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# Change in adiposity minimally affects the lipid profile in youth with recent onset type 1 diabetes

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## Abstract

**Objective—**Dyslipidemia contributes to the increased risk of cardiovascular disease in persons with type 1 diabetes (T1D). Weight control is commonly recommended as a treatment for dyslipidemia. However, the extent to which decreases in weight affect the lipid profile in youth with T1D is not known. Therefore, we tested the hypothesis that decreases in BMI-z score (BMIz) were associated with concomitant changes in the lipid profile in youth with T1D.

**Study Design—**We studied 1142 youth with incident T1D who had at least 2 fasting lipid measurements over 2 years (initial visit mean: age=10.8±3.9 years, BMIz=0.55±0.97, T1D duration=10.7±7.6 months; 47.5% female, 77.9% non-Hispanic white) in the SEARCH for Diabetes in Youth study. Longitudinal mixed models were used to examine the relationships between changes in BMIz and changes in total, LDL-C, HDL-C, non-HDL cholesterol, and log

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triglycerides adjusted for initial age, sex, race/ethnicity, clinical site, season of study visit, T1D duration and glycated hemoglobin (HbA1c).

**Results—**We found that over 2 years all lipid levels, except LDL-C, increased significantly ($p<0.05$). Decreases in BMIz were associated with favorable changes in HDL-C and TG only and the magnitude of these changes depended on the initial BMIz value (interaction $p<0.05$), so that greater improvements are seen in those with higher BMIz.

**Conclusions—**Our data suggest that weight loss may be an effective, but limited, therapeutic approach for dyslipidemia in youth with T1D.

### Keywords

body mass index; lipids; pediatrics

## Introduction

Cardiovascular disease is the leading cause of death in adults with type 1 diabetes (T1D) (1, 2). Previous work has shown that the atherosclerotic process begins in youth (3, 4) and dyslipidemia is a major contributing risk factor (4, 5). Initial therapy for dyslipidemia In T1D includes optimization of blood glucose control and lifestyle modification with weight control if needed (6–8). However, there is little information regarding whether weight control in youth is sufficient to achieve target lipid values in T1D (9).

Therefore, using observational data in the SEARCH for Diabetes in Youth Study cohort we tested the hypothesis that in youth with T1D decreases in BMI z-score (BMIz) over a 2 year period will be associated with a change in the lipid profile, with reduction in BMIz being associated with a more favorable lipid profile.

## Methods

SEARCH is a multi-center, population-based, observational study of diabetes mellitus in youth that began to conduct case ascertainment of youth <20 years of age with diabetes in 2001. Participants in this analysis were SEARCH study participants identified in geographically defined populations in Colorado, Ohio, South Carolina, and Washington, among health plan enrollees in California, and Indian Health Service beneficiaries from several American Indian populations. A detailed description of the SEARCH study and methods has been published (10).

The longitudinal cohort component of SEARCH includes follow up visits for newly diagnosed diabetes cases at 12, 24, and 60 months after their initial visits. This manuscript includes information on physician diagnosed T1D participants in the 2002–2005 incident cohorts and the corresponding initial, 12- and 24-month visits for those who had at least two visits where both lipids and BMI were obtained to contribute for analysis. Of the 1142 participants in this analysis, fasting lipids were measured twice in 618 participants and three times in 524 participants over the 24 month period.

## Patients and Methods

Date of birth, type of diabetes, and date of diagnosis were assessed at the time of case validation, race/ethnicity (Hispanic, American Indian, non-Hispanic black, Asian/Pacific Islander, non-Hispanic white) was obtained as part of a short initial survey, and current medication use was collected at each study visit. Participants on lipid lowering medications (n=8) at either their initial or follow up visits were excluded from these analyses. The study was reviewed and approved by local institutional review boards.

Measurements for blood pressure, height, weight, and blood samples were obtained after at least 8 hours of fasting (11). Height was measured to the nearest 0.1 centimeter by stadiometer and weight was measured to the nearest 0.1 kilogram using an electronic scale. Anthropometric measurements were taken twice and averaged. BMI was calculated as $kg/m^2$ and measures were compared with standards published by the National Center for Health Statistics to calculate a standard deviation score (z score).

