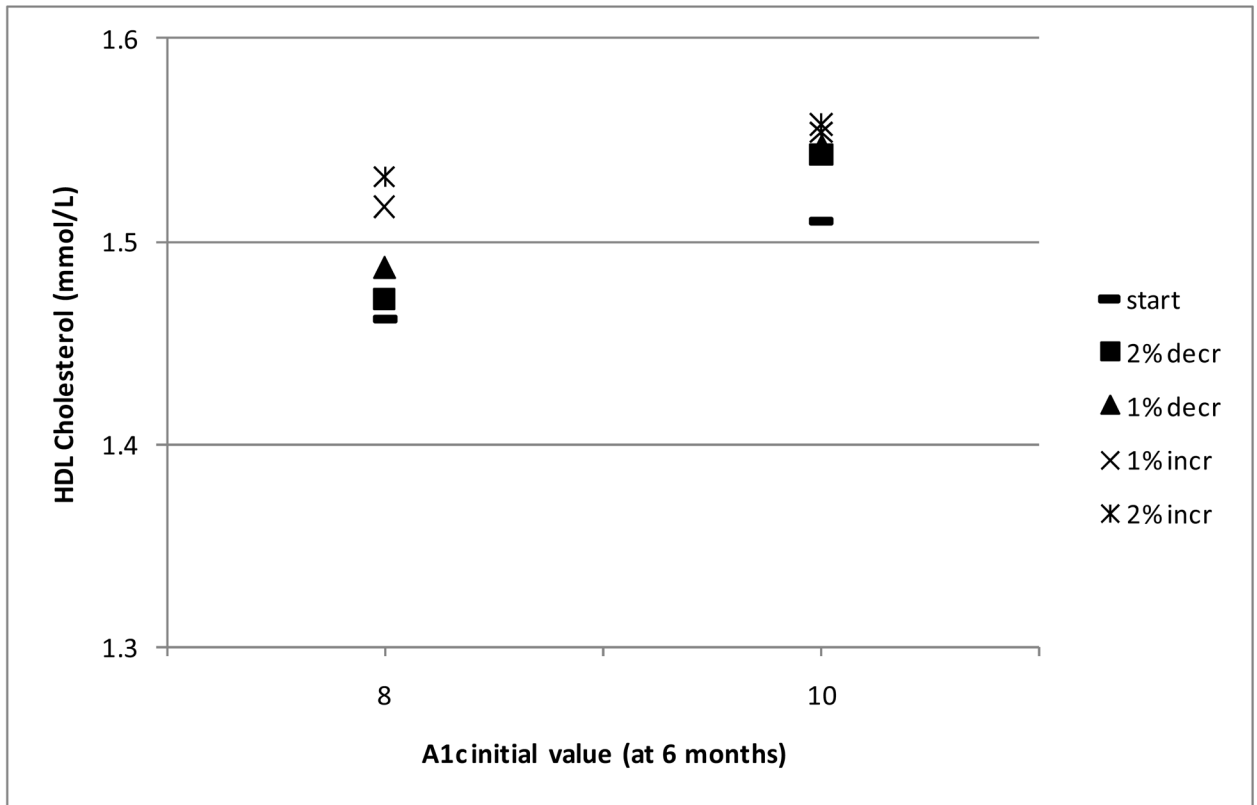


Figure 1c

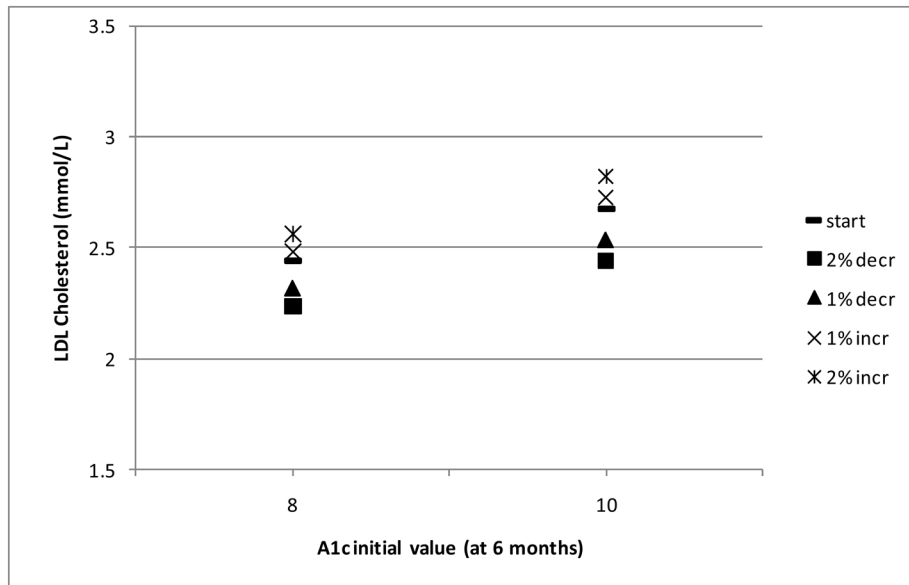


