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Longitudinal association between eating frequency and HbA1c and serum lipids in diabetes in the SEARCH for Diabetes in Youth Study

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Abstract

Background—Few studies have evaluated the prospective association of eating frequency with HbA1c levels and cardiovascular disease risk markers among youth with diabetes.

Objective—To examine the 5-year longitudinal association of eating frequency with HbA1c and serum lipid levels among youth with type 1 diabetes (T1D) or type 2 diabetes (T2D).

Methods—1,049 youth (≥10 years old) with incident T1D (n=821) or T2D (n=228) who participated in the SEARCH for Diabetes in Youth Study were included. Eating frequency (≤3, 4-5 or 6-10 times/day) measured at baseline and follow-up visits was related to HbA1c and serum lipid levels measured repeatedly over 5 years.

Results—Increased eating frequency was associated with larger increases in HbA1c among youth T1D. For example, for youth with T1D who ate ≤ 3 times/day at the outset and ate 6-10 times/day 5 years later, the longitudinal model predicted greater absolute increases in HbA1c (2.77%); whereas for youth with T1D who ate 6-10 times/day at the outset and ate ≤3 times/day 5 years later, the model predicted lesser absolute increases in HbA1c (1.33%). Eating frequency was not associated with changes in serum lipid levels among youth with T1D or T2D.

Conclusions—Youth with T1D who increased their eating frequency vs. those who decreased it had larger increases in HbA1c over 5 years.

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Keywords

diabetes; youth; eating frequency; longitudinal analysis and nutrition

Introduction

The metabolic effect of eating frequency in diabetes is unclear. Increased eating frequency has been associated with multiple metabolic benefits in adults with type 2 diabetes (T2D) ([1]). Consuming small meals 6-13 times/day over 2 days has beneficial effects on insulin sensitivity and blood glucose levels compared with consuming larger meals 2 or 3 times/day among adults with T2D ([1, 2]). However, this benefit was not confirmed in a relatively longer-term study (4 weeks) ([3]) conducted among 13 adults with T2D. More recent studies ([4, 5]) reported similar metabolic benefits associated with increased eating frequency in healthy adults, including a more favorable glucose response, increased insulin sensitivity and improved lipids profiles. Baechle et al. conducted a cross-sectional study among youth with type 1 diabetes (T1D) and reported that eating frequency differed between adolescents with early stage T1D and their non-diabetic peers and that there were non-significant associations between eating frequency and Hemoglobin A1c (HbA1c) levels [6]. Meanwhile, Overby et al. reported youth with T1D on intensive insulin treatment who skipped main meals and have more snacking have poorer glycemic control and less healthy dietary and sedentary habits. [7, 8] Previous studies [1–3] that reported on this topic had small sample sizes, short duration of follow up and cross-sectional designs. To our knowledge, no published studies have evaluated the long-term relationship between eating frequency and glycemic and metabolic outcomes among youth with T1D or T2D, even though diabetes is a growing public health concern in youth ([9]).

Increased eating frequency with constant energy intake could spread energy and nutrient load to prolong absorption of carbohydrates and fiber ([1, 10–12]). Previous studies have reported that increased eating frequency is related to lower postprandial insulin secretion and improved insulin sensitivity ([11, 12]), whereas reduced eating frequency has been related to reduced postprandial energy expenditure ([5]), which over the long term can lead to weight gain. However, increased eating frequency has also been accompanied by higher total energy intake ([13, 14]), which may raise blood glucose levels and cause dyslipidemia. Thus, it is plausible that eating frequency can influence the metabolic profile among youth with T1D or T2D.

HbA1c[15] and serum lipid levels, including high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TGs), are important biomarkers of diabetes control and care and are affected by diet. In order to discover the long-term relationship between eating frequency and HbA1c and serum lipids among youth with T1D and T2D, we utilized 5-year longitudinal data from the SEARCH for Diabetes in Youth Study.

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Methods

Study design and population

The SEARCH for Diabetes in Youth study is an ongoing population-based, observational study of non-gestational diabetes among youth <20 years old. Clinical centers involved in this study are located in Ohio, Colorado, Washington, South Carolina and California. The SEARCH study has been described in detail previously ([16]).

The participants in this analysis were 1,049 youth (<20 years old at the initial visit) with T1D or T2D diagnosed between 2002 and 2005 who joined the SEARCH study and had at least one follow-up visit at 1, 2 or 5 years after the initial visit. In total, we recruited 821 youth with T1D (mean age=13.6, SD=2.4) and 228 youth with T2D (mean age=15.1, SD=2.5). There were 523 (49.9%) females and 526 males (50.1%).

