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Glycemic Variability Predicts Inflammation in Adolescents with Type 1 Diabetes

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Abstract

Background: Adolescents with type 1 diabetes (T1D) have increased risk of cardiovascular disease as well as elevations in biomarkers of systemic inflammation, plasma protein oxidation and vascular endothelial injury. It is unclear whether hyperglycemia itself, or variations in blood glucose are predictors of these abnormalities.

Methods: This study was designed to determine the relationship of inflammatory (C-reactive protein, CRP), oxidative (total anti-oxidative capacity, TAOC) and endothelial injury (soluble intracellular adhesion molecule 1, sICAM1) markers to glycemic control measures from 3 days of continuous glucose monitoring (CGM) and to hemoglobin A_{1c} (HbA_{1c}), and HbA_{1c} × duration area under the curve (A1cDur).

Results: Seventeen adolescents (8 F/9M; age, 13.1 ± 1.6 years (mean ± SD); duration, 4.8 ± 3.8 years, BMI, 20.3 ± 3.1 kg/m²; A1c, 8.3 ± 1.2%) were studied. Log CRP but was not related to age, duration, body mass index (BMI), HbA_{1c}, or A1cDUR. TAOC increased as logA1cDUR increased (n = 13, r = 0.61, p = 0.028). CRP and sICAM were not related to CGM average glucose but log CRP increased as 3 day glucose standard deviation increased (r = 0.66, p = 0.006). TAOC increased as glucose standard deviation increased (r = 0.63, p = 0.028).

Conclusions: Increased glucose variability is associated with increased inflammation in adolescents with T1D. Increased TAOC with increasing variability may be an effort to compensate for the ongoing oxidative stress.

Keywords: glucose variability; inflammation; oxidation; type 1 diabetes; vascular endothelial injury/stress.

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Introduction

Cardiovascular disease is the major cause of death for patients with type 1 diabetes (T1D) [1] and there is clear evidence that cardiovascular disease has its origins in childhood and adolescence [2–5]. Inflammation and vascular endothelial injury are early events in nearly all forms of cardiovascular disease and several studies have shown that these biomarkers are also elevated in adolescents with type 1 diabetes prior to the clinical development of cardiovascular complications [6, 7]. Given the increased prevalence of T1D in children and its strong link to early heart disease in adulthood it is critical that we learn more about early predictors of complications and relationships among blood glucose abnormalities and biomarkers of disease processes to enable improved strategies for prevention and/or therapy.

Current clinical management of T1D relies heavily on the average glycemia measure of hemoglobin A_{1c} (HbA_{1c}), but some very recent reports (mostly in adults) suggest that variations in blood glucose, rather than absolute or time-averaged values, may be more strongly linked to unfavorable outcomes. Specifically, in type 2 diabetes microvascular complications and coronary artery disease are consistently related to increased glucose variability although these relationships have not been found in adults with T1D [8]. Thus, the significance of increased glucose variability in T1D is controversial [9, 10]. Pathophysiologically, increased glucose variation may increase oxidative tissue damage more than continuous hyperglycemia [11, 12].

The goal of this study was to determine the relationship of biochemical inflammatory, oxidative, and endothelial markers to fasting glucose, 72 h mean glucose and glucose variability, HbA_{1c} and HbA_{1c} over time in adolescents with T1D. High sensitivity C-reactive protein (CRP) is the most studied inflammatory marker in pediatric type 1 diabetes. In healthy adults, CRP levels predict future cardiovascular disease and are linked to endothelial dysfunction [13–15]. Most [6, 7, 16–22], but not all studies [23, 24], have demonstrated significant increases in CRP levels in pediatric T1D patients. Soluble intracellular adhesion molecule 1 (sICAM 1) is biochemical marker of endothelial damage and inflammation and is again elevated in pediatric T1D [7, 20, 25–27].

Materials and methods

Subjects

Seventeen adolescents (eight female, nine male) with T1D were recruited from the Pediatric Diabetes Clinic of Nationwide Children's Hospital (NCH). The study was approved by the NCH Institutional Review Board and informed consent was obtained from parent or legal guardian. Proper assent was obtained from all subjects.

Screening included a history, physical exam, Tanner staging, and fasting laboratory testing. T1D was defined by American Diabetes Association criteria plus a fasting C-peptide of <0.4 ng/mL, insulin monotherapy since diagnosis, and an absence of a history of oral hypoglycemic agents and acanthosis nigricans on exam.