Figure 1d

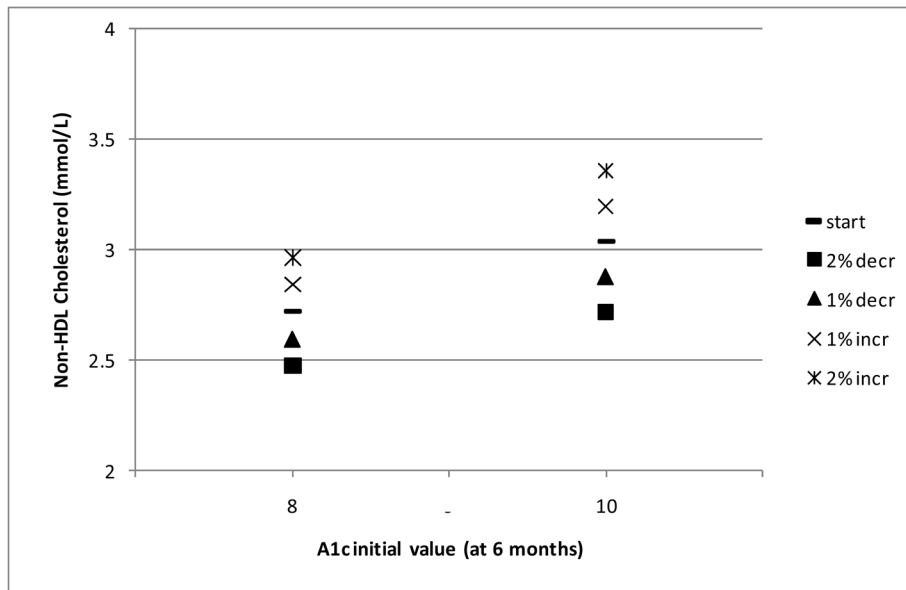
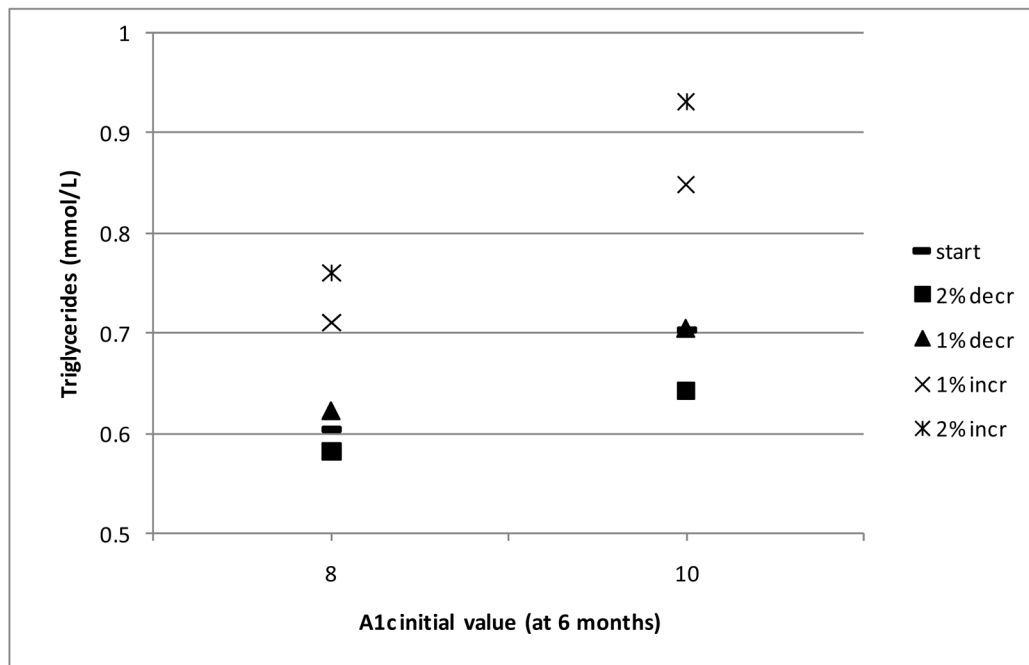


