Glycemic Variability Is Associated with Markers of Vascular Stress in Adolescents

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Objectives We used continuous glucose monitoring to test the hypothesis that mean amplitude of glycemic excursions (MAGE) is associated with circulating markers of oxidative and vascular stress in adolescents with habitually low physical activity classified as healthy weight, healthy obese, or obese with type 2 diabetes mellitus (T2DM).

Study design A group of 13- to 21-year-olds (healthy weight = 12, healthy obese = 10, T2DM = 12) wore a continuous glucose monitor and step activity monitor for 5 days.

Results Physical activity was similar among groups (6551 ± 401 steps/d), but aerobic fitness (peak rate of oxygen consumption) was lower ($P < .05$) in T2DM (15.6 ± 1.8 mL/kg/min) than either healthy weight (26.2 ± 2.2) or healthy obese (24.4 ± 2.5). MAGE (mg/dL) was higher ($P < .01$) in T2DM (82 ± 10) vs healthy obese (33 ± 3) and healthy weight (30 ± 3). Average glucose followed a similar pattern as MAGE. Oxidized low density lipoprotein was higher ($P < .05$) in T2DM (70.3 ± 5.0 U/L) and healthy obese (58.1 ± 3.8) than healthy weight (48.4 ± 2) and positively correlated with MAGE (r = 0.77). Other stress markers that were both elevated in T2DM and correlated with MAGE included E-selectin (r = 0.50), intercellular adhesion molecule 1 (r = 0.35), and C-reactive protein (r = 0.52); soluble receptor for advanced glycosylation end product was lower in T2DM and inversely correlated with MAGE (r = −0.38).

Conclusions MAGE is highest in obese youth with T2DM. The associations between MAGE and oxidative stress markers support the proposed contribution of glycemic variability to risk for future cardiovascular disease. *(J Pediatr 2016;172:47-55)*.

Obesity is a major risk factor for prediabetes and type 2 diabetes mellitus (T2DM) in children and adults.[1,2] The progression from insulin resistance to T2DM tends to be faster in adolescents compared with adults.[3] Among the many factors that influence this progression, plasma glucose concentration, both fasting and post prandial, is the best predictor for the development of T2DM.[4] Glycemic control also determines the future risk of micro- and macrovascular complications, including cardiovascular disease.[5-7]

Optimal glycemic control is important for prevention of long-term complications in diabetes.[8,9] Although keeping the average blood glucose tightly controlled is intuitively valuable, recent studies of adults with diabetes showed that it may be equally, or even more important to avoid large daily fluctuations in blood glucose in order to maintain healthy vascular function.[10-12] Those studies showed that an increase in glycemic variability, whether measured in free-living adults with T2DM[11] or experimentally induced for 2 days in adults with or without T2DM[10] is positively correlated with urinary concentration of 8-iso prostaglandin F2α, a marker of oxidative stress. However, to our knowledge, the relationship between glycemic variability and measures of oxidative stress in adolescents with T2DM or their nondiabetic healthy weight or obese peers has not been previously published. Because evidence has demonstrated the difficulty of preventing the progression of T2DM and related complications in youth,[13] it is important to increase our understanding of how glycemic control and its association with vascular health is regulated in children and adolescents, especially in those with elevated risk for cardiometabolic diseases.

AUC	Area under the curve	MAGE	Mean amplitude of glycemic excursions
BMI	Body mass index		
CGM	Continuous glucose monitoring	NEFA	Nonesterified fatty acids
CRP	C-reactive protein	OGTT	Oral glucose tolerance test
HbA1c	Hemoglobin A1c	oxLDL	Oxidized low density lipoprotein
HDL-C	High density lipoprotein-cholesterol	sRAGE	Soluble receptor of advanced glycation end-products
ICAM-1	Intercellular adhesion molecule 1	T2DM	Type 2 diabetes mellitus
iHOMA2	Interactive homeostatic model of assessment 2	VCAM-1	Vascular cellular adhesion molecule 1
LDL-C	Low density lipoprotein-cholesterol	VO_2peak	Peak rate of oxygen consumption