All subjects were Tanner stage 2–4 in order to minimize the effects of starting or finishing puberty. In order to limit confounding effects on endothelial function, subjects with BP > 95%, smoking, pregnancy, and uncorrected hypothyroidism, were excluded. Subjects with microalbuminuria, overt nephropathy, or early renal failure (random urine microalbumin/creatinine > 0.02 mg albumin/mg creatinine; serum creatinine > 1.0 mg/dL) were, also, excluded.

Protocol

Subjects were admitted to the Clinical Research Center of the Wexner Medical Center at the Ohio State University at 07:30 after having fasted from 22:00 the night before. Subjects were instructed to take their usual basal insulin the night before or to remain on their usual basal insulin infusion rates if using continuous subcutaneous insulin. Subjects withheld their morning insulin bolus until breakfast was given after the study completion. A blood sample was then collected for measurement of fasting glucose and biochemical markers. Eleven patients then participated in an insulin clamp study to assess the effects of glucose normalization and hyperglycemia. Results on this study have been previously reported [28] as have results on endothelial function [29]. Subjects were then placed on a continuous glucose monitor (CGM, Medtronic Guardian, Fridley, MN, USA) for 3 days after which the CGM was returned and the data downloaded using the Medtronic Carelink website to determine the mean glucose level and standard deviation.

Laboratory measurements

CRP, total plasma antioxidant capacity (TAOC), a measure of oxidative stress, and sICAM1 were measured. TAOC is a non-specific assay of anti-oxidant defense which measures the ability of constituents in plasma to absorb oxidation (BioVision Research Products, Mountain View, CA, USA). TAOC results were available in only 13 subjects. Serum sICAM levels were determined using a commercially available assay (R & D Systems, Minneapolis, MN, USA; Cat # BBE 1B).

Statistical analysis

Hemoglobin A_{1c} by duration area under the curve (A1cDur) was calculated using the trapezoidal rule. Pearson's regression analysis was

used to assess the relationship between biochemical markers and the various measures of glucose control. Data was log normalized, as needed. All analysis was performed using Systat 13 (Systat Software Inc, Chicago, IL, USA). Results are reported as mean ± SD.

Results

Age, duration, BMI effects and blood pressure effect

Mean demographic, glucose, and laboratory values for the subjects are shown in Table 1. Age and BMI were not significantly related to any of the measures (Table 2). Systolic blood pressure (SBP) but not diastolic pressure (DBP) increased as duration of diabetes increased ($r=0.62$, $p=0.009$). Neither was significantly related to age or BMI. TAOC increased as diabetes duration increased and logCRP tended to do the same. LogCRP increased as systolic blood

Table 1: Demographic and biochemical parameters.

Age, years	13.1 ± 1.6
Duration, years	4.8 ± 3.8
BMI, kg/m ²	20.3 ± 3.1
Systolic pressure, mmHg	106 ± 6
Diastolic pressure, mmHg	61 ± 9
HbA _{1c} , %	8.3 ± 1.2
Fasting glucose, mg/dL	160 ± 67
72 h mean glucose, mg/dL	200 ± 46
72 h glucose standard deviation, mg/dL	80 ± 20
C-reactive protein, ng/mL	1.45 ± 2.93
Soluble intracellular adhesion molecule, ng/mL	196 ± 80
Total anti-oxidant capacity, units	130 ± 40

Table 2: Correlation coefficient relationships of high sensitivity C-reactive protein (hsCRP), total anti-oxidant capacity (TAOC) and soluble intracellular adhesion molecule (sICAM) to age, duration, BMI, and glucose control variables in adolescent type 1 diabetes.

	LoghsCRP	TAOC	LogsICAM
Age	0.03	0.23	-0.36
Duration	0.42 ^a	0.61 ^b	0.24
BMI	0.34	0.22	-0.3
SBP	0.49 ^a	0.08	0.44
DBP	0.18	-0.02	0.35
Fasting glucose	-0.11	0.16	-0.27
Log 72 h mean glucose	0.15	0.39	0.24
72 h standard deviation	0.66 ^b	0.63 ^a	0.46
Hemoglobin A _{1c}	0.15	0.38	0.27
LogA1cAUC	0.39	0.61 ^a	0.42

^a $p < 0.05$, ^b $p < 0.01$.

pressure increased and logsICAM tended to do the same. DBP was not related to hsCRP, TAOC, or sICAM.

Glucose control effects

SBP increased as logA1cDur increased ($r=0.63$, $p=0.007$) but was not related to any of the other glycemic control measures. DBP was not related to any of the glycemic control measures. HbA_{1c} increased in older subjects ($r=0.55$, $p=0.021$).

