Impaired Endothelial Function in Preadolescent Children With Type 1 Diabetes

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OBJECTIVE—We evaluated the prevalence of endothelial dysfunction as measured by flow-mediated dilatation (FMD) of the brachial artery and carotid intima-media thickness (c-IMT) in relationship to vascular inflammatory biomarkers in preadolescent children with type 1 diabetes.

RESEARCH DESIGN AND METHODS—We studied 21 type 1 diabetic children (aged 8.3 ± 0.3 years with diabetes duration of 4.3 ± 0.4 years) and 15 group-matched healthy siblings (aged 7.6 ± 0.3 years). Fasting plasma glucose (FPG), lipid profile, HbA_{1c}, high-sensitivity C-reactive protein (hs-CRP), fibrinogen, homocysteine, and erythrocyte (red blood cell [RBC]) folate were evaluated in all subjects. Each subject underwent c-IMT and brachial artery FMD percentage (FMD%) measurements using high-resolution vascular ultrasound.

RESULTS—Type 1 diabetic children had higher FPG (173.4 ± 7.9 mg/dL vs. 81.40 ± 1.7 mg/dL; $P < 0.0001$), HbA_{1c} (8.0 ± 0.2% vs. 5.0 ± 0.1%; $P < 0.0001$), and hs-CRP (1.8 ± 0.3 vs. 0.70 ± 0.2; $P = 0.017$) than control children without significant differences in BMI, homocysteine, and fibrinogen levels; RBC folate content; and c-IMT between the groups. Children with type 1 diabetes had lower FMD% than control children (7.1 ± 0.8% vs. 9.8 ± 1.1%; $P = 0.04$), whereas c-IMT did not differ between groups.

CONCLUSIONS—Preadolescent children with type 1 diabetes and mean diabetes duration of 4 years displayed evidence of low-intensity vascular inflammation and attenuated FMD measurements. These data suggest that endothelial dysfunction and systemic inflammation, known harbingers of future cardiovascular risk, are present even in preadolescent children.

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Patients with type 1 diabetes have two to four times the risk of developing cardiovascular disease relative to the nondiabetic population (1). Type 1 diabetes causes endothelial dysfunction and early atherosclerosis (2). Endothelial dysfunction and alterations in vascular structure are early indicators of future cardiovascular events (3). Berenson et al. (4) observed that atherosclerotic changes begin much earlier than the appearance of clinical disease, as shown by young-adult autopsy findings. Their work prompted multiple small studies (5–9) that have consistently demonstrated abnormal vascular homeostasis and inflammation in children with type 1 diabetes. These studies have consistently demonstrated that children and adolescents with type 1 diabetes have endothelial dysfunction relative to nondiabetic age-matched control children, as measured by flow-mediated dilation (FMD) in the brachial artery (5,7,8).

In addition, adverse carotid remodeling, known to portend future cardiovascular risk, also has been consistently reported in this population (10–13). However, these studies have not rigorously assessed pubertal status, and it remains unknown whether the adverse effects of type 1 diabetes on vascular homeostasis are apparent even during the preadolescent stage. We hypothesized that prepubertal children with type 1 diabetes would also manifest early signs of abnormal vascular homeostasis, including impaired endothelial function, increased carotid intima-media thickness (c-IMT), and elevated circulating markers of inflammation. We evaluated our hypothesis in a cross-sectional study of type 1 diabetes and healthy matched sibling control subjects.