Data collection and measurement

Local institutional review boards that had jurisdiction over the individual study populations reviewed and approved this study before data collection. We obtained written informed consent at the beginning of each study visit.

Trained and certified staff collected data by following standardized protocols for the initial and follow-up visits ([16]). Data were collected by questionnaires, physical examinations and laboratory tests.

Exposure—The food frequency questionnaire (FFQ) used in this study was an 85-item, self-administered, semi-quantitative instrument that was adapted from the Block Kids Questionnaire ([17, 18]). Participants reported the frequency and portion size of food consumed in the past week. The FFQ also contained one question asking about eating frequency behavior: “Last week, about how many times each day did you eat (including meals & snacks)?” The responses to this question were categorized as follows: 1, 2, 3, 4-5, 6-7 or 8-10 times/day. Eating frequency was further categorized as follows: ≤3, 4-5 or 6-10 times/day, as adapted from similar previous studies ([13, 19]).

Laboratory tests—SEARCH staff obtained fasting blood samples under metabolic-stability conditions (8 hours of fasting and no episode of diabetic ketoacidosis in the previous month) at each visit. The blood samples were shipped with dry ice to the central laboratory in Seattle, WA within 24 hours to measure HbA1c, LDL, HDL and TG levels. An ion-exchange high-performance liquid chromatography instrument (TOSOH, Bioscience, Inc., Dan Francisco, CA) was used to measure HbA1c levels. LDL, HDL and TG levels were analyzed enzymatically on a Hitachi 917 auto analyzer (Boehringer Mannheim Diagnostics, Indianapolis, Ind). The Friedewald equation ([20]) and the Lipid Research Clinics beta quantification ([21]) were used to calculate LDL levels for individuals with TG concentrations less than and more than 400 mg/dl (4.52 mmol/l), respectively.

Other covariates—Information on gender, age, race/ethnicity, parental education, health insurance and household income were obtained from an initial survey at baseline ([22]). Body mass index (BMI) *z* score, total energy intake, physical activity, Dietary Approaches to

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Stop Hypertension (DASH) score, diabetes duration and any previous or current treatment for diabetes and/or dyslipidemia were collected at each visit.

Physical activity was evaluated by a question adapted from the Youth Risk Behavioral Survey questionnaires ([23]) that was asked at each study visit: “On how many of the past 7 days did you exercise or participate in a physical activity for at least 20 minutes that made you sweat and breathe hard, such as basketball, soccer, running, swimming laps, fast bicycling, fast dancing or similar aerobic activities?”

All youth participated in standardized physical examinations. Height and weight were measured by a stadiometer and electronic scale, respectively, at each visit. To calculate BMI (kg/m^2), weight (kg) was divided by height squared (m), and age- and gender-specific BMI *z* scores were obtained using the Centers for Disease Control and Prevention growth curves ([24]).

DASH diet scores were calculated based on a participant’s diet habits collected from the FFQ ([25]), which was administered at each visit. The DASH score was adherent to eight DASH food groups (grains, vegetables, fruits, dairy, meat, nuts/seeds/legumes, fats/oils and sweets), as described in detail previously ([26, 27]). Higher DASH scores imply healthier diets.

Information on treatment for diabetes and/or dyslipidemia was collected from medical records at each visit. Diabetes treatment was coded as “insulin pump,” “insulin more than three times per day,” “insulin less than three times per day” or “no treatment or oral medication.” Dyslipidemia treatment was dichotomized as “yes” or “no.”

Statistical methods

Demographic data are shown as the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables.

Longitudinal mixed models were fit separately for individuals with T1D and those with T2D to characterize the relationship between time-varying eating frequency and time-varying HbA1c and serum lipid levels, which were included as random effects. Multivariate mixed models were used to evaluate the effects of eating frequency on HbA1c and serum lipid levels measured at the initial visit and the 1-year, 2-year and 5-year follow-up visits. Duration of diabetes (number of months since diabetes diagnosis) was included in these mixed models as an indicator of time for each participant. Unstructured covariance matrix was selected for all mixed models. All models were expanded to include the fixed/non–time-varying covariates: gender, age at initial visit, race/ethnicity, highest parental education, type of health insurance and household income and the time-varying covariates: BMI z score, total intake of calories, DASH score, physical activity and treatment for diabetes and/or dyslipidemia ([28, 29]).

All statistical analyses were performed in SAS (version 9.4, SAS Institute Inc, Cary, NC). Mixed models were used to fit longitudinal statistical models. $P< 0.05$ was used as the standard of significance.

