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Cross-sectional and longitudinal relationships of body mass index with glycemic control in children and adolescents with type 1 diabetes mellitus

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Abstract

Aims—Weight gain is an oft-cited outcome of improved glycemic control in adults with type 1 diabetes, though few studies have investigated this in youth. The purpose of this paper was to examine cross-sectional and longitudinal associations of body mass index (BMI, kg/m²) with glycemic control in youth with type 1 diabetes (n=340, 12.5±1.7y, 49% female, duration 1year) participating in a 2-year multicenter intervention study targeting family diabetes management.

Methods—BMI was calculated from height and weight measured at clinic visits. Glycohemoglobin (HbA1c) at each visit was assayed centrally. Cross-sectional associations of baseline BMI with glycemic control, and of change in BMI and HbA1c with baseline values, were examined. Longitudinal associations of time-varying BMI and HbA1c were examined using a multilevel linear mixed effects model controlling for time-varying time (months), insulin dose (units/kg/day), regimen, Tanner stage, and time invariant baseline diabetes duration, BMI, treatment group and sociodemographic characteristics.

Results—Baseline HbA1c was unrelated to baseline BMI, but was related positively to subsequent BMI change (p=0.04) and inversely to HbA1c change (p=0.002). Baseline BMI was inversely related to BMI change (p=0.01) and unrelated to HbA1c change. In multilevel regression, BMI was related inversely to HbA1c (%) ($\beta \pm SE = -0.11 \pm 0.02, p < 0.001$) and positively to insulin dose ($0.23 \pm 0.07, p = 0.001$). In the treatment group only, BMI was positively related to pump regimen ($0.18 \pm 0.08, p = 0.02$).

Conclusions—Increased insulin administered to improve glycemic control may contribute to increased BMI in youth with type 1 diabetes, indicating the importance of determining ways to minimize weight gain while optimizing glycemic control.

Keywords

BMI; children; adolescents; longitudinal

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Introduction

Cardiometabolic risk is a primary concern for patients with type 1 diabetes mellitus[1]. Despite improvements in glycemic control and reduced microvascular complications demonstrated with intensive insulin therapy[2,3], weight gain is a frequently noted side-effect [4–6] that may contribute to increased cardiometabolic risk[7–9]. Weight gain occurring as a result of intensive insulin therapy in patients with type 1 diabetes has been attributed to improved energy utilization and decreased glycosuria[5,10], increased insulin administration[7,11], and increased dietary flexibility[12]. Reported health consequences of this weight gain include increased blood pressure and dyslipidemia[7–9], which increase risk of adverse micro- and macrovascular outcomes[13]. Cardiovascular disease is the major cause of mortality in adults over 30 years of age with type 1 diabetes[13]. Evidence suggests atherosclerosis begins during adolescence, with elevated risk of adult cardiovascular disease in adolescents with known risk factors[14,15], underscoring the importance of elucidating influences on risk factor development in this population.

Findings are mixed regarding the relationship between BMI and glycemic control, with studies in youth and adults showing positive[9,16], inverse[7,17], and no associations[18,19]. Previous studies were conducted in samples on earlier insulin regimens, and none in the US. The mixed findings observed may be attributable to the limitations in data collection and analytic methods. Prospective studies are important both for confirming the cross-sectional association between glycemic control and BMI as well as for assessing the direction of causality. Appropriate analytic methods must be applied in order to maximize the informative value of repeated measures on subjects in a prospective study design while also accounting for within-subject correlation. Further, multivariable methods are necessary in order to assess the possibility of confounding in bivariate associations.

The objective of this study was to examine the cross-sectional and longitudinal associations of glycemic control with BMI in a sample of children and adolescents with type 1 diabetes assessed at multiple times over two years. We first examine bivariate baseline associations between BMI and glycemic control, and the association of baseline values of BMI and glycemic control with subsequent change in each. We then examine the longitudinal relationship of BMI with glycemic control using a multilevel linear regression model controlling for insulin dose, insulin regimen, treatment group, and other diabetes-related and sociodemographic covariates.