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Hemoglobin A1c (HbA1c) is the most commonly used measure of glycemic control but does not reflect daily glucose variability[14] and may not be a reliable predictor for cardiovascular events.[15] Continuous glucose monitoring (CGM) has become a useful tool to measure glucose fluctuations at high frequency resolution over several days. CGM systems measure interstitial glucose but have been shown to be a valid and reliable surrogate for blood glucose concentration during glycemic variations.[16] A recent report demonstrated that CGM could be used in overweight or obese adolescents without diabetes and that average glucose over 2-3 days, and the time spent above selected glycemic thresholds (120 or 140 mg/dL) was positively correlated with HbA1c and 2-hour glucose during an oral glucose tolerance test (OGTT).[17] However, that study did not assess the relationship between glycemic variability and markers of oxidative stress or vascular risk in adolescents. Thus, the goal of the current study was to use CGM to measure glycemic variability in adolescents and to test the hypothesis that the mean amplitude of glycemic excursions (MAGE), a summary measure of glycemic variability,[18,19] is significantly correlated with circulating markers of oxidative stress in adolescents with T2DM vs age-matched, healthy-weight, or obese peers without diabetes and similarly low habitual physical activity.

Methods

Boys and girls between 13 and 21 years old with Tanner pubertal staging ≥2 were enrolled into 1 of 3 study groups. The healthy weight (N = 12) group had body mass index (BMI) between the 25th and 75th percentile for age and sex on the Centers for Disease Control standard growth curves. The obese (N = 10) group had BMI ≥95th percentile. The T2DM group (N = 12) was obese and met the criteria for T2DM defined by the American Diabetes Association. The recruitment strategy was to enroll similar numbers of boys and girls into each group. In addition, all participants had low habitual physical activity, defined as <30 minutes of moderate-to-vigorous intensity physical activity on ≤2 d/wk. We did not attempt to match the groups for other characteristics, such as body size or body composition of the healthy obese and T2DM groups, for example. Participants were excluded if they had endocrine causes of obesity, or metabolic, cardiovascular, or other medical conditions, or were using medications that were expected to impact the study outcomes. The exception for medications was the use of metformin by 9 of the 12 participants with T2DM because this compound is extensively used in clinical practice and excluding participants who use metformin would impair recruitment and generalizability of the results. None of the participants with T2DM used exogenous insulin.

Participants (and parents of participants <18 years of age) provided oral and written consent/assent in accordance with the policies of the University of Oklahoma Health Sciences Center Institutional Review Board. During the initial visit, a pediatric endocrinologist performed a medical history and physical examination. Total body and regional fat and lean tissue were measured using dual energy X-ray absorptiometry (GE/Lunar iDXA; GE Healthcare, Fairfield, Connecticut). Exercise fitness was measured as described below. On a separate morning at least 2 days after the fitness test, participants returned following a 10-hour overnight fast for collection of 2 venous blood samples, separated by 5 minutes. These samples were used for measurement of all analytes described below. The average concentration measured in the 2 separate samples from each person was used for data analyses. Healthy weight and healthy obese participants then completed a standard 2-hour OGTT with a 75-g glucose load to confirm that they did not have T2DM. The T2DM group did not perform the OGTT because of concerns that the test would exacerbate their hyperglycemia. During the OGTT, blood was collected at −8, −3, 30, 60, 90, and 120 minutes before and after glucose ingestion, respectively. The concentrations of glucose, insulin, and nonesterified fatty acids (NEFA) were measured at each collection time.

CGM was performed for 5 consecutive days using the iPro2 from Medtronic MiniMed (Northridge, California). During the second visit, the device was installed on the abdomen. Participants were given a finger stick glucose analyzer and instructed to check their glucose at least 3 times per day in order to synchronize the readings with the CGM. Glucose analyzers were calibrated according to the manufacturer. Each participant was also instructed to wear a step activity monitor, as described below, and to maintain their normal patterns of physical activity, particularly avoiding novel vigorous activities prior to, and during the 5-day monitoring period. They were asked to keep a diary of their physical activity, timing of food intake with approximate portion sizes, and the use of medications, to confirm consistency of behavior during the measurement period.

Measurements

MAGE. MAGE is the arithmetic average of all increases (or decreases) in glucose concentrations that exceed 1 SD of the total set of glucose values. MAGE can be computed manually using the data downloaded from the CGM, or using computer software as previously described.[19,20] We developed a program to calculate the number of excursions and MAGE using the free software environment *R*.[21,22] The program algorithm was designed to calculate the mean and SD for each set of glucose values, define the inflection points at which glucose concentration changed from either increasing or decreasing, count the number of excursions (upward or downward changes in glucose concentration that exceeded 1 SD), and determine the amplitude of each excursion. Separate MAGE values for each participant were calculated for each day and for the entire measurement period using the corresponding SD for glucose concentration within the specific time interval. For each participant, all of the available glucose concentration values from the CGM, without filtering or smoothing, were used to calculate MAGE. The iPro2 device records glucose concentration every 5 minutes (288 data points per day). We did not attempt to interpolate

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