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Results

There were 821 youth with T1D and 228 youth with T2D in this study (Table 1). Frequency of eating was different in youth with T1D and those with T2D. Among youth with T1D, 184 (22.4%) ate ≤3 times/day, 246 (30.0%) ate 4-5 times/day, and 391 (47.6%) ate 6-10 times/day. In comparison, among youth with T2D, 94 (41.2%) ate ≤3 times/day, 32 (14.0%) ate 4-5 times/day, and 102 (44.8%) ate 6-10 times/day. The participants were similar with respect to age, gender, race, socioeconomic status and health insurance status across the categories of eating frequency among those with T1D or T2D. Youth with T1D who ate 4-5 times/day were leaner than those eating ≤3 or 6-10 times/day ($p<0.05$). No such difference was seen in youth with T2D (Table 1).

Youth who reported eating 6-10 times/day consumed more energy than those eating 4-5 times/day (mean 1,966 versus 1,774 calories/day for T1D, $p<0.05$; mean 2,185 versus 1,704 calories/day for T2D, $p<0.05$) (Table 1). Mean caloric intakes for those eating ≤3 times/day and 4-5 times/day were similar in youth with T1D and those with T2D (Table 1). Youth with T2D who consumed ≤3 times/day had diets with higher fructose composition compared with those eating 4-5 times/day ($p<0.05$). The distribution of other nutrients was similar across categories of eating frequency in youth with T1D and T2D.

Longitudinal mixed models

HbA1c levels increased significantly over time among youth with T1D and T2D. LDL and TG levels increased significantly over time only among youth with T1D. Initial eating frequency (negatively) and time-varying eating frequency (positively) were associated with changes in HbA1c levels among youth with T1D after adjusting for age at initial visit, gender, race, physical activity, parental education, household income, health insurance type, BMI *z* score, DASH score, treatment for diabetes and/or dyslipidemia and total calorie intake. In other words, at baseline, youth with T1D who ate ≤ 3 times/day tended to have higher HbA1c levels than those who ate 4-5 or 6-10 times/day. However, HbA1c increased faster if youth with T1D increased their eating frequency over time. There was no significant longitudinal association between eating frequency and HbA1c among youth with T2D. Eating frequency per day was not associated with changes in HDL, LDL or TG levels among youth with T1D or T2D or with changes in HbA1c levels among youth with T2D.

Predicted model

The estimates in Table 3 are statistically significant results from the multivariate mixed models presented in Table 2. Table 3 demonstrates the predicted time varying changes at select time points in HbA1c among youth with T1D from the initial visit (n=1049) to 5 years of follow-up (n=575).

HbA1c increased on average from the initial visit to the 5 years follow-up visit among youth with T1D. The magnitude of HbA1c increase was smaller in those who decreased eating frequency (6-10 times/day to ≤ 3 times/day) over time and larger in those who increased it. For instance, the HbA1c value for youth who ate 6-10 times/day at the initial visit and ≤ 3 times/day at the 5 years follow-up visit increased less than those who ate ≤ 3 times/day at

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the initial visit and 6-10 times/day at the 5 years of follow-up visit (1.34% vs. 2.77%; Table 3).

Discussion

In the present study, youth with T1D who consumed meals ≤3 times/day had higher HbA1c levels at baseline and had a negative association with increases of HbA1c over time after accounting for energy intake and other factors. There was no difference in HbA1c and eating frequency changes among youth with T2D. Eating frequency was not associated with longitudinal changes in serum lipid levels among youth with either T1D or T2D. To our knowledge, this is the first study to prospectively evaluate potential long-term metabolic effects of eating frequency in youth with diabetes.

The American Diabetes Association (ADA) guidelines recognize nutrition therapy as an essential component of diabetes treatment and recommend that individualized dietary counseling be part of the overall diabetes treatment plan ([30]). Previous ADA statements regarding nutrition principles reported that increased eating frequency was related to lower mean blood glucose and insulin levels in adults with T2D ([31]). However, the most recent ADA guidelines on nutrition therapy do not specify optimal eating frequencies ([30]). Jenkins et al. ([1]) and Bertelsen et al. ([2]) have compared the effects of larger meals 2 or 3 times/day with smaller meals 6-13 times/day among adults with T2D over 2 days. Both studies showed that increased eating frequency could increase insulin sensitivity and lower blood glucose concentrations over the day the meals were consumed. Similar metabolic advantages, such as reductions in serum lipid levels and lipid concentrations, have also been observed in healthy subjects ([4, 5, 12]). However, a relatively longer study (4 weeks) conducted by Arnold et al. ([32]) on the impact of eating frequency on metabolic effects among 13 adults with T2D did not confirm the potential benefits of increased eating frequency. Another randomized crossover study (24 weeks) conducted among adults with T2D reported that eating 2 large meals a day could reduce body weight, hepatic fat content, fasting plasma glucose, C-peptide and glucagon levels and increase oral glucose insulin sensitivity as compared to eating 6 meals a day ([33]).

