

Impaired Endothelial Function in Adolescents with Type 1 Diabetes Mellitus

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Objective To evaluate the effect of a high-fat meal on endothelial function in adolescents with type 1 diabetes mellitus (T1D).

Study design Twenty-three children with T1D, aged 12 to 18 years, and age- and sex-matched healthy control subjects were assessed for baseline macronutrient intake, and endothelial function was measured both fasting and after a standardized fast-food, high-fat breakfast.

Results Endothelial function, assessed noninvasively by peripheral arterial tonometry, was impaired in the T1D group in the fasting state as compared with control subjects (T1D 1.78 ± 0.4 , control subjects 2.06 ± 0.4 , $P = .02$), and worsened postprandially in both groups (T1D 1.45 ± 0.3 , control subjects 1.71 ± 0.3 , $P = .01$). Both groups demonstrated significantly elevated triglyceride levels 3.5 hours after ingestion of the high-fat meal (T1D 114.8 ± 42.8 and control subjects 126.7 ± 54.9 mg/dL). Nutrient intake in both groups showed higher than recommended intakes of total fat, saturated fat, and cholesterol.

Conclusions Patients with T1D exhibited worse endothelial function both before and after a high-fat breakfast than their peers. This suggests that patients with T1D are at greater risk of vascular impairment after a high-fat meal, the cumulative effect of which may contribute to the higher atherosclerotic burden observed in T1D. (*J Pediatr* 2008;152:557-62)

Type 1 diabetes mellitus (T1D) is a significant risk factor for atherosclerosis, with pathologic and clinical evidence of coronary artery disease manifesting before 30 years of age.¹⁻³ Measures to reduce cardiovascular risk in pediatric patients have recently been emphasized, including the use of techniques that can help in the early detection of patients at risk.^{3,4} To this extent, several markers have been proposed, including endothelial function (EF), which is used as a surrogate marker of cardiovascular risk and offers the advantage of a noninvasive, subclinical measure to assess for early vascular changes in high-risk patient groups.⁵

In patients with T1D, poor metabolic control is associated with elevated levels of total cholesterol and triglyceride rich and highly atherogenic particles, which may affect EF.^{6,7} Fasting measures of lipids do not take into account the exposure of the vascular endothelium to the effect of nonfasting levels of circulating lipids throughout most of the day. In adults, elevations in postprandial TG levels have been shown to impair EF and are associated with increased risk for future atherosclerotic events,⁸⁻¹¹ but this has not been investigated in children or adolescents with T1D.

We hypothesized that consumption of a high-fat meal would impair EF in adolescents and that this effect would be greater in patients with T1D than in healthy control subjects. The aim of this study was to determine the effects of a "real-world" high-fat, fast-food meal on endothelial function in adolescents with T1D and in age- and sex-matched control subjects. We also used a validated food frequency questionnaire to examine dietary choices, with particular interest in fat intake, in both patient groups.

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BP	Blood pressure	PAT	Peripheral arterial tonometry
EF	Endothelial function	TG	Triglycerides
HDL	High-density lipoprotein	T1D	Type 1 diabetes
LDL	Low-density lipoprotein		

METHODS

Study Population

Subjects with T1D diagnosed according to Canadian Diabetes Association criteria¹² at least 2 years before inclusion, aged 12 to 18 years, were recruited in our Pediatric Diabetic Clinics. Healthy age- (within 1 year) and sex-matched control subjects were recruited from friends of the study participants. Subject and parental written informed consent was obtained for all participants. Exclusion criteria included blood pressure (BP) greater than 95%, weight greater than 95th percentile, active smoking, use of vasoactive medications, personal or family history (first-degree relative) of familial hypercholesterolemia, or other current significant medical illness. Smoking history was elicited through a confidential questionnaire. The study protocol was approved by the University of Western Ontario Research Ethics Board.

Food Frequency Questionnaire

The Youth/Adolescent Food Frequency Questionnaire (Harvard University, Boston, MA) is a validated food frequency questionnaire designed for children ages 9 to 18 years.^{13,14} It was used to determine the dietary intake of energy, total fat (including saturated, polyunsaturated, mono-unsaturated subtypes), carbohydrates, and protein, with percentage from each source shown. Each survey was completed confidentially and separately by each study subject with the aid of a research assistant. Data sheets from each subject were coded and analyzed by computer.