RESEARCH DESIGN AND METHODS

—Twenty-one prepubertal children with type 1 diabetes, aged 8.5 ± 0.3 years (diabetes duration of 4.3 ± 0.3 years), were recruited from the Children's Hospital of Wisconsin Diabetes Clinic, which is affiliated with the Medical College of Wisconsin. Children with type 1 diabetes were either on multiple daily insulin, consisting of bedtime insulin glargine and premeal aspart insulin, or continuous subcutaneous insulin infusion (CSII) with insulin aspart. We reviewed 2-week, seven-point, self-monitored blood glucose logs to determine mean blood glucose and SDs as well as rates of moderate (blood glucose $<60\ mg \cdot dL^{-1} \cdot week^{-1}$) or severe hypoglycemia (blood glucose $<50\ mg \cdot dL^{-1} \cdot week^{-1}$ with altered mental status). In addition, 15 group-matched healthy siblings of the diabetic cohort were recruited as control subjects. Inclusion criteria consisted of prepubertal children aged 6–9 years. Exclusion criteria included known dyslipidemia, hypertension, microvascular complications, anemia (hemoglobin <11.0 g/dL), congenital heart disease, allergy to ultrasound gel, or family history of hypercholesterolemia or premature cardiovascular disease. The study protocol was approved by the Children's Hospital of Wisconsin Institutional Review

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Board. Informed consent and assent was obtained from the study parents or guardians and the subjects.

Laboratory studies

Peripheral venous blood samples were obtained to determine the complete blood-count plasma glucose, HbA_{1c}, lipids, high-sensitive C-reactive protein (hs-CRP), fibrinogen, chemistry panel, homocysteine, and erythrocyte folate (red blood cell [RBC] folate) between 0800 h and 1000 h after an overnight 12-h fast. The study procedures were rescheduled if the patients had a self-monitored blood glucose ≥200 mg/dL or <80 mg/dL on the morning of the study day. Each subject had breakfast after the completion of all studies. Children with type 1 diabetes received their bolus insulin aspart doses according to their home regimen.

Complete blood-count testing was done on the Abbott automated Cell-Dyn instrument (probably the 4000 model). Fasting plasma glucose (FPG) concentrations were measured with a Glucose Analyzer II (Beckman Instruments, Brea, CA), using a glucose oxidase procedure. Replicate readings were repeated to within 3 mg/dL in triplicates. Fasting plasma triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol levels were determined by spectrophotometry using kits from Stanbio Laboratory (San Antonio, TX), Roche-Boehringer (Indianapolis, IN), Roche-Boehringer (after phosphotungstic acid/MgCl 2 precipitation), and Trinity Biotech (Berkeley Heights, NJ), respectively. All determinations were performed in triplicates. Quality controls were performed to assure stability and reliability of the assays. The intra-assay and interassay coefficients of variation (CVs) for the lipid analyses were 4.7 and 5.3% for triglycerides, 5.5 and 6.7% for cholesterol, 5.7 and 6.1% for HDL cholesterol, and 6.9 and 7.5% for LDL cholesterol, respectively.

hs-CRP was determined using a solid-phase enzyme-linked immunosorbent assay from MP Biomedicals (West Chester, PA), with a sensitivity of 0.1 mg/L and an intraassay CV ranging from 4.1 to 2.3% with increasing concentrations. Plasma fibrinogen was determined by the Clauss method (Quest Diagnostics, Nichols Institute, San Clemente, CA), with intra-assay and interassay CVs of 2.6 and 4.2%, respectively.

A homocysteine assay was performed by using the Siemens Immulite platform (chemiluminescence) and the Immulite Homocysteine kit (Diagnostic Products, Flanders, NJ). The intra-assay and inter-assay CVs for homocysteine were 2.7 and 3.4%, respectively. HbA_{1c} was determined by the Bayer DCA (Bayer Diagnostic, Tarrytown, NY) 2000 instrument (nondiabetic range of 4.5–5.7%). Erythrocyte folate concentrations were measured by the use of a radioimmunoassay technique (Quest Diagnostics, Nichols Institute) with intra-assay and interassay CVs of 3.9 and 5.6%, respectively. Chemistry profile testing was done on the VITROS 5,1 FS (Ortho Clinical Diagnostics).

FMD

High-resolution ultrasound (GE Pro Logiq 500) was used to assess reactive hyperemia (FMD) in each subject after they had remained in the supine position for 10 min in a stable room temperature (14,15). The methods for determining, analyzing, and reporting the FMD percentage (FMD%) in the brachial artery as a surrogate of endothelial function were performed in our vascular laboratory, as previously described (16).