The main purpose of increasing eating frequency is to spread nutrient load and avoid hyperglycemia and hypoglycemia while holding the total intake of calories constant. In this study, we provided evidence that increased eating frequency is associated with more increase in HbA1c among youth with T1D over time. Meanwhile, the baseline effect was that higher eating frequency predicted lower HbA1c levels. One possible reason might be that youth consume more calories along with increased eating frequency as they grow older. Because caloric intake was underestimated by the FFQ used in this study, (Liese et al 2015) and ([15]), and youth with T1D eating 6-10 times/day consumed more total calories, it is possible that adjustment for total calories was incomplete, and the association between eating frequency and HbA1c over time was driven in part by increased caloric intake. Similar findings were also reported by studies conducted among adults free of diabetes ([14]) and those with T2D ([34]). Eating frequency was not associated with serum lipid levels in this analysis. Maahs and colleagues found that a 2% change in HbA1c levels was associated with changes in serum lipid levels in this cohort of adolescents with diabetes. The

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changes in HbA1c levels associated with eating frequency were much smaller than 2%, which is probably the reason we were not able to observe any changes in serum lipid levels here.

This study has several potential limitations. First, the main exposure, eating frequency, was measured by one question in the food frequency questionnaire, which may have led to some misclassification of self-reported eating frequency. However, eating frequency assessment has been validated in a number of studies,[35] including among US youth.[36] In a validation study conducted among US children, correlation coefficient, kappa statistic and percent agreement were 0.71, 0.76, and 93 respectively for breakfast, and 0.70, 0.67 and 0.87 for meal frequency.[35] In the future research, it would be beneficial to use a food diary to measure eating frequency with more validity. Second, residual confounding was possible. However, we adjusted for many potential confounders in the analyses, including total caloric intake, age, gender, race, physical activity, parental education, household income, health insurance type, BMI *z* score, DASH score and treatment for diabetes and/or dyslipidemia. The associations reported in this paper were independent of these potential confounders. Third, our analysis was not able to separate breakfast consumption behavior from total eating frequency, given that several previous studies have shown that breakfast consumption is associated with beneficial health outcomes among adults at risk of T2D ([13, 19]).

Despite these limitations, this study also had several strengths. First, the large sample for this analysis was drawn from the SEARCH for Diabetes in Youth Study population, which is the largest prospective investigation among youth with T1D or T2D and includes all major US ethnic groups. Second, to our knowledge, this was the first longitudinal study design, including 5 years of follow-up data, to evaluate the relationship between eating frequency and HbA1c and serum lipid levels among youth with T1D or T2D. Third, eating frequency was evaluated independent of other dietary variables and potential confounders.

In conclusion, HbA1c levels increased to a lesser extent over 5 years among youth with T1D who decreased their eating frequency. There was no difference in HbA1c and eating frequency changes among youth with T2D. Eating frequency was not associated with longitudinal changes in serum lipid levels among youth with either T1D or T2D.

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Table 1

Demographic and clinical characteristics of participants at the initial visit: SEARCH for Diabetes in Youth, 2002-2005

	T1D (n=821)[a]	T2D (n=228)[a]
Demographics		
Gender		
Female	384 (46.8)	139 (61.0)
Male	437 (53.2)	89 (39.0)
Race		
Non-Hispanic white	617 (75.1)	49 (21.5)
African American	81 (9.9)	82 (36.0)
Hispanic	90 (11.0)	52 (22.8)
Other[a]	33 (4.0)	45 (19.7)
Age	13.6 (2.4)	15.1 (2.5)
Highest parental education		
Bachelor degree or more	383 (46.7)	36 (15.9)
Some college with associate degree	279 (34.2)	80 (35.4)
High school	122 (14.9)	76 (33.6)
Less than high school	33 (4.0)	34 (15.0)
Annual household income		
<$25,000	106 (13.0)	95 (41.7)
$25,000-49,000	160 (19.6)	58 (25.4)
$50,000-74,000	172 (21.1)	25 (11.0)
≥$75,000	327 (40.1)	20 (8.8)
DK/Ref	51 (6.2)	30 (13.2)
Insurance		
Medicaid/Medicare	128 (15.7)	90 (39.7)
Private	660 (81.1)	119 (52.4)
Other	9 (1.1)	10 (4.4)
None	17 (2.1)	8 (3.5)
Clinical characteristics		
HbA1c(%)	7.7 (1.7)	7.2 (2.1)
BMI *z* score	0.6 (0.9)	2.14 (0.6)
Diabetes treatment		
Insulin pump	71 (8.7)	0 (0.0)
Insulin 3+ times per day	428 (52.4)	25 (11.0)
Insulin <3 times per day	305 (37.3)	50 (22.0)
No treatment or oral meds only	13 (1.6)	152 (67.0)
HDL(mg/dl)	51.8 (12.2)	41.0 (9.4)
LDL (mg/dl)	93.0 (26.3)	100.9 (28.4)
TG (mg/dl)	72.6 (59.7)	137.4 (93.6)

