Real-Life Glycemic Control in Children with Type 2 Diabetes: A Population-Based Study

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Objectives To characterize children and adolescents with type 2 diabetes mellitus (T2DM) insured by a large health maintenance organization, and to identify variables associated with treatment quality and disease outcome.

Study design Children and adolescents diagnosed with T2DM over a 9-year period were identified from the database of Clalit Health Services, a large health maintenance organization in Israel (1 213 362 members aged 0-18 years). Demographic, anthropometric, clinical, and laboratory data were analyzed.

Results A total of 96 patients (47 males) met our inclusion criteria. The mean age at diagnosis of T2DM was 14.25 ± 2.51 years. At the time of diagnosis, the median hemoglobin A1c (HbA1c) level was 7.8%, and additional components of the metabolic syndrome were present in 14.9%-67.4% of the patients. At the end of the follow-up period (3.11 ± 1.75 years), >50% of the patients were being treated with insulin; the median HbA1c value was 7.97%, and 44.6% of the patients achieved the target HbA1c of <7.0%. On multivariate linear regression analysis, the variables found to predict worse glycemic control (ie, higher HbA1c) were a higher HbA1c at diagnosis, a higher body mass index SD score at diagnosis, fewer annual HbA1c tests, and Arabic ethnicity [$F(4,81) = 7.139$; $P < .001$; $R^2 = 0.271$].

Conclusion This population-based study of pediatric patients with T2DM demonstrates that reasonable glycemic control can be achieved in both community and outpatient hospital settings. Nevertheless, there is room for improvement in intervention programs to optimize outcomes and decrease the risk of complications. *(J Pediatr 2017;188:173-80).*

Overweight and obesity currently affect approximately one-third of all children and adolescents in the US, constituting a major recent rise in incidence.[1] A concomitant increase in obesity-related health risks, including metabolic syndrome and type 2 diabetes (T2DM), has been documented.[2-4]

The main components of the pathogenesis of T2DM are insulin resistance along with β-cell dysfunction and relative insulin deficiency. The disease is diagnosed when fasting or stimulated blood glucose levels exceed accepted thresholds.[5,6] Children and adolescents with T2DM show a rapid deterioration in β-cell function over time, but no significant change in peripheral or hepatic insulin sensitivity in the absence of a change in weight or body mass index (BMI).[4,6] Longitudinal studies have reported high rates of comorbidities and complications,[4] with risks increasing with the duration of diabetes and impairment of glycemic control.[4] According to the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial, the strongest predictors of glycemic control are initial β-cell reserve and hemoglobin A1c (HbA1c) concentration at randomization.[7] There is evidence suggesting that T2DM may be a more aggressive disease in the pediatric age group than in adults.[4,6] In addition, within the pediatric age group, T2DM may have more severe consequences than type 1 diabetes mellitus (T1DM).[7] A population-based cohort study from Australia comparing T2DM and T1DM found that T2DM was associated with significant excess mortality (11% vs 6.8%; $P = .03$) and an increased risk of all-cause death (HR, 2.0; 95% CI, 1.2-3.2; $P = .003$) and of cardiovascular death.[8] In addition, death occurred after a significantly shorter disease duration in the T2DM group.

Studies in obese children with prediabetes found that glucose tolerance may normalize with interventions leading to weight reduction.[9,10] Indeed, some children have been found to revert to normal glucose tolerance even without treatment if the baseline measures are favorable and there is sufficient weight reduction on entry to puberty.[11] In children with diabetes, the TODAY trial reported a significant difference in β-cell deterioration between patients who maintained glycemic control and those who

AAP	American Academy of Pediatrics
BMI	Body mass index
BMI-SDS	Body mass index standard deviation score
CHS	Clalit Health Services
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HMO	Health maintenance organization
LDL	Low-density lipoprotein
SES	Socioeconomic status
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth

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did not.[7] Therefore, to prevent the risk of microvascular and macrovascular complications of T2DM, achieving and sustaining adequate metabolic control as early as possible are imperative.[4]

Thus, the goals of T2DM treatment are to achieve target weight, achieve target glycemic control, and control hypertension and dyslipidemia. Once the diagnosis is made, treatment should focus initially on lifestyle modifications for weight reduction and normalization of hyperglycemia. If these steps fail, then oral hypoglycemic drugs and insulin therapy are introduced.[4] However, the American Academy of Pediatrics (AAP) acknowledges that some primary care clinicians might not be confident in their ability to successfully treat T2DM in a child. The AAP guidelines, with the cooperation of the American Diabetes Association, Pediatric Endocrine Society, American Academy of Family Physicians, and Academy of Nutrition and Dietetics, suggest that better results might be achieved when lifestyle modifications are integrated with medication in the initial treatment of T2DM. Many children and adolescents with T2DM do not achieve optimal glycemic control and remain at increased risk of future health complications.[4,12] Few studies have addressed the outcomes of treatment in real-life situations for this patient group.[13]