## Laboratory Data

Blood samples were collected and processed locally at the clinical sites and shipped to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle) within 24 hours of collection. Samples were analyzed for total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were performed enzymatically using Roche reagent on a Hitachi Modular P autoanalyzer (Roche Diagnostics, Indianapolis, Indiana). Low density lipoprotein cholesterol (LDL-C) levels were calculated by the Friedewald equation for individuals with TG levels < 400mg/dl and by the Lipid Research Clinics Beta Quantification for those with triglyceride levels of ≥ 400mg/dl. Non HDL-C concentration was computed as TC minus HDL-C. Hemoglobin A1c (HbA1c) levels were measured by ion-exchange high-performance liquid chromatography (TOSOH Biosciences Inc, South San Francisco, California). Using recommended cut points for lipids in children and adolescents (TC >200mg/dl, HDL-C <35mg/dl, LDL-C >130mg/dl, TG level of >150mg/dl and non-HDL-C >160mg/dl) from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (12) and the American Diabetes Association guidelines (13) we calculated the frequency of lipid abnormalities in this cohort at initial visit.

## Statistics

Proportions (%), means ± SD, or medians (interquartile ranges) were calculated for each variable of interest using data from the initial visit. Longitudinal mixed models using all data from the initial and subsequent visits were fit to examine the relationship between BMIz (initial value and time-varying values) and time-varying (change in) lipid levels (TC, HDL-C, LDL-C, log TG, and non-HDL-C). Duration of type 1 diabetes (number of months since diabetes diagnosis) was used as a marker of time from each visit.

Multivariable modeling focused on the main effects of the initial BMIz and the time-varying effects of BMIz on lipids adjusted for initial BMIz and diabetes duration using similar methodology to our previous analysis of change in HbA1c and change in lipids (14). We also included an interaction term (initial BMIz by time varying BMIz) to determine whether

the association of change in BMIz with changes in lipids was different depending on the initial BMIz value. If the interaction was significant, the main effects were not evaluated. Each model also included age at initial visit, sex, race/ethnicity (non-Hispanic white vs other groups), clinic site, season of the study visit (autumn vs each other season), and initial HbA1c since these are all potential confounders. Since Tanner staging was not available for all participants due to some centers' Institutional Review Board restrictions, the correlation between Tanner staging and participant age was examined where the data was available (n=698). Participant age and Tanner stage were highly correlated ($r=0.87$, $p<0.0001$), thus the inclusion of age in the above models was considered a surrogate for pubertal stage. Beta-coefficient and 95% confidence intervals (13) are reported for our models. All statistical analyses were conducted using SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

## Results

Table 1 describes the characteristics of the 1142 individuals with T1D at their initial visit. The participants were a mean age of 10.8 ± 3.9 years; 47.5% were females and 77.9% were non-Hispanic white. The average HbA1c was 7.6 ± 1.4%. Twenty percent of the cohort was overweight (BMI ≥85$^{th}$–94$^{th}$ percentile) and 13% was obese (BMI ≥ 95$^{th}$ percentile).

The initial mean fasting lipids for youth in this cohort were: TC 161 ± 29 mg/dl, HDL-C 54 ± 13mg/dl, LDL-C 94 ± 24mg/dl, TG [median (Q1,Q3)] 55 (42, 73) mg/dl, and non HDL-C 107 ± 26mg/dl (Table 1). The annualized change in TC, HDL-C, LDL-C, TG and non-HDL-C are also listed in Table 1. The median interval between first and last observation was 24 months. The mean change in BMIz was 0.039 ± 0.608.

Of the 1142 participants, 8.1% had a TC >200mg/dl, 4.6% had a HDL-C <35mg/dl, 6.6% had a LDL-C >130mg/dl (36.3% had a LDL-C >100mg/dl), 2.9% had a TG level of >150mg/dl and 3.0% had a non-HDL-C >160mg/dl. These frequencies are similar to prior reports documenting lipid abnormalities in adolescents with T1D (15, 16)

The longitudinal mixed models are presented in Table 2. These data demonstrate the effect of change in BMIz on change in lipids adjusted for potentially confounding variables. T1D duration indicates whether the lipid value significantly increased over time. Initial BMIz and time varying BMIz indicate whether the initial BMIz or the change in BMIz was significantly associated with a change in the lipids while the interaction term indicates whether the change in lipids were dependent on the initial BMIz. Again, if the interaction was significant, the main effects were not evaluated.