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	T1D (n=821)[a]	T2D (n=228)[a]
Nutrient characteristics		
Total calorie intake (cal)	1835.3 (741.7)	1762.8 (754.9)
Total carbohydrates (g/1,000cal)	115.3 (18.5)	116.6 (22.1)
Percent of calories from carbohydrates (%)	46.0 (7.4)	46.4 (8.7)
Fructose (g/1,000cal)	10.2 (6.4)	13.5 (9.8)
Glucose (g/1,000cal)	11.3 (5.5)	13.9 (8.6)
Total fat (g/1,000cal)	43.4 (6.6)	43.2 (7.5)
Percent of calories from fat (%)	39.1 (6.0)	38.9 (6.6)
Total protein (g/1,000cal)	40.2 (5.7)	38.9 (6.7)
Percent of calories from protein (%)	16.1 (2.3)	15.6 (2.7)
Total sugar (g/1,000cal)	53.4 (18.0)	56.3 (24.1)

[a]Values are shown as n (%) or mean (SD).

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Table 2

Adjusted longitudinal associations of changes in means of HBA1c and serum lipids among youth with T1D and T2D: SEARCH for Diabetes in Youth

	HbA1c (%)	HDL (mg/dl)	LDL (mg/dl)	TG (mg/dl)
T1D				
Diabetes duration (β1)	0.0342	0.1246	0.1223	0.4121
Baseline EF (β2)[a,b]				
4-5	−0.4723 [c]	−1.4900	−2.2728	−11.56 [c]
6-10	−0.4838 [c]	−0.5220	0.5402	−9.5287
Time-varying EF (β3)[a,b]				
4-5	0.1651	−0.6085	1.2722	7.1405
6-10	0.3597 [c]	−1.0855	0.6434	5.3496
T2D				
Diabetes duration (β1)	0.0206	0.0531	−0.0279	0.1144
Baseline EF (β2)[a,b]				
4-5	0.2520	3.1302	3.8614	3.9671
6-10	−0.4275	0.5471	−8.0777	11.3304
Time-varying EF (β3)[a,b]				
4-5	−0.2838	−0.6174	−5.0856	−25.8508
6-10	0.2296	1.9035	1.0479	−30.9923

HDL, high-density lipoprotein; LDL, low-density lipoprotein; T1D, type 1 diabetes; T2D, type 2 diabetes.

[a]The reference group was ≤3 times per day.

[b]Outcome=β0 +β1 (duration)+β2 (baseline EF)+β3 (time-varying EF) +β4 (other covariates) + ε.

[c]$p<0.05$.

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Table 3

Estimated[a,b] HbA1c resulting from change in eating frequency after a 5-year interval among youth with T1D: SEARCH for Diabetes is Youth[c]

	=<3 meals per day to 6-10 meals per day	6-10 meals per day to =<3 meals per day
HbA1c (%), initial visit	8.70	8.45
HbA1c (%), 5-year follow-up visit	11.47	9.78
Change	2.77	1.34
HbA1c, hemoglobin A1c		

HbA1c, hemoglobin A1c.

[a]Estimates were generated from the following mixed model: Outcome = β0 + β1(duration) + β2(initial exposure) + β3(time-varying exposure) +β4(other covariates) + ε.

[b]The reference groups for the adjusted covariates in the mixed models were as follows: age at initial visit=10 years old, gender=male, race=non-Hispanic white, physical activity=0 days, highest parental education=less than high school, income= less than $25k per year, insurance=none, BMI zscore=0, Kcal=1500, DASH score=25, diabetes treatment=insulin pump, and lipids treatment=none.

[c]Only significant results from the mixed models in Table 2 are presented.