Patient Testing

Subjects were asked to fast from 10 PM the evening before the study and to avoid caffeine for the preceding 24-hour period. On the day of testing, subjects presented in the morning for measurement of weight, height, waist circumference, and peripheral arterial tonometry (PAT) testing (see below), immediately followed by taking a fasting blood sample from the non-tested arm. All subjects were provided with a standardized high-fat meal (McDonalds breakfast and drink; 940 calories, 55 g fat [53% of energy from fat], 22 g saturated fat [21% of energy from saturated fat], 73 g carbohydrate) and supervised to ensure full consumption. Patients with T1D used their established insulin scales to adjust their pre-breakfast insulin dose. Three hours after breakfast, study subjects completed a second PAT assessment, followed by taking a blood sample 30 minutes later. This time period was determined to coincide with peak levels of postprandial lipids on the basis of previous studies.¹⁵⁻¹⁷ Glucose levels and lipid profiles were determined in both blood samples; in the fasting sample we also measured hemoglobin A1C, Lipoprotein (a) (Terumo Medical, NJ), apolipoprotein B (Roche Diagnostics, Basel, Switzerland), and hs C-reactive peptide (Beckman Coulter, Fullerton, CA).

PAT Testing

Details of PAT (Itamar Medical, Israel) testing have been reviewed elsewhere.¹⁸⁻²² Briefly, PAT is a noninvasive technology that uses pneumatic probes designed to measure pulsatile volume changes at the finger tips. These probes, which resemble a thimble, cap the finger over the distal phalanx and apply a uniform pressure field around the digit, which allows for measurement of the pulsatile oscillations of the digital vascular bed microcirculation.

PAT probes are placed on finger II or III of each hand. After a 5-minute equilibration period, a blood pressure cuff is inflated on the study arm 40 mm Hg above systolic BP for 5 minutes. The cuff is then deflated, and bilateral tonometric recording is completed for an additional 5 minutes. An automated algorithm calculates the reactive hyperemia PAT index (PAT-RH) for each patient. Lower PAT-RH index scores are reflective of greater endothelial dysfunction and risk for atherosclerosis.

Data Analysis

All measures are expressed as mean value \pm standard deviation (SD). Baseline characteristics were compared by use of paired *t* tests and McNemar test. Associations between baseline characteristics, dietary components, macronutrient intake, and baseline laboratory measurement levels were quantified with Pearson Correlation Coefficients. Linear regression was used to determine whether baseline factors were associated with postlipid levels and PAT levels. To determine whether the association differed between patients with T1D and control subjects, a dummy variable indicating disease status and an interaction term were included in the model. For each group, a paired *t* test was used to determine whether PAT levels differed from baseline to post. A 2-sample *t* test was used to determine whether the change in PAT levels differed between T1D and control subjects. All analyses were conducted with SAS, version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

As shown in Table I, there were no differences in baseline characteristics between patients with diabetes and control subjects except for fasting glucose, which was higher in patients with T1D than in control subjects ($P < .001$). There were no active smokers by patient self report. One patient with T1D had autoimmune hypothyroidism and was euthyroid on levothyroxine at the time of testing. Two subjects (aged 18 years, a pair) were receiving oral contraceptives and were tested in the first 2 weeks of their cycle. No study subject had dietary restrictions, including for celiac disease. Albumin to creatinine ratios were normal (less than 2) in all patients with T1D, and no patients had background retinopathy.

Macronutrient intake is summarized in Table II; total daily energy totals were similar between patients with T1D and control subjects. Similar total carbohydrate intake was noted, but patients with T1D had a greater proportion of complex to simple carbohydrates.

Table I. Baseline characteristics

	Type I Diabetes (n = 23)	Control (n = 23)	P value
Age (years)	14.6 ± 1.75	14.7 ± 1.95	.42
Sex	9 F/14 M	9 F/14 M	—
BMI (kg/m ²)	20.3 ± 3.5	20.8 ± 2.9	.63
Waist circumference (cm)	72.9 ± 9.7	72.1 ± 10.5	.77
Systolic BP (mm Hg)	110.7 ± 5.7	110.6 ± 5.8	.93
Diastolic BP (mm Hg)	69.7 ± 3.8	68.9 ± 4.5	.49
Smoking	None	None	—
HbA1c (%)	8.3 ± 1.5 (Range 5.8-12.7)	—	—
Diabetes duration (years)	5.8 ± 3.6	—	—
Albumin/creatinine ratio	0.85 ± 0.5	—	—
Glucose			<.001
mg/dL	200.8 ± 100	91.8 ± 7.6	
mmol/L	11.1 ± 5.5	5.1 ± 0.42	
Total cholesterol			.46
mg/dL	156.6 ± 22	162.6 ± 35	
mmol/L	4.05 ± 0.6	4.2 ± 0.9	
LDL cholesterol			.25
mg/dL	89.3 ± 21	96.7 ± 31	
mmol/L	2.3 ± 0.54	2.5 ± 0.81	
HDL cholesterol			.38
mg/dL	54.9 ± 12	52.4 ± 9	
mmol/L	1.42 ± 0.3	1.35 ± 0.23	
TG			.63
mg/dL	62.7 ± 29	67.4 ± 35	
mmol/L	0.71 ± 0.33	0.76 ± 0.39	
Apolipoprotein B (g/L)	0.64 ± 0.13	0.7 ± 0.22	.18
LDL/Apolipoprotein B Ratio	3.6 ± 0.55	3.58 ± 0.29	.82