All lipids increased significantly over time ($p<0.05$) except LDL-C. Decreases in BMIz were associated with changes in only TG and HDL-C after adjustment for initial age, race/ethnicity, sex, clinical site, season of the year, T1D duration and HbA1c. These relationships were linear across the range of the BMIz and lipid data. For TG and HDL-C, there was a significant interaction between initial BMIz and time varying BMIz indicating that the effect of change in BMIz on change in lipid values differed based on the initial BMIz value ($p<0.05$). For youth with a higher initial BMIz, a decrease in BMIz was associated with a more favorable lipid profile (less TG increase and more HDL-C increase) compared to a

normal weight youth with no change in BMIz. For example, in obese youth a 0.5 decrease in BMIz was associated with a 10.6% (7.2–14.2) increase in TG and a 2.9 mg/dl (2.1–3.9) increase in HDL-C, whereas in normal weight youth a 0.5 decrease in BMIz was associated with an 11.9% (8.5–15.3) increase in TG (in contrast to a 14.2% increase with no BMIz change) and a 2.7 mg/dl (1.9–3.4) increase in HDL-C. See Table 3 for more clinical scenarios using the data from the longitudinal mixed models in Table 2.

While our focus was on the association of change in BMIz with change in lipids, some initial covariates were independently associated with a TG and HDL-C (data not shown). Initial HbA1c was associated with higher TG and HDL-C. Female sex was significantly associated with higher TG but not HDL-C while non-Hispanic black race was associated with higher HDL-C and lower TG (compared to non-Hispanic white). For HDL-C the quadratic term for age was significant and negative (with a positive linear term), with estimates suggesting a positive association at younger ages with a reversal to a negative association at older ages. For TG the quadratic term for age was significant and positive (with a positive linear term) showing a consistently positive (and increasing) association between TG and age.

## Discussion

This study demonstrates that decreases in BMIz are associated with statistically significant favorable change in HDL-C and TG over 2 years in youth with T1D after adjustment for initial age, HbA1c, race/ethnicity, sex, clinical site, season of the year and T1D duration. This study also shows that in participants with T1D who have a higher starting BMIz, decreases in BMIz appear to have a slightly more substantial beneficial effect on the lipid profile (less TG increase, more HDL-C increase) than those who start at a lower BMIz. These findings support the current guidelines from the American Diabetes Association (8) and the American Heart Association (7) which suggest weight control should be a part of the treatment for dyslipidemia in youth with T1D, especially in those that are overweight or obese.

Prior work in T1D youth using cross sectional and longitudinal data have shown that changes in BMI and BMIz are associated with changes in the lipid profile. Using cross sectional data with over 29000 German and Austrian youth with T1D, Schwab et al found a positive relationship between higher BMI and higher LDL-C and TC and lower HDL-C levels (17). In a longitudinal evaluation of 895 T1D youth from four regions of the UK who had a median age 14.5 years, Marcovecchio et al. found that changes in BMIz were related to changes in LDL-C, HDL-C and non HDL-C and TG over a 5 year period (18). A limitation of this study was that the lipid panels were non-fasting, calling into question the accuracy of the TG and LDL-C levels, although recent data suggests the differences in fasting and non-fasting lipids may be small (19). Subsequently, in a small study of 46 youth over 3 years, Reh et al. found changes in BMIz were associated with an increase in LDL-C only (16). However, past studies have not quantified the independent contribution of changes in BMIz on changes in the lipid profile longitudinally.