Carotid artery studies

All studies were performed according to a predetermined, standardized scanning protocol for the far wall of the common carotid artery, as described previously (17). A longitudinal section of the common carotid artery 1 cm proximal to the carotid bulb was imaged, and the image was magnified. The c-IMT for each subject was the average of 10 measurements (five from the right and five from the left common carotid artery) (17). All images were recorded and analyzed with carotid imaging software (Medical Imaging, Iowa City, IA). A single vascular sonographer, blinded to the participant's diagnosis, analyzed all the recorded ultrasound scans.

Statistical analysis

Our primary outcome was an observed difference in FMD%. With 15 type 1 diabetic and 21 control subjects, we had over 90% power to detect a 25% difference in FMD% between groups at $\alpha = 0.05$. Data are expressed in means ± SE, unless stated otherwise. Differences in the means were evaluated with the Student *t* test. Univariate associations between the study variables were estimated by calculating the Spearman rank correlation because some of the data were skewed or nonnormal. All statistical analyses were performed using the SAS 9 statistical analysis system (SAS Institute, Cary, NC). A P value <0.05 was defined as statistically significant.

RESULTS—Table 1 summarizes the demographic, metabolic, and vascular characteristics of the participants. Children with type 1 diabetes had higher FPG, HbA_{1c}, and hs-CRP ($P < 0.05$). Interestingly, the overall plasma HDL cholesterol

Table 1—*Characteristics of preadolescents with type 1 diabetes and healthy control subjects*

Parameters	Type 1 diabetic subjects	Control subjects	*P*
n	21	15	
Age (years)	8.3 ± 0.3	7.6 ± 0.3	0.118
Sex (% female)	57.1	60.0	0.857
BMI *z* score	0.52 ± 0.19	0.31 ± 0.37	0.588
Mean SBP (mmHg)	97.4 ± 1.8	90.4 ± 3.2	0.053
Mean DBP (mmHg)	58.1 ± 1.3	56.7 ± 1.7	0.510
FPG (mg/dL)	173.4 ± 7.9	81.4 ± 1.7	<0.0001*
HbA_{1c} (%)	8.0 ± 0.2	5.0 ± 0.1	<0.0001*
Triglycerides (mg/dL)	61.8 ± 7.3	64.0 ± 8.3	0.844
Cholesterol (mg/dL)	168.6 ± 5.8	160.9 ± 7.2	0.406
LDL cholesterol (mg/dL)	104.9 ± 6.5	103.3 ± 5.6	0.861
HDL cholesterol (mg/dL)	51.4 ± 3.1	44.6 ± 2.2	0.108
Cholesterol–to–HDL cholesterol	3.5 ± 0.2	3.7 ± 0.2	0.0056†
hs-CRP (mg/L)	1.8 ± 0.4	0.70 ± 0.20	0.036‡
Homocysteine (μmol/L)	4.3 ± 0.30	3.9 ± 0.40	0.419
RBC folate (ng/mL)	353.6 ± 13.5	331.1 ± 19.0	0.327
Fibrinogen (mg/dL)	313.0 ± 11.7	301.8 ± 11.9	0.517

Data are means ± SE. *$P < 0.0001$; †$P < 0.01$; ‡$P < 0.05$.

concentration tended to be higher among type 1 diabetic subjects than control subjects, whereas the cholesterol-to-HDL ratio was significantly lower in type 1 diabetic subjects than in control subjects. There were no significant differences in BMI, BMI *z* score, mean systolic (SBP) and diastolic (DBP) blood pressure, triglycerides, total cholesterol, LDL cholesterol, homocysteine, RBC folate, and fibrinogen between type 1 diabetic and control subjects.