LogCRP was not related to fasting glucose, 72 h mean glucose, HbA_{1c} or A1cDur but was significant related to 72 h glucose standard deviation (Figure 1). TAOC increased as logA1cDur increased as glucose standard deviation increased but was not related to the other measures. Log-sICAM tended to increase as glucose standard deviation and A1cAUC increased.

Discussion

Our study is the first to report on the relationship of glucose variability to markers of inflammation, oxidation, and endothelial damage in adolescents with T1D. The results demonstrate that increasing glucose variability is associated with increasing inflammation as indicated by increasing levels of CRP. There was no relationship of inflammation to other measures of short, intermediate, or long-term glycemic control. Surprisingly, increased glucose variability was associated with increased, not decreased, TAOC. This may be compensation for increased oxidative stress. This hypothesis is supported by the positive relationships between TAOC and duration and A1cDur.

Hyperglycemia-induced oxidative stress plays a key role in increasing inflammation [30, 31]. Animal studies

have suggested that intermittent hyperglycemia has a more pronounced effect than sustained hyperglycemia [10, 32, 33], although thus far human studies have been less convincing. We have previously found no relationship between glucose variability and endothelial function or endothelial progenitor cells in adolescents with T1D [29]. In adults with T1D Gordin et al. [34] found no relationship between glucose variability and arterial stiffness and Cesana et al. [35] found no relationship to carotid intimal thickness. No relationship was found between glucose variability and microvascular or macrovascular complications in the Diabetes Control and Complications Trial [36–38]. Prospective studies have yielded variable results. In adults with T1D, Buse et al. [39] used sensor augmented pump therapy to reduce glucose variability in comparison to multiple daily injections and found a decrease in inflammatory ligand CD40L levels in the pump group but an increase in the injection group although the difference was not significant. In a single group study Dal et al. [32] found no effect of flexible insulin therapy designed to reduce glucose variability although mean amplitude glucose excursion also did not change. Jamiolkowska et al. [40] found that reducing glucose variability improved endothelial function in adolescents with T1D.

From our study it is unclear what the long-term effects of increased glucose variability and inflammation in adolescent T1D will be. We found no relationship between glucose variability and blood pressure and subjects with evidence of early diabetes complications were excluded. We did find increased systolic blood pressure in subjects with long-standing poor diabetes control. We studied a small number of subjects so there may be additional relationships that were not detected. This is particularly true regarding sICAM were several of the correlation coefficients suggest possible relationships.

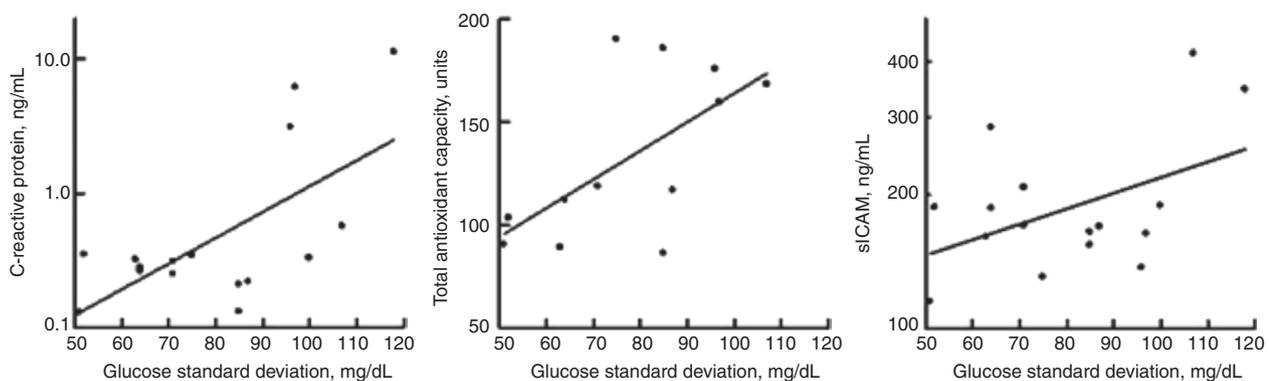


Figure 1: Relationship of c-reactive protein ($r=0.63$, $p=0.006$), total anti-oxidant capacity ($r=0.63$, $p=0.028$) and soluble intracellular adhesion molecule ($r=0.46$, $p=0.070$) to 72 h glucose standard deviation in adolescents with type 1 diabetes.

In conclusion, increased glucose variability in adolescents with type 1 diabetes is associated with increased inflammation. Future longitudinal studies will be needed to explore the long term effects.

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