Our data demonstrate that decreases in BMIz have a statistically significant effect on the lipid profile but these changes are clinically modest. In addition, the effect of a decrease in weight is limited to changes in TG and HDL-C only and is likely mediated through improvements in insulin resistance (20–23). The latter finding is discordant with previous reports of an association between change in weight and TC or LDL-C (16, 18). Discrepancies among studies may be due to younger age of participants or shorter duration of diabetes in our study. Given that there was no association with non-HDL-C or LDL-C, our data suggest weight reduction alone is likely to not have a large enough impact to achieve treatment goals for youth with T1D suggesting other strategies such as dietary and likely pharmacologic interventions are needed to supplement the weight loss, especially if the focus is on LDL-C or non-HDL-C as a primary target (24).

In the present study, race/ethnicity, initial HbA1c and the quadratic term for age were independently associated with changes in both TG and HDL-C. SEARCH previously reported a statistically significant but clinically small association of HbA1c change on lipid change in this cohort (14). Here, we found HDL-C tended to increase over time with a reversal (decreasing HDL-C over time) in older youth, while TG tended to increase over time at all ages. This is likely because adiposity increases with age (25) and is strongly associated with dyslipidemia. These findings underscore the importance of healthy weight in childhood.

This study has some limitations. First, we lack Tanner stage data on some of the participants. However, the strong correlation with age allowed it to be used as a surrogate for pubertal stage. Second, the majority of participants in this study were non-obese (average baseline BMI 19.8 ± 4.4, BMIz 0.55 ± 0.97), non-Hispanic white with relatively short duration of diabetes at the initial visit (10.7 ± 7.6 months) and a relatively young age. Thus it is possible that in minority populations or in overweight or obese participants with longer duration of diabetes and/or older age, the associations between BMIz and lipids may be different. Also, we recognize BMIz is not the only measure that can be used to represent adiposity but chose it as a surrogate to test our hypothesis. Finally, SEARCH is an observational study and not a randomized, controlled trial of weight loss and thus the associations showed here are model-based estimates based on our observed longitudinal data. The strengths of this study include a large cohort, longitudinal follow up data over 2 years and the ability to quantify the independent contribution of changes in BMIz on changes in lipids.

We quantified the association of longitudinal changes in BMIz on lipids among youth with T1D. Decreases in BMIz are associated with favorable change in TG and HDL-C concentrations in youth with T1D over a 2 year period. The greatest improvements in these measures were seen in those individuals who had the highest baseline BMIz. This study did not find an effect of change in BMIz on LDL-C. These findings are important for a number of reasons. First, BMIz is a modifiable risk factor. Second, the effect of change in BMIz on change in HDL-C and TG is modest and may not be sufficient to reach target lipid goals. Third, change in BMIz was not significantly associated with LDL-C which is the lipid parameter most frequently used for decisions to initiate pharmacologic therapy. Thus, while reduction in BMIz may improve some components of the lipid profile and is important for

long term health, youth with T1D will also likely require intensification of glycemic control, dietary modifications and possibly pharmacologic interventions to achieve all lipid goals. Further research is needed to establish the independent roles of diet, exercise and pharmacological therapy on improving cardiovascular health in this population.

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## Abbreviations

| | |
|---|---|
| **T1D** | type 1 diabetes |
| **BMI** | body mass index |
| **TC** | total cholesterol |
| **HDL-C** | high density lipoprotein cholesterol |
| **TG** | triglycerides |
| **LDL-C** | low density lipoprotein cholesterol |
| **HbA1c** | hemoglobin A1c |

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## Table 1

Characteristics of Participants with Type 1 Diabetes at the time of Initial Study Visit (n=1142): The SEARCH for Diabetes in Youth Study