Measures of vascular homeostasis in prepubescent children with type 1 diabetes

As shown in Fig. 1*A*, children with type 1 diabetes displayed lower brachial artery FMD% change than control subjects (7.1 ± 0.8% vs. 9.8 ± 1.1%; $P = 0.04$). Although the overall brachial diameter in the type 1 diabetic group was larger than that of the control group (2.4 ± 0.1 mm vs. 2.2 ± 0.1 mm; $P = 0.04$), there was no significant correlation between brachial diameter and FMD% in the study group ($r = 0.054$, $P = 0.841$), which suggests that group differences in baseline diameter did not significantly influence this relationship. There were no statistically significant differences in peak hyperemic flow between the two groups (249 ± 270% vs. 191 ± 157%; $P = 0.84$). In addition, the type 1 diabetic and control groups had similar c-IMT (0.48 ± 0.01 mm vs. 0.48 ± 0.02 mm; $P = 0.976$) (Fig. 1*B*).

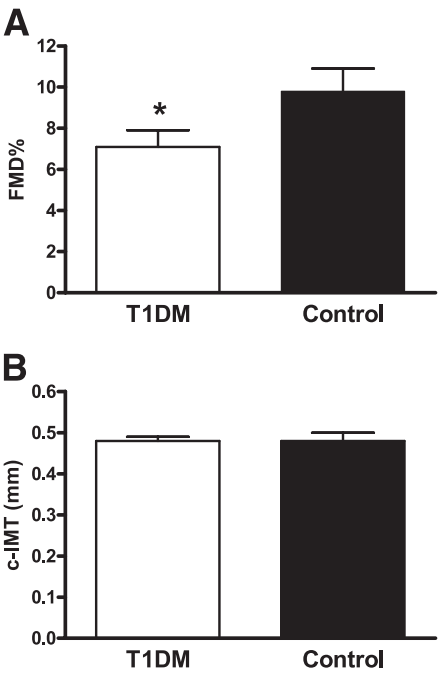

Figure 1—*Evaluation of endothelial function in type 1 diabetic (T1DM) and control subjects.* A*: Change in FMD%,* *P = *0.04.* B*: c-IMT in type 1 diabetic and control subjects,* P = *0.98.*

Table 2 summarizes the clinical and vascular characteristics of preadolescents with type 1 diabetes stratified according to glycemic control. Children with suboptimal glycemic control had higher 2-week mean blood glucose and SDs, HbA_{1c}, and FMD% compared with those with optimal glycemic control ($P < 0.05$). There were no significant differences in duration of diabetes, insulin requirement, insulin regimen, FPG, rate of moderate hypoglycemia, BMI *z* score, mean SBP and DBP, lipid profile, hs-CRP, homocysteine, RBC folate, fibrinogen, and c-IMT between subgroups. Also, there were no sex (male vs. female) differences with regard to glycemic control (8.1 ± 0.3% vs. 7.9 ± 0.3%; $P = 0.649$) control and FMD% (8.0 ± 0.9% vs. 6.4 ± 1.21%; $P = 0.359$) and glucose variability and hypoglycemia rates (data not shown).

Relationships between measures of vascular homeostasis and systemic inflammation

Table 3 summarizes the Spearman correlation between FMD% and other clinical and biochemical parameters among type 1 diabetic children. We noted positive correlations between FMD% and HbA_{1c} ($r = 0.47$, $P = 0.033$) and FMD% and 2-week blood glucose SD ($r = 0.50$, $P = 0.021$), adjusted for diabetes duration. However, there was no correlation between FMD% and HbA_{1c} and 2-week blood glucose SD among control subjects (data not shown). There were no significant correlations between FMD% and BMI *z* score, diabetes duration, FPG, plasma lipids, hs-CRP, homocysteine, RBC folate, fibrinogen, mean c-IMT, mean SBP and DBP, and baseline brachial artery diameter.

Table 4 summarizes the Spearman rank correlations between c-IMT and clinical and biochemical parameters among type 1 diabetic children. There

Table 2—*Characteristics of preadolescents with type 1 diabetes according to glycemic control*

Parameters	Optimal (HbA_{1c} <8.0%)	Suboptimal (HbA_{1c} ≥8.0%)	*P*
n	11	10	
Age (years)	8.5 ± 0.3	8.1 ± 0.4	0.438
Sex (% female)	72.7	40.0	0.287
Diabetes duration	4.8 ± 0.6	3.8 ± 0.4	0.190
Insulin regimen (% CSII)	63.6	30