Data are presented as mean ± SD. Plasma levels were obtained in the fasting state.

Premeal measures of lipids were similar between the 2 groups. Low-density lipoprotein (LDL) to apolipoprotein B levels, as a measure of small, dense pro-atherosclerotic particles, were not significantly different between the groups. Lp(a) levels were undetectable (<5 mg/dL) in 22 of the 46 participants, elevated values (>50 mg/dL) were not found. C-reactive protein (CRP) levels were below the lower detection limit of <0.2 mg/L in 13 of 23 participants in each group. Of the remaining subjects, 8 of 10 patients with T1D had a CRP level greater than the sex-specific 75th percentile in Canadian adolescents compared with 4 of 10 subjects in the healthy group.¹⁹

Testing was completed in all subjects during 2 visits (fasting and postmeal) occurring on the same day in 40/46 subjects and on the subsequent day (postmeal PAT) in the remainder. Both groups demonstrated significant elevations in triglyceride (TG) levels after ingestion of the high-fat meal. Mean fasting TG levels in T1D and controls increased by 53% ± 12% and 55% ± 16% ($P = .001$ for both groups compared with baseline), respectively, after the meal. Postprandial levels of Tchol and low-density lipoprotein-cholesterol (LDL-C) were 152.4 ± 21.0 and 158.2 ± 35.8 mg/dL

and 76.2 ± 16.1 and 81.5 ± 28.3 mg/dL for the T1D and control groups ($P = .5$ and $P = .43$).

As illustrated in the Figure, patients with T1D had significantly lower PAT-RH scores compared with control subjects both fasting (1.78 ± 0.4 vs 2.06 ± 0.4, $P = .02$) and in the postprandial state (1.45 ± 0.3 vs 1.71 ± 0.3, $P = .01$). Within the T1D and control groups, the decrease in PAT-RH in the postprandial state was significant ($P < .0001$ and $P = 0.0004$, respectively), the change in PAT-RH scores after the meal did not differ between groups (−0.33 ± 0.23 and −0.36 ± 0.41, $P = .73$).

Pearson correlation coefficients comparing preprandial or postprandial PAT-RH scores with glucose, HbA1c or fasting or postprandial lipids were not significant. The change in PAT-RH scores did not correlate with the change in glucose ($P = .9$) or TG levels ($P = .2$). Glucose was not correlated to baseline, postprandial PAT-RH score, or change in PAT-RH score.

In the premeal state, only BMI and waist circumference were found to be correlated with a more atherogenic lipid profile. For all participants combined, increasing BMI correlated with higher total cholesterol ($r = 0.32$, $P = .03$), TG ($r = 0.44$, $P = .002$), LDL-C ($r = 0.38$, $P = .01$), and lower high-density lipoprotein (HDL) ($r = -0.31$, $P = .03$). Macro-nutrient intake did not correlate with baseline or postmeal lipid assessments.

In linear regression, BMI and diabetic status were significantly associated with postmeal total cholesterol ($r^2 = 0.3$, $P = .0015$), LDL-C ($r^2 = 0.3$, $P = .0003$), and TG ($r^2 = 0.22$, $P = .05$), and but not HDL ($r^2 = 0.08$, $P = 0.31$). The duration of diabetes, HbA1c, and sex were not significant predictors of postprandial lipid levels.

DISCUSSION

The increase in TG observed after a high-fat meal is similar to that reported in a study of T1D (mean HbA1c 9.2%) and healthy adolescents.¹⁵ Studies in obese and insulin-resistant children, in relation to healthy control subjects, have also shown significant elevations in baseline and postprandial lipids, depending on the test meal provided.^{16,17} We chose a fast-food breakfast for several reasons, including patient familiarity, standardization of meal size and content, and palatability, and also wanted to assess the impact of a meal that an adolescent could consume in a real-world setting.

