Obesity in Youth with Type 1 Diabetes in Germany, Austria, and the United States

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Objective To examine the current extent of the obesity problem in 2 large pediatric clinical registries in the US and Europe and to examine the hypotheses that increased body mass index (BMI) z-scores (BMIz) are associated with greater hemoglobin A1c (HbA1c) and increased frequency of severe hypoglycemia in youth with type 1 diabetes (T1D).

Study design International (World Health Organization) and national (Centers for Disease Control and Prevention/German Health Interview and Examination Survey for Children and Adolescents) BMI references were used to calculate BMIz in participants (age 2-<18 years and ≥1 year duration of T1D) enrolled in the T1D Exchange (n = 11 435) and the Diabetes Prospective Follow-up (n = 21 501). Associations between BMIz and HbA1c and severe hypoglycemia were assessed.

Results Participants in both registries had median BMI values that were greater than international and their respective national reference values. BMIz was significantly greater in the T1D Exchange vs the Diabetes Prospective Follow-up ($P < .001$). After stratification by age-group, no differences in BMI between registries existed for children 2-5 years, but differences were confirmed for 6- to 9-, 10- to 13-, and 14- to 17-year age groups (all $P < .001$). Greater BMIz were significantly related to greater HbA1c levels and more frequent occurrence of severe hypoglycemia across the registries, although these associations may not be clinically relevant.

Conclusions Excessive weight is a common problem in children with T1D in Germany and Austria and, especially, in the US. Our data suggest that obesity contributes to the challenges in achieving optimal glycemic control in children and adolescents with T1D. *(J Pediatr 2015;167:627-32)*.

Historically, obesity was rare in people with type 1 diabetes (T1D) because of the ineffective methods to achieve glucose control. In 1993, the Diabetes Control and Complications Trial (DCCT) established the importance of intensive diabetes management in adults and adolescents with T1D,[1,2] but this therapy paradigm was accompanied by increased weight gain in intensively treated participants.[3,4] In the follow-up to the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, increased body mass index (BMI) was associated with increased cardiovascular disease risk factors and markers of atherosclerosis (coronary artery calcification and carotid intima media thickness).[5] In a similar time period as the transition to intensive therapy for patients with T1D, Western countries have experienced an epidemic of pediatric obesity,[6] and youth with T1D are unlikely to have been spared from these effects. Increased BMI in youth with T1D has been reported in clinic-based and national cohorts[7-14] and is associated with a more atherogenic cardiovascular disease risk profile.[11,13,15] Increased BMI increases insulin resistance; however, the association of BMI, insulin resistance, hemoglobin A1c (HbA1c), severe hypoglycemia, and daily insulin doses is complex. International data comparing BMI in youth with T1D and the association of BMI with glucose control across countries do not exist.

The T1D Exchange (T1DX) registry in the US and the Diabetes Prospective Follow-up (DPV) registry in Germany and Austria are 2 large consortia of

BMI	Body mass index	HbA1c	Hemoglobin A1c
BMIz	BMI z-scores	IRB	Institutional review board
CDC	Centers for Disease Control and Prevention	KiGGS	German Health Interview and Examination Survey for Children and Adolescents
DCCT	Diabetes Control and Complications Trial	T1D	Type 1 diabetes
DPV	Diabetes Prospective Follow-up	T1DX	T1D Exchange
EDIC	Epidemiology of Diabetes Interventions and Complications	WHO	World Health Organization

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pediatric diabetes centers that were established with an objective of improving the care of children with T1D through sharing of best practices and the collection of clinical outcome data in large numbers of patients. In this collaborative study, both T1DX and DPV used queries of their databases to describe the prevalence of increased BMI z-scores (BMIz) in youth with T1D who were 2 to <18 years of age and had ≥1 year duration of diabetes. In addition, we tested the hypothesis that increased BMIz was associated with poorer metabolic control (greater HbA1c and increased frequency of severe hypoglycemia) in both registries.