Subjects

Data for this analysis come from a multicenter randomized controlled trial testing the impact of a family-based behavioral intervention on glycemic control and adherence conducted from January 2006 to March 2009 at four pediatric endocrinology clinics located in the United States (Massachusetts, Florida, Illinois, Texas). The intervention focused on enhancing parent-child teamwork and problem-solving skills for diabetes management. BMI was not a primary or secondary outcome of the study, and the intervention delivery did not involve health care providers or impact the participants' treatment regimen or medical care. The intervention was designed to assist families in adhering to the tasks of day-to-day diabetes management during the pre-adolescent and early adolescent developmental period, which is marked by transitions in parent-child roles and during which adherence and glycemic control generally declines. Further details on the study design, recruitment, behavioral intervention and primary outcomes have been published previously[20]; the intervention had a positive effect on glycemic control at 2-year follow-up.

Study enrollment criteria included age 9 to 14.9 years, diagnosis of type 1 diabetes mellitus diagnosed by ADA criteria [21] for at least 3 months, minimum insulin dose 0.5 u/kg/day for those diagnosed ≥ 1 year or 0.2 u/kg/day for those diagnosed <1 year with at least 2 daily injections or use of insulin pump, most recent HbA1c $>6.0\%$, 42 mmol/mol and $<12.0\%$, 108 mmol/mol (for those diagnosed <1 year, HbA1c of $>6.0\%$, 42 mmol/mol at any time following diagnosis), and no other major chronic disease (except well-controlled thyroid, asthma, or celiac disease), cognitive disability, or psychiatric diagnosis. Additional parent/family eligibility criteria included geographically stable home with telephone access, English-speaking, history of at least 2 clinic visits within the previous 12 months, and no major psychiatric diagnoses in participating parents. For this analysis, subjects with diabetes duration of less than 1 year ($n=45$) at the time of the baseline home visit were excluded due to the effect of residual insulin production on insulin dose and HbA1c in those recently diagnosed. Informed consent and assent were obtained from parents/guardians and children. Procedures were approved by the Institutional Review Boards of the participating institutions.

Materials and methods

Families were enrolled in the study for 2 years; data were collected at routine clinic visits occurring approximately every 3–4 months. There was 92% retention at the 2-year follow-up. Child sex, diabetes duration, race/ethnicity, parent income and parent education were assessed at baseline; insulin regimen and insulin dose were assessed at each visit. Frequency of blood glucose monitoring was obtained at each visit by blood glucose meter download. Tanner stage (1–5) was assessed as per each clinic's standard of care and obtained from the medical record; data were available for 84% of all visits. BMI was calculated from measured height and weight obtained from medical records for each visit. Centers for Disease Control and Prevention age- and sex-specific BMI percentile (BMI%ile) was calculated in order to generate weight categories, defined as low ($<85^{\text{th}}$ %ile), overweight (85^{th} %ile, $<95^{\text{th}}$ %ile), and obese ($\geq 95^{\text{th}}$ %ile). The “low” BMI group combines both underweight ($<5^{\text{th}}$ %ile) and normal weight (5^{th} – 85^{th} %ile) youth due to the very low number ($<1\%$ at baseline) of underweight subjects. Blood samples were obtained at each visit, and HbA1c assayed at a central laboratory (Joslin Diabetes Center, Tosoh HbA1c 2.2 Plus Glycohemoglobin AnalyzerTM, Tosoh Medics, South San Francisco, CA). Simultaneous samples were processed with the DCA-2000 on site; results were used to impute replacement values if samples were lost or damaged (1.2% of values).

Statistical analysis

Baseline subject characteristics were summarized using means and standard deviations for continuous variables and frequencies for categorical variables. T-tests and chi-squares (or Fisher's exact when insufficient numbers for chi-square, and Kruskal-Wallis rank test where equal variance assumption was not satisfied) were used to evaluate differences in baseline BMI, insulin regimen, insulin dose and sociodemographic characteristics by categories of baseline HbA1c ($\leq$ or $> 8.0\%$, 64 mmol/mol) and weight (low, overweight, obese). Cross-sectional associations of baseline categories of weight and glycemic control with subsequent changes in BMI and HbA1c were also evaluated using t-tests and analysis of variance (or Kruskal-Wallis rank test where appropriate).