The association between postprandial dyslipidemia and atherosclerosis was originally proposed more than 25 years ago, and numerous studies in adult subjects have shown that increased postprandial hypertriglyceridemia is associated with impaired endothelial function and coronary artery disease in both healthy and insulin-resistant adults.^{10,11,23-25} Our participants were not obese, yet higher BMI was correlated with a more atherogenic premeal lipid profile, and both BMI and the presence of T1D were associated with higher postmeal lipid levels.

In this study, a significant increase in plasma TG levels was observed with deterioration in endothelial function in

Table II. Macronutrient Intake In Study Groups in comparison with Recommended Intake from the CDA and ADA

	CDA/ADA* Guidelines	Type I Diabetes (n = 23)	Control (n = 23)	P value
Energy (Kcal)	—	2902.4 ± 981	2822.7 ± 947	.78
Total protein (g)	—	123.1 ± 37.2	118.2 ± 39.1	.91
Total carbohydrate (g)	—	377.6 ± 125	372.4 ± 137.9	.74
Complex carbohydrates		47.8%	31.8%	.04
Simple carbohydrates		52.2%	68.2%	.03
Total fat (g)	—	110.6 ± 47.9	104.67 ± 33.7	.69
Trans fats (%)	Less than 10%	3.9 ± 1.7	4 ± 1.4	.64
Cholesterol (mg)	<300 mg	333.7 ± 141.7	337.5 ± 114.3	.74
Dietary fiber (g)		24.8 ± 9.2	24.8 ± 9.8	.8
Protein intake (% of total energy)	15-20%	17.1 ± 1.8	15.7 ± 2	.37
Carbohydrate intake (% of total energy)	50%-60%	51.1 ± 3.5	52.3 ± 4.8	.7
Sucrose	Up to 10%	9.3 ± 2.8	8.1 ± 2.1	.13
Fat intake (% of total energy)	Less than 30%	31.8 ± 3	32 ± 4	.77
Saturated fats (%)	Less than 10%	11.7 ± 2.2	11.7 ± 2.3	.95
Polyunsaturated fats (%)	Less than 10%*	5.7 ± 1.1	5.9 ± 1	.57
Monounsaturated fats (%)	Less than 10%*	11.7 ± 1.2	11.5 ± 1.7	.84

CDA, Canadian Diabetes Association; ADA, American Diabetes Association.

*Refers to ADA-specific recommendations.

both groups in the postprandial state. However, the change in EF could not be explained by the concomitant increase in TG levels or change in glucose levels. These data suggest that additional factors inherent to the diabetic state may impact vascular function. These may include markers of oxidative stress and advanced glycation end products, all of which have been shown to be impaired in childhood.^{26,27}

We used PAT to assess EF, which focuses on small resistance vessels to evaluate endothelium-dependent flow-mediated dilation. This dynamic testing method allows for the evaluation of endothelial cell response to mechanical stress (reactive hyperemia) to test for the presence of endothelial dysfunction as a systemic disorder. In adults, PAT-RH has been shown to correlate closely with other measures of endothelial-dependent dilation (brachial artery ultrasound scanning), as well as direct measures of coronary arterial function.^{20,21} Our experience shows that PAT is a promising noninvasive technique to evaluate EF that was well tolerated in this pediatric cohort. The limitations of PAT, and other surrogate measures of EF in children, are the absence of strong correlation of these measures with invasive measures of EF in children, as well as their ability to predict future cardiovascular risk or events that may occur during adulthood.

Although the number of patients in this study was limited, it is unlikely that the procedure of repeat testing was responsible for a decrease in PAT-RH score because we observed a similar trend in lower PAT-RH scores in 6 patients for whom premeal and postmeal PAT testing was completed on separate days. In addition, the nitric oxide-cyclic GMP cascade, which mediates endothelium-dependent vasodilation, would be replenished in the time interval between tests.²⁸

Interestingly, adolescents with T1D had a near-identical dietary pattern as their peers without diabetes, with a higher than recommended intake of total and saturated fats in both groups. These results are similar to those of a larger series of patients with T1D, which observed that only 11.8% and 5% of 10- to 14-year-olds met dietary recommendations for percentage of total and saturated fat, respectively.²⁹ It is notable that the 23 subjects with T1D had a total of 35 visits with a Dietician as part of their clinic visits in the preceding year. These data emphasize the significant influence of peer interactions on eating behavior during adolescence and suggest that effective nutritional counseling should include strategies to balance peer pressure with healthy eating.³⁰

Larger studies of adolescent T1D clinics have shown that 15% and 10% of patients have elevated LDL-C (>130 mg/dL) and TG levels (>150 mg/dL), respectively.³¹ Assessment of cardiovascular risk factors in more than 27,000 young patients with T1D has shown that 17% of patients have 2 or more risk factors present, including measures of metabolic control, BP, BMI, smoking, and lipid levels.³² We did not observe abnormal lipid levels in our patients with T1D in this study. Our patients had a mean HbA1c of 8.3% ± 1.5%, which is above the 7% recommended glycemic target for adolescents but lower than HbA1c of adolescents in the intensive therapy arm of the DCCT.³³ Apart from improving glycemic control and advocating smoking avoidance, these patients would not be targeted for cardiovascular risk reduction, despite eating a typical teen diet and having impaired EF present in both the fasting and postprandial state.