In Israel, the 1995 National Health Insurance Law stipulates that all citizens are entitled to health care services and to register with any 1 of the 4 approved health maintenance organizations (HMOs) that supply primary care services and are responsible for their members' quality of care.[14] Clalit Health Services (CHS) is a large HMO in Israel that insures 53% of the national population (48.7% of patients aged 0-18 years). CHS operates primary care community clinics, expert physician community clinics, hospitals, and outpatient hospital clinics, including laboratory and pharmaceutical services, and aggregates the data for each member from all these sources into a centralized data warehouse. This makes it an ideal database for assessing the real-life outcomes of children and adolescents with T2DM.

Like youths in other Western countries, Israeli youths have shown an increasing rate of obesity.[15] The aims of the present study were to evaluate the incidence of T2DM in children and adolescents insured by CHS and to identify variables affecting treatment outcomes (ie, glycemic control and other targets) in this population.

Methods

Between November 2000 and May 2009, a total of 1 213 362 individuals aged 0-18 years were insured nationwide by CHS. For the present study, we searched the CHS database for all patients diagnosed with diabetes (diabetes and non–insulin-dependent diabetes) within this population. Those who met the criteria for T2DM of the American Diabetes Association's Classification and Diagnosis of Diabetes[16] were included in the study: fasting blood glucose ≥126 mg/dL, HbA1c ≥6.5%, or nonfasting glucose ≥200 mg/dL and lack of evidence of diabetic autoimmunity (ie, absence of specific diabetes autoantibodies: anti-GAD, anti-islet, and anti-insulin), or prescription of oral hypoglycemic medications. The diagnosis of T2DM was verified by questioning the primary care physician of each patient (by name and identification number) via e-mail. The primary physicians were asked to confirm the diagnosis of T2DM, date of diagnosis, mode of therapy, and additional components of the metabolic syndrome.

Background and follow-up data were collected retrospectively from the CHS database for each patient included in the study: sex and ethnicity; diabetes follow-up setting (ie, community primary physician or expert physician in a community or hospital outpatient clinic), BMI, blood pressure measurements, laboratory lipid profiles, HbA1c levels, and medications prescribed. In addition, data on socioeconomic status (SES) were derived from the Israel Central Bureau of Statistics. SES was based on the SES of the clinic and categorized as low, moderate, or high, as described in the Results section. To compare BMI values across ages and by sex, the BMI SD score (BMI-SDS) was calculated. Total cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol levels were measured using an enzymatic colorimetric method with an automated analyzer (Hitachi 904; Roche Diagnostics, Basel, Switzerland). HbA1c levels were measured via a turbidimetric inhibition immunoassay (Hitachi 911; Roche Diagnostics; normal range, 4.3%-5.8%).

Obesity was defined as BMI above the 95th percentile for age and sex, according to Centers for Disease Control and Prevention growth charts.[17] Hypertension was defined as systolic and diastolic blood pressure above the 95th percentile for height and age.[18] Dyslipidemia was defined as triglycerides >150 mg dL/L and HDL cholesterol <40 mg dL/L,[12] or low-density lipoprotein (LDL) cholesterol >130 mg dL/L. The primary outcome measure of the study was adequacy of glycemic control at the end of the follow-up period, defined as the time of the last HbA1c measurement obtained. Secondary outcomes were presence of other components of the metabolic syndrome.

The study was approved by the Institutional Review Board and the Ethics Committee of CHS.

Statistical Analyses

Baseline characteristics are presented as mean ± SD for continuous variables and as frequency and percentage for categorical variables. Relationships among continuous variables were analyzed using the independent-samples *t* test, and those among categorical variables were assessed using the χ^2 test.

One-way ANOVA was used to compare 2 groups for continuous variables. Discrete variables were compared using the Pearson χ^2 test or the Fisher exact test, as appropriate, and the Mann-Whitney *U* test was applied for skewed distributions. A backward stepwise linear regression model was formulated to test the effects of the variables of interest on the last HbA1c value. Variables entered in the first step included HbA1c value at diagnosis, treatment type, treatment setting, ethnicity (Jewish/Arabic), age at diagnosis, sex, BMI-SDS at diagnosis, number of annual HbA1c measurements, LDL cholesterol level at diagnosis, HDL cholesterol level at diagnosis, and triglyceride