The longitudinal relationship of time-varying BMI with time-varying glycemic control was examined using a multilevel linear mixed effects model, which accounts for correlated repeated measurements within subjects. The model allowed for baseline variation in BMI by including a random intercept, and allowed the relationship of time and BMI to vary between subjects by including a random coefficient for the time variable (months). The use of

maximum likelihood estimation accounts for varying time intervals between outcome measurements and different numbers of observations at each time point [22]. The model included time-invariant covariates for child sex, baseline age, baseline diabetes duration, baseline BMI, highest parent education, household income, baseline child age (years), child race/ethnicity and treatment assignment. Time-varying covariates included time from baseline (months), insulin regimen, insulin dose (daily units/kg), and Tanner stage. Potential effect modification of glycemic control, insulin regimen and insulin dose by intervention group assignment was examined using multiplicative interaction terms and stratified analyses where warranted.

Results

Baseline characteristics

The sample was predominantly White (76%), was highly educated (59% college graduate or above) and represented a wide income range (Table 1). Nearly forty percent of the sample had baseline HbA1c $\geq 8.0\%$ (64 mmol/mol) (Table 2). Subjects with more optimal glycemic control at baseline had shorter diabetes duration ($p=0.03$), were more likely to be on pump regimen ($p=0.03$), and exhibited more frequent blood glucose monitoring ($p<0.0001$) than those with poorer glycemic control. Approximately one-third of the sample (34%) had a BMI at or above the 85th ile. Baseline weight category was positively related to baseline insulin dose ($p=0.048$) and Tanner stage ($p=0.001$). Between baseline and the last clinic visit, 32 normal weight (BMI $\leq 5^{\text{th}}$, $<85^{\text{th}}$) subjects (12%) became overweight or obese, 19 overweight subjects (23%) moved to the normal weight category, and 10 obese subjects (27%) moved to the overweight category (not shown). There was no statistically significant association of baseline BMI with baseline glycemic control.

Associations of baseline weight status and HbA1c category with subsequent change in BMI and glycemic control

There was an overall increase in BMI (mean $\pm$ SD 1.6 ± 1.8) and HbA1c ($0.5 \pm 0.1\%$, 5 ± 1 mmol/mol) over the study period, with significant differences in change in BMI and HbA1c by baseline glycemic control (Figure 1). Those with lower HbA1c at baseline had a smaller subsequent increase in BMI over follow-up (mean $\pm$ SE 1.38 ± 0.17 for baseline HbA1c $\leq 8.0\%$ versus 1.82 ± 0.12 for baseline HbA1c $>8.0\%$, $p=0.04$) and a greater subsequent increase in HbA1c ($0.73 \pm 0.1\%$, 8 ± 1 mmol/mol versus $0.28 \pm 0.1\%$, 3 ± 1 mmol/mol, $p=0.002$) (Figure 1A). Baseline weight category was not significantly associated with subsequent change in HbA1c, but was inversely related to subsequent change in BMI (mean $\pm$ SE BMI change $=1.84 \pm 0.1$, 1.40 ± 0.2 , 0.55 ± 0.6 for low, overweight and obese baseline BMI, $p<0.001$) (Figure 1B).