| Variable | Initial in-person visit Mean ± Standard deviation or N, % |
|---|---|
| **Initial Visit Values** | |
| Age at visit, years | 10.8 ± 3.9 |
| T1D duration, months | 10.7 ± 7.6 |
| Sex, % female | 542, 47.5% |
| Race/ethnicity | |
| Asian-Pacific Islander | 18, 1.6% |
| Non-Hispanic black | 111, 9.7% |
| Hispanic | 120, 10.5% |
| American Indian | 4, 0.4% |
| Non-Hispanic White | 889, 77.9% |
| HbA1c, % (N=1136) | 7.6 ± 1.4 |
| Body mass index, kg/m$^2$ | 19.8 ± 4.4 |
| Body mass index, z-score | 0.55 ± 0.97 |
| Total Cholesterol, mg/dl | 161.0 ± 29.4 |
| High-density lipoprotein cholesterol, mg/dl | 54.0 ± 12.7 |
| Low-density lipoprotein cholesterol, mg/dl | 94.4 ± 24.2 |
| Triglycerides, median (Q1,Q3), mg/dl | 55.0 (42, 73) |
| Non-high density lipoprotein cholesterol, mg/dl | 107.0 ± 26.4 |
| **Annualized Change** | |
| Total cholesterol, mg/dl | 2.9 ± 15.9 |
| High-density lipoprotein cholesterol, mg/dl | 1.0 ± 6.6 |
| Low-density lipoprotein cholesterol, mg/dl | 0.8 ± 11.9 |
| Triglycerides, median (Q1,Q3), mg/dl | 3.2 (−4.0, 12.5) |
| Non-high density lipoprotein cholesterol, mg/dl | 2.0 ± 13.7 |

## Table 2

Results of Multivariable Models Examining the Associations of Change in BMIz to Change in Lipids among Youth with Type 1 Diabetes: The SEARCH for Diabetes in Youth Study*

| Covariates of interest | Beta | 95% confidence limits | p-value |
|---|---|---|---|
| **Total cholesterol** | | | |
| Time-varying BMI-z | 0.426 | −1.571, 2.422 | 0.676 |
| Initial BMI-z | −0.126 | −2.548, 2.295 | 0.919 |
| T1D duration (month) | 0.214 | 0.154, 0.275 | <0.001 |
| **HDL-C** | | | |
| Time-varying BMI-z | −0.847 | −1.684, −0.009 | |
| Initial BMI-z | −1.245 | −2.273, −0.218 | |
| T1D duration (month) | 0.089 | 0.064, 0.115 | <0.001 |
| Initial BMI-z × time dependent BMI-z | −0.367 | −0.697, −0.038 | 0.029 |
| **LDL-C** | | | |
| Time-varying BMI-z | 1.043 | −0.476, 2.561 | 0.178 |
| Initial BMI-z | 0.596 | −1.360, 2.552 | 0.556 |
| T1D duration (month) | 0.029 | −0.016, 0.073 | 0.207 |
| **Non-HDL-C** | | | |
| Time-varying BMI-z | 1.427 | −0.345, 3.199 | 0.114 |
| Initial BMI-z | 1.166 | −1.076, 3.409 | 0.308 |
| T1D duration (month) | 0.122 | 0.067, 0.177 | <0.001 |
| **Triglycerides (log)** | | | |
| Time-varying BMI-z | 0.033 | −0.000, 0.066 | |
| Initial BMI-z | 0.028 | −0.010, 0.066 | |
| T1D duration (month) | 0.006 | 0.005, 0.007 | <0.001 |
| Initial BMI-z × time dependent BMI-z | 0.018 | 0.005, 0.030 | 0.005 |

* Each multivariable model also adjusts for: age at initial visit, sex, race/ethnicity, clinic site, season of the year (autumn vs. other) and initial HbA1c.

## Table 3

Clinical Scenarios demonstrating the relationship between change in BMIz and changes in TG and HDL-C

| Initial BMIz | Change in BMIz | Change in Triglycerides | Change in HDL-C |
|---|---|---|---|
| 0.5 (normal weight) | No change | ↑14.2% (11.4–17.1) | ↑2.14 mg/dl (1.54–2.75) |
| 0.5 (normal weight) | ↓ by 0.5 | ↑11.9% (8.5–15.3) | ↑2.66 mg/dl (1.91–3.41) |
| 1.25 (overweight) | ↓ by 0.5 | ↑11.1% (7.7–14.6) | ↑2.80 mg/dl (2.03–3.57) |
| 1.75 (obese) | ↓ by 0.5 | ↑10.6% (7.2–14.2) | ↑2.89 mg/dl (2.10–3.68) |
| Data are % or mg/dl (95% confidence interval) | | | |

BMIz- body mass index z score; HDL-C- High density lipoprotein cholesterol