Methods

The T1DX Clinic Network includes 70 US-based pediatric and adult endocrinology practices in 34 states. A registry of more than 26 000 individuals with T1D commenced enrollment in September 2010.[16] Each clinic received approval from a local institutional review board (IRB). Informed consent was obtained according to IRB requirements. Data were collected for the registry's central database from the participant's medical record and by having the participant or parent complete a comprehensive questionnaire, as previously described.[16]

The DPV registry is a prospective longitudinal, standardized, and computer-based documentation system for patients with all types of diabetes. Currently, more than 90% of German and more than 70% of Austrian children with diabetes are included in the registry. Data are documented locally by the 391 participating centers in an electronic health record. Twice yearly, anonymized data are exported and transmitted for central analyses. Missing and inconsistent data are reported back to the centers for correction. Data collection is approved by the ethics committee at Ulm University and by the IRBs at the participating centers.[17,18]

This report includes data on 32 936 children 2 to <18 years of age with a T1D duration of at least 1 year and available height and weight data; 11 435 participants enrolled in the T1DX from September 2010 to August 2012 at 59 sites who care for pediatric patients and 21 501 patients from 262 sites in the DPV who had at least one office visit in either 2011 or 2012. All eligible T1DX and DPV participants were included in this analysis. Median HbA1c over the year before the registry assessment, calculated from all available for the previous year but excluding any values obtained within 3 months of diagnosis, was used to represent HbA1c in this analysis. For both the T1DX and DPV, all HbA1c values were DCCT-standardized.[19,20] Severe hypoglycemia was defined by both registries as a hypoglycemic event in which seizure or loss of consciousness occurred. The numbers given correspond to the percent of patients with at least one severe hypoglycemia event during the previous year. BMI percentiles and z-scores were calculated from height and weight and adjusted for age and sex, using both international (World Health Organization [WHO]) and national (Centers for Disease Control and Prevention [CDC] for T1DX and German Health Interview and Examination Survey for Children and Adolescents [KiGGS] for DPV) reference tables.[21-26] Extreme BMIz <−3 and >+3 were truncated. In the WHO and the national reference populations, a BMIz of 0 represents the mean value of the population; values above the mean are positive and values below the mean are negative. BMI categories were defined using BMIz according to pediatric standards for each source.[22,26,27] Underweight individuals were excluded from analyses that assessed glucose control, because underweight status in adolescents with T1D often is caused by eating disorders, and psychiatric disorders have a strong impact on HbA1c and severe hypoglycemia.

In the T1DX, data were obtained through a combination of clinic and participant-report. Method of insulin delivery (pump/injection), height, weight, HbA1c values, and frequency of severe hypoglycemia were extracted retrospectively from the medical chart. Rates of self-monitoring of blood glucose and insulin dose were obtained from participant report via completion of a questionnaire. Conversely, all data from the DPV were extracted from the electronic medical record, as documented by members of the local diabetes team during routine patient care. All data from T1DX were obtained at the enrollment visit and data from DPV were collected from office visits that occurred during 2011 or 2012 (a similar time period as T1DX enrollment).

Statistical Analyses

To compare BMI between the 2 registries, a mixed model was used with BMIz calculated from the WHO reference tables. The model accounted for site differences and adjusted for T1D duration, sex, age group, and the interaction between registry and age group. Mixed models also were used to assess whether BMI was associated with HbA1c or severe hypoglycemia, overall (WHO reference and adjusted for T1D duration, sex, age group, registry, and random site effect) and within each registry (CDC or KiGGS reference and adjusted for T1D duration, sex, age group, and random site effect). Tests of significance were reported from models using BMIz as a continuous variable; adjusted means were reported from models using BMI as a categorical variable. Underweight individuals (based on corresponding cutoffs for underweight categorization) were excluded from these analyses. Although BMIz adjusts an individual BMI value for age and sex of the reference population, these factors were not fully adjusted for in our population and thus were included in the statistical models to account for residual confounding that could be present in this analysis cohort. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina). All *P* values are 2-sided. A priori, in view of the large sample size and multiple comparisons, only *P* values <.01 were considered statistically significant.

Results

Participant characteristics of children in the T1DX and DPV registries can be found in **Table I**. Children in both registries were similar with respect to sex, total daily insulin dose per