Longitudinal relationship of BMI and glycemic control

Results from the multivariable multilevel linear regression model indicated that time-varying BMI was inversely related to time-varying HbA1c ($p<0.001$) and positively related to time-varying insulin dose ($p=0.001$) (Table 3). There was no main effect of insulin regimen on BMI. Time-varying BMI was positively related to baseline BMI ($p<0.001$) and inversely related to household income ($p=0.008$). There were no statistically significant associations of time-varying BMI with other baseline demographics or time-varying Tanner stage. However, there was a positive relationship between BMI and treatment group ($\beta \pm \text{SE} = 0.10 \pm 0.05$, $p=0.03$), indicating that BMI was 0.10 kg/m^2 higher for a given individual if he/she was in the treatment group versus the control group after controlling for glycemic control, insulin dose and insulin regimen and all other covariates. Additional analyses indicated a significant treatment group by regimen interaction ($p=0.007$), such that BMI was positively associated with pump regimen for subjects in the intervention group (0.18 ± 0.08 ,

p=0.02), but BMI was not significantly related to insulin regimen in the control group (results not shown). There were no significant interactions between treatment group and glycemic control or insulin dose.

Discussion

The present study describes cross-sectional and longitudinal relationships of BMI with glycemic control in a large, multisite sample of children and adolescents with type 1 diabetes in the United States. We observed no significant baseline associations between weight category and HbA1c, and no significant differences in subsequent change in HbA1c by baseline weight category. However, subjects with higher baseline HbA1c demonstrated a larger subsequent increase in BMI and a smaller subsequent decrement in glycemic control over the study period as compared to subjects with a more optimal baseline HbA1c, suggesting relatively increased efforts to achieve glycemic control in those with suboptimal baseline HbA1c coincident with relatively increased BMI. In addition, time-varying BMI was inversely related to HbA1c and positively related to insulin dose in the multilevel linear regression model. Taken together, these findings are consistent with the hypothesis that the inverse relationship observed between BMI and glycemic control may be partly attributed to increased insulin administration independent of regimen.

The sample exhibited similar prevalence of overweight/obesity (BMI ≥85thile) as in the general U.S. youth population[23,24], and in other samples of youth with type 1 diabetes mellitus[11]. Similar relationships between baseline glycemic control and subsequent increase in body weight in adults have been reported in previous studies[4,5,7], and the lack of a significant relationship between baseline BMI and subsequent change in HbA1c is also consistent with previous research[16]. The non-significant association between baseline glycemic control and BMI does not replicate some previously reported positive cross-sectional associations of HbA1c with BMI[9] and body fat[19] in children and adolescents. However, our finding of a positive relationship between baseline glycemic control and subsequent weight change, and an overall inverse relationship between time-varying BMI and HbA1c, was also seen in adolescents in early research on intensive insulin therapy[6] and somewhat more recently among adults[17]. Differences in these relationships across studies may be attributed to differences in sample characteristics, study design and analytic methods. Our findings indicate the relationship between BMI and glycemic control is complex, suggesting the importance of longitudinal study designs and appropriate analyses for evaluating the temporality and direction of causality of the observed association between BMI and glycemic control.

Our finding of a positive relationship between insulin dose and body weight is consistent with previous research in adults[7] and adolescents[12,19,25], although some studies have failed to find a significant association[4,5,9,18]. Similarly, while previous studies have demonstrated a non-significant relationship between insulin regimen and body weight [9,19] consistent with the findings of the present study, other studies have shown weight gain resulting from initiating intensive insulin therapy in adults[4,5,7] and adolescents[12,18]. The interaction of insulin regimen and treatment group reported herein was unexpected, and is not easily interpreted. The significant positive relationship between BMI and pump regimen only in the treatment group may be due to a spurious finding or unobserved factors, and will require replication and further examination in other samples. Insulin itself leads to weight gain through its influence on appetite[26], lipolysis[27] and lipogenesis[28], whereas the regimen for insulin administration is hypothesized to contribute to weight gain via its influence on dietary flexibility[12,18]. Thus, the variability in the influence of insulin regimen on dietary behaviors[29] relative to the hormonal effects of insulin on weight gain may contribute to conflicting findings.