Atherosclerosis is increasingly recognized as a postprandial phenomenon with nonfasting, triglyceride-rich lipoproteins preferentially promoting atherogenesis.^{34,35} Our find-

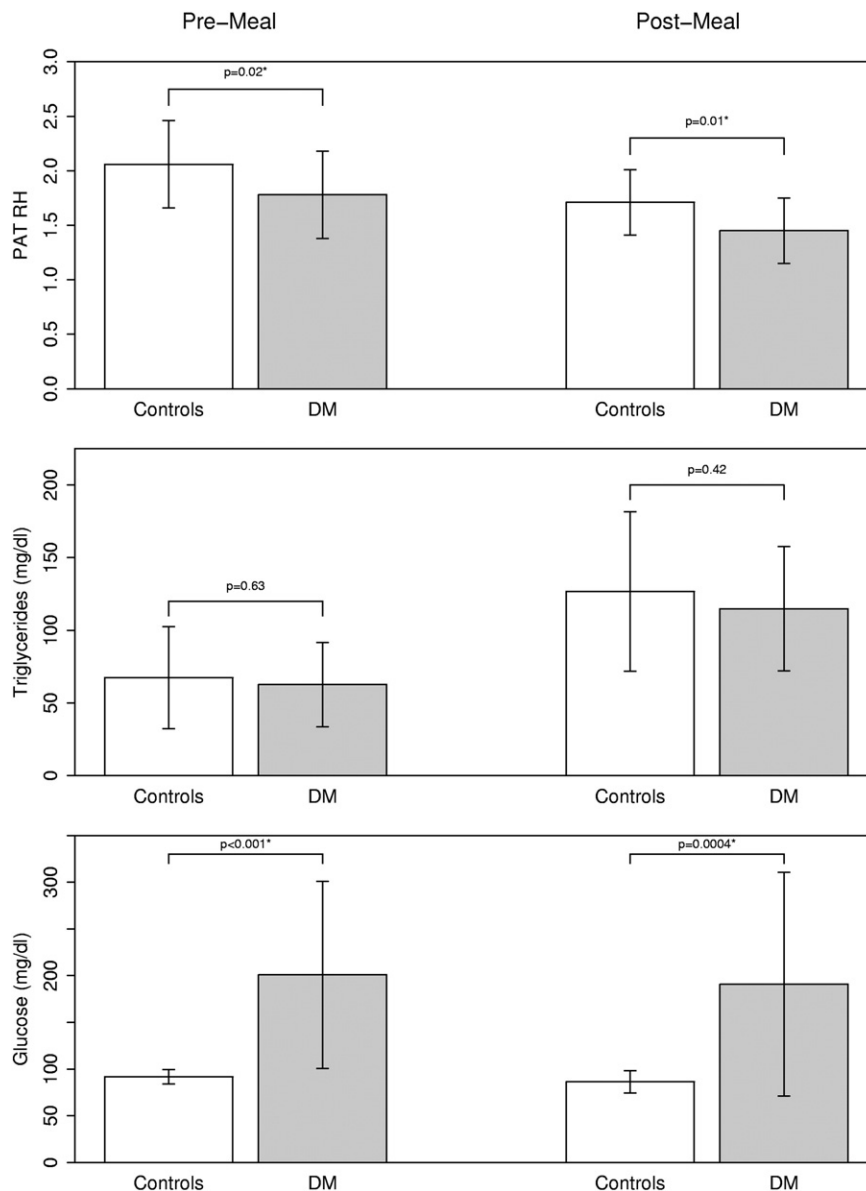


Figure. Premeal and postmeal results (after 3.5 hours) of PAT-RH, triglycerides, and glucose measurements in control (*white*) and T1D (*light gray*) adolescent subjects. Results are presented as mean \pm SD. Pre- and post-PAT levels were significantly different among patients with diabetes ($P < .0001$) and control subjects ($P = .0004$).

ings indicate that adolescents with T1D are at even greater atherosclerotic risk related to postprandial lipemia.^{36,37}

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