Overweight Is Highly Prevalent In Children with Type 1 Diabetes And Associates with Cardiometabolic Risk

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Objectives To determine the prevalence of traditional cardiometabolic risk factors and to assess the effect of overweight/obesity on the occurrence of these risk factors in a cohort of children with type 1 diabetes mellitus (T1DM).

Study design Two hundred eighty-three consecutive patients (3 to 18 years of age) attending an outpatient clinic for T1DM care were included. The prevalence of cardiometabolic risk factors, the metabolic syndrome, and high alanine aminotransferase, were assessed before and after stratification for weight status.

Results Of all children (median age, 12.8 years; interquartile range, 9.9 to 16.0; median diabetes duration, 5.3 years; interquartile range, 2.9 to 8.6), 38.5% were overweight/obese (*Z*-body mass index ≥1.1). Overall, median HbA1c levels were 8.2% (interquartile range, 7.4 to 9.8), and HbA1c ≥7.5% was present in 73.9%. Microalbuminuria was found in 17.7%, high triglycerides (>1.7 mmol/L) in 17.3%, high LDL-cholesterol (>2.6 mmol/L) in 28.6%, low HDL-cholesterol (<1.1 mmol/L) in 21.2%, and hypertension in 13.1% of patients. In the overweight/obese children with T1DM, versus normal-weight children, a higher prevalence of hypertension (23.9% vs 5.7%), the metabolic syndrome (25.7% vs 6.3%), and alanine aminotransferase >30 IU/L (15.6% vs 4.5%) was found (all $P < .05$).

Conclusions Overweight/obesity and cardiometabolic risk factors were highly prevalent in a pediatric cohort with T1DM. Hypertension, the metabolic syndrome, and high alanine aminotransferase were significantly more prevalent in overweight/obese compared with normal-weight children with T1DM. *(J Pediatr 2010;156:923-9)*.

The increasing prevalence of obesity and associated risk factors for cardiovascular disease (CVD) constitute a major global health problem, affecting both children and adults.[1] Currently, however, the effects of weight gain on CVD morbidity and mortality in patients with type 1 diabetes mellitus (T1DM) have been studied less extensively.[2] Although intensive insulin therapy has been shown to lower the development of microvascular,[3] and ultimately macrovascular complications in people with T1DM,[4] its beneficial effects may be partially off-set by its weight gain–promoting properties, which are paralleled by the occurrence of obesity-associated cardiometabolic risk factors.[5]

CVD has become the leading cause of mortality in patients with T1DM, with a 4- to 8-fold increase in mortality compared with nondiabetic age-matched individuals.[6] In these patients, CVD risk factors may have their onset in childhood and persist throughout adulthood, leading to the early development of atherosclerotic lesions and accelerated progression to CVD.[7] Previous studies have shown more severe atherosclerotic lesions in children with T1DM occurring at a younger age as compared with healthy control subjects.[8] In addition, two studies reported a high prevalence of risk factors and a positive family history in Norwegian and German children with T1DM.[9,10] Most studies evaluating the occurrence of these risk factors in pediatric populations with T1DM, however, did not address the role of overweight or obesity on the prevalence of these factors. Finally, the prevalence of the metabolic syndrome (MetS), a clustering of cardiometabolic risk factors (including obesity, dyslipidemia and hypertension), which encompasses increased risk for CVD in both obese adult and pediatric populations, was also not determined in these studies.[11,12]

The present study determined the prevalence of cardiometabolic risk factors in a cohort of children with T1DM. We also assessed the occurrence of MetS, according to an adjusted pediatric definition, and assessed the influence of overweight and obesity on the prevalence of these CVD risk factors.

ACR	Albumin-to-creatinine ratio
ADA	American Diabetes Association
ALT	Alanine aminotransferase
BMI	Body mass index
CVD	Cardiovascular disease
MetS	Metabolic syndrome
T1DM	Type 1 diabetes mellitus
WC	Waist circumference

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Methods

We studied a cohort of consecutive children (age 3 to 18 years) with T1DM who attended a Dutch specialized Pediatric Diabetes Center in Rotterdam in the period 2007 to 2008. Data were collected according to a standardized treatment protocol and cross-sectional analyses were performed to assess cardiometabolic risk factors within this cohort.

T1DM was diagnosed according to criteria of the American Diabetes Association (ADA), including measurements of autoantibodies (islet cell antibodies [ICA], glutamic acid decarboxylase [GAD], tyrosine phosphatase-like insulinoma antigen 2 [IA-2]) and C-peptide at diagnosis.[13] Children with incomplete data sets (n = 157), except for ALT (n = 153), were excluded from the study . In addition, to prevent bias, children with only clinical diagnosis of T1DM (n = 87), maturity-onset diabetes of youth, or secondary causes of T1DM (n = 24) and type 2 diabetes mellitus (n = 2) were excluded from the study. Therefore, a sample of 283 was included in this study. Children who were excluded due to incomplete data sets were not different with respect to baseline characteristics (sex, age, ethnicity, z-body mass index [BMI], and diabetes duration).