Strengths of this study include the longitudinal study design, the large sample size, the inclusion of patients from several geographically diverse clinics, and the wide income range, supporting the external validity of these findings to youth with type 1 diabetes in the US within this age range. The racial/ethnic distribution of subjects in this study is similar to that seen in national estimates in US youth with type 1 diabetes[30,31], and the income range is comparable to that seen in non-Hispanic Whites in the US [32]. In addition, these findings are relevant to those following contemporary insulin regimens, which may differ from earlier regimens examined in prior research, and may be differentially related to health outcomes. The use of both cross-sectional and longitudinal analytic methods allowing for adjustment for several important covariates strengthen the internal validity of these findings and help to elucidate mechanisms for observed associations.

This is a post-hoc observational analysis of data collected in the context of a behavioral intervention trial addressing family teamwork and problem-solving for improving diabetes management adherence. Health care providers were not involved in intervention delivery, and the intervention condition did not impact the prescribed diabetes care regimen. The generalizability of our findings may be limited given that participants were recruited from major medical centers in large metropolitan areas. Another limitation is that no diet or physical activity data were available to determine their contribution to BMI. In addition, body composition measurements were not obtained, so the relative contribution of fat and fat-free mass to BMI change cannot be determined. Whereas the accumulation of fat-free mass may indicate correction of underweight due to improved glucose utilization through insulin therapy[4,6], accumulation of fat mass may indicate excessive energy intake leading to increased cardiometabolic risk. Our data indicated no significant difference in baseline BMI according to baseline glycemic control, suggesting that the relatively modest increase in BMI may be attributable to increased fat mass. Measures of body composition and blood lipids should be obtained in future longitudinal research given previous studies finding weight gain in patients with T1DM attributed to both fat and fat-free mass[5,10], and the different health implications of each.

In conclusion, these findings suggest that youth with type 1 diabetes may be susceptible to modest weight gain as a result of efforts to control blood glucose through increased insulin administration, similar to findings in adult populations. Due to considerations for potential harmful health effects of excess body weight in patients with type 1 diabetes, care of adolescents should consider approaches to prevent excessive weight gain while optimizing glycemic control in order to minimize long-term cardiometabolic risk.

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Figure 1. Change in BMI and glycemic control by baseline values

(A) Change in BMI (kg/m²) (p=0.04) and HbA1c (mmol, %) (p=0.002) by baseline HbA1c category (≤8.0%, 64 mmol/mol, versus >8.0%, 64 mmol/mol) and (B) change in BMI (p=0.01) and HbA1c (p=0.59) by baseline weight category (low=BMI%ile<85; overweight=BMI%ile 85, <95; obese=BMI%ile 95). Same subscripts indicate significantly different (p<0.05) pairwise differences adjusted for multiple comparisons (B only).

Table 1

Sample characteristics (n = 340)

	N (%)
Race	
Non-Hispanic White	241 (76)
Non-Hispanic Black	26 (8)
Hispanic	34 (11)
Other	18 (6)
Parent education (highest)	
High-school or less	43 (13)
Beyond HS, but not college grad	99 (29)
College grad	155 (46)
Graduate or professional school	43 (13)
Income (\$ thousands)	
<30	69 (20)
30-<50	37 (11)
50-<70	48 (14)
70-<100	76 (22)
100-<150	62 (18)
150	48 (14)