Figure 1e



**Figure 1.**  
 Figure 1a: Estimated Total cholesterol resulting from change in A1c after a 24 month interval  
 Figure 1b: Estimated HDL cholesterol resulting from change in A1c after a 24 month interval  
 Figure 1c: Estimated LDL cholesterol resulting from change in A1c after a 24 month interval

Figure 1d: Estimated non-HDL cholesterol resulting from change in A1c after a 24 month interval

Figure 1e: Estimated Triglycerides resulting from change in A1c after a 24 month interval

**Table 1**

Initial Characteristics of Youth with Type 1 Diabetes (N=1193)

Variable	Initial in-person visit mean±SD or N, %
Age at visit, years	10.6±4.1
T1D duration, months	10.3±7.4
Sex, n, % female	569, 48%
Race/ethnicity, n, %	
Asian-Pacific Islander	38, 3.2%
Non-Hispanic Black	113, 9.5%
Hispanic	131, 11.0%
American Indian	4, 0.3%
Non-Hispanic White	907, 76.0%
A1c, %	7.7±1.4
BMI, z-score (N=1135)	0.55±0.98
Waist Circumference, cm (N=1124)	70.2±14.0
Insulin dose per kg (N=1113)	0.63±0.42
Total Cholesterol, mmol/l	4.17±0.76
HDL-c, mmol/l	1.39±0.33
LDL-c, mmol/l	2.45±0.63
TG, median (Q1,Q3), mmol/l	0.62 (0.47, 0.81)
Non-HDL-c, mmol/l	2.78±0.69
Total Cholesterol, mg/dL	161±29
HDL-c, mg/dL	54±13
LDL-c, mg/dL	95±24
TG, median (Q1,Q3), mg/dL	55 (42, 72)
Non-HDL-c, mg/dL	108±27

**Table 2**

Associations of Change in A1c to Change in Lipids: mmol/l [mg/dL]

Covariates of interest *	95% CI			p-value
	Beta	Lower	Upper	
<b>TC</b>				
Initial A1c (%)	-0.084 [-3.234]	-0.170 [-6.559]	0.002 [0.092]	
Time-Dependent A1c (%)	0.034 [1.307]	-0.033 [-1.286]	0.101 [3.900]	
Initial × TD A1c interaction	0.013 [0.512]	0.005 [0.181]	0.022 [0.843]	0.0025
T1D duration (month)	0.002 [0.062]	-0.000 [-0.002]	0.003 [0.126]	0.0572
<b>HDL-c</b>				
Initial A1c (%)	0.066 [2.569]	0.031 [1.192]	0.102 [3.946]	
Time-Dependent A1c (%)	0.061 [2.360]	0.033 [1.275]	0.089 [3.444]	
Initial × TD A1c interaction	-0.006 [-0.222]	-0.009 [-0.360]	-0.002 [-0.084]	0.0016
T1D duration (month)	0.002 [0.652]	0.001 [0.038]	0.002 [0.093]	<0.0001
<b>LDL-c</b>				
Initial A1c (%)	-0.034 [-1.326]	-0.104 [-4.022]	0.035 [1.371]	
Time-Dependent A1c (%)	0.027 [1.041]	-0.027 [-1.032]	0.081 [3.114]	
Initial × TD A1c interaction	0.007 [0.266]	-0.000 [-0.001]	0.014 [0.532]	0.0506
T1D duration (month)	-0.002 [-0.067]	-0.003 [-0.116]	-0.001 [-0.019]	0.0062
<b>Non-HDL-c</b>				
Initial A1c (%)	-0.149 [-5.761]	-0.227 [-8.794]	-0.071 [-2.728]	
Time-Dependent A1c (%)	-0.025 [-0.974]	-0.086 [-3.336]	0.036 [1.387]	
Initial × TD A1c interaction	0.018 [0.713]	0.011 [0.411]	0.026 [1.015]	<0.0001
T1D duration (month)	-0.000 [-0.002]	-0.002 [-0.060]	0.001 [0.056]	0.94
<b>TG (log) **</b>				
Initial A1c (%)	-0.121	-0.171	-0.070	
Time-Dependent A1c (%)	-0.037	-0.078	0.003	
Initial × TD A1c interaction	0.013	0.008	0.018	<0.0001
T1D duration (month)	0.004	0.003	0.005	<0.0001

\* Multivariable model also adjusts for: site, BMI z-score, gender, race/ethnicity, age and age<sup>2</sup>, and season of the year

\*\* Coefficients are unchanged since log-transformation means that unit conversion is captured in the intercept term