During visits to the outpatient clinic, a detailed history, including glycemic control and insulin regimen, was collected. A family history of type 2 diabetes and CVD was assessed yearly by questionnaire. Measurements of height and weight to calculate BMI, waist circumference (according to a previously described method),[14] and blood pressure were performed every visit. Three consecutive blood pressure measurements were performed in the nondominant arm, with at least a 1-minute interval, in the seated position and after 10 minutes of rest, using a validated oscillometric device (Omron705 IT). Blood samples for nonfasting lipid levels and HbA1c were drawn and urinary albumin and creatinine in spot urine were determined to calculate the albumin-to-creatinine ratio (ACR).

Cardiometabolic risk factors (smoking, obesity, glycemic control, elevated level of LDL-cholesterol, elevated level of triglycerides, decreased level of HDL-cholesterol, and microalbuminuria) and a positive family history for premature CVD and type 2 diabetes were identified according to the ADA guidelines for children and adolescents with T1DM.[15] BMI and waist circumference (WC) were standardized using *Z*-scores (*Z*-BMI and *Z*-WC, respectively) according to Dutch reference values, with a cutoff value for overweight defined as a *Z*-BMI $\geq$1.1.[16,17] Lipid levels were evaluated according to the reference values recently proposed by the ADA (LDL-cholesterol <2.6 mmol/L, HDL-cholesterol >1.1 mmol/L, and triglycerides <1.7),[15] and blood pressure values were considered abnormal when values were above the 95th percentile according to European reference values for height and sex.[18] Target levels for HbA1c were defined as HbA1c <7.5%.[18] Microalbuminuria was diagnosed when ACR determined in spot urine were $\geq$2.5 mg/mmol for boys and $\geq$3.5 mg/mmol for girls.[19] A positive family history was defined as a family history positive for premature CVD (ie, occurring before 55 years of age) and/or T2DM in a first- or second-degree family member.

The prevalence of MetS was determined, using a modified definition, assuming all children had elevated plasma glucose and using reference values for lipid levels in children with T1DM.[20,21] Hence, MetS was diagnosed when 2 or more of the following additional components were present: Z-BMI $\geq$2 (obesity), low HDL-cholesterol, high triglycerides and/or hypertension.[20,21] The prevalence of fatty liver was estimated using a cutoff value of 30 IU/L for ALT.[22] Children were divided into 2 age groups: a prepubertal age group, which included childhood and prepuberty (<11 years of age), and a pubertal group ($\geq$11 years of age), covering early adolescence and puberty because Dutch children reach puberty on average at an age of 11 years.[16]

We used *Z*-BMI>*Z*-WC to define a gluteal-femoral fat distribution pattern and *Z*-BMI<*Z*-WC to define an abdominal fat distribution pattern in overweight/obese children.

Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured in the nonfasting state,[10] by enzymatic methods on the Hitachi Cobas C501 analyzer (Roche, Mannheim, Germany) with an intra-assay and interassay coefficient of variation of <2.1%. HbA1c, urinary albumin, and creatinine were measured on a DCA 2000+ analyzer (Bayer, Dublin, Ireland). HbA1c was measured by a colorimetric assay with intra-assay and interassay coefficients of variation of <3.7% and <4.3%, (reference range, 4% to 6%), and urinary albumin and creatinine were measured by a turbidimetric assay and a colorimetric assay, with intra-assay and interassay of <6.1% and <6.6%, respectively. ALT was measured by an enzymatic assay on a Hitachi Cobas C501 analyzer (Roche, Mannheim, Germany) with intra-assay and interassay coefficients of variation of <2.0%.

Mean (standard deviation), median (interquartile range [IQR]) for variables with a skewed distribution, or n (percentages) are shown, after stratification for weight status. Differences between group proportions were analyzed by logistic regression analysis and differences between group means/medians were analyzed by linear regression analysis, all adjusted for sex, age, ethnicity, and diabetes duration where appropriate.

Logistic regression analysis was performed to assess the associations between *Z*-BMI, *Z*-WC, glycemic control, and ACR with presence of other cardiometabolic risk factors. Results of these analyses are expressed as odds ratio (OR) and 95% confidence intervals (95% CI), with adjustment for sex, age, ethnicity, and *Z*-BMI (where appropriate). Confounders were identified within the analysis, and stratification was applied in case effect modification was present.

A *P* value <.05 was considered statistically significant, whereas a *P* value of <.10 was used to indicate effect modification. All analyses were performed with SPSS, version 15.0 (for Windows) (SPSS Inc., Chicago, Illinois).