Table 2Baseline characteristics by baseline HbA1c and BMI^a

	Full Sample (n=340)	Baseline HbA1c (%mmol/mol)			Baseline Weight Category ^b			P
		8.0, 64 (n=132)	> 8.0, 64 (n=206)	P ^c	Low (n=224)	Overweight (n=79)	Obese (n=34)	
Age (y)	12.5 ± 1.7	12.2 ± 1.8	12.6 ± 1.7	0.04	12.4 ± 1.7	12.6 ± 1.7	12.6 ± 1.8	0.79
Sex								
Male	172 (51)	61 (46)	106 (51)	0.35	125 (54)	31 (41)	12 (38)	0.05
Female	168 (49)	71 (54)	100 (49)		106 (46)	45 (59)	20 (63)	
BMI (kg/m ²)	20.9 ± 3.7	20.8 ± 0.3	20.9 ± 0.3	0.86	19.0 ± 2.0 ^a	23.3 ± 1.7 ^a	28.5 ± 4.1 ^a	<0.001
Tanner stage	2.7 ± 1.4	2.6 ± 1.4	2.6 ± 1.4	0.39	2.5 ± 1.3 ^{a,b}	3.0 ± 1.5 ^a	3.2 ± 1.6 ^b	0.001
Diabetes duration (y)	5.4 ± 3.0	5.0 ± 3.0	5.7 ± 3.1	0.03	5.5 ± 3.1	5.2 ± 3.0	5.7 ± 3.1	0.68
Insulin regimen								
Injection – conventional *	112 (33)	42 (32)	68 (33)	0.03	71 (31)	26 (34)	15 (47)	0.09
Injection - glargine/lantus	101 (30)	30 (23)	71 (34)		75 (32)	16 (21)	10 (31)	
Pump	127 (37)	60 (45)	67 (33)		85 (37)	34 (45)	7 (22)	
Insulin dose (units/kg)	0.96 ± 0.3	0.94 ± 0.3	0.98 ± 0.3	0.20	1.0 ± 0.3 ^a	1.0 ± 0.3	1.1 ± 0.2 ^a	0.048
Blood glucose monitoring (times/day)	4.5 ± 5.5	5.1 ± 0.2	4.0 ± 0.1	<0.0001	4.6 ± 2.1	4.3 ± 1.9	3.7 ± 1.6	0.09
HbA1c (%mmol/mol)	8.4 ± 1.1, 69 ± 12	7.4 ± 0.5, 57 ± 5	9.1 ± 0.8, 76 ± 9	<0.001	8.4 ± 1.1, 68 ± 12	8.6 ± 1.1, 70 ± 12	8.4 ± 1.2, 69 ± 13	0.58

* Conventional injection regimen indicates insulin delivery by injection using any combination of insulin types except for glargine/lantus. Patients in this classification reported a mean(SD) of 2.6(0.8) daily injections. Glargine/lantus insulin regimen indicates insulin delivery by injections using lantus/glargine plus any combination of other insulin types. Patients using glargine/lantus reported a mean(SD) of 4.3(0.8) daily injections.

^aValues are means ± SD or n (%)

^bLow=BMI%ile < 85; Overweight=BMI%ile 85 and <95; Obese=BMI%ile 95.

^cT-test or ANOVA (Kruskal-Wallis rank test) of overall relationship; same superscripts indicate significant pair-wise differences

Table 3

Coefficient estimates from multilevel linear regression model relating time-varying BMI (kg/m²) to time-varying glycated hemoglobin (HbA1c).

	Independent variables	Coefficient ± SE	P
Time-varying	Glycated hemoglobin (%)	-0.11 ± 0.02	<0.001
	Insulin regimen (injection = ref)		
	Glargine/lantus	0.006 ± 0.05	0.90
	Pump	0.02 ± 0.06	0.71
	Insulin dose (units/ kg)	0.23 ± 0.07	0.001
	Time (month)	0.07 ± 0.004	<0.001
	Tanner stage	0.004 ± 0.02	0.88
Time-invariant	Treatment (control=ref)	0.10 ± 0.05	0.03
	Baseline BMI	0.99 ± 0.008	<0.001
	Baseline age (y)	0.03 ± 0.02	0.22
	Diabetes duration (y)	0.0005 ± 0.0007	0.51
	Sex (male=ref)	-0.03 ± 0.05	0.58
	Parent education ^a	0.002 ± 0.03	0.96
	Household income ^b	-0.05 ± 0.02	0.008
	Race/ethnicity (NHwhite=ref)		
	Non-hispanic black	-0.08 ± 0.10	0.45
	Hispanic	-0.02 ± 0.08	0.78
	Other	-0.02 ± 0.10	0.45

^a Categorical variable: 0=high school or less, 1=post high school but not college graduate, 2=college graduate, 3=graduate or professional school.

^b Categorical variable in \$ (thousands): 0=<30, 1=30-<50, 2=50-<70, 3=70-<100, 4=100-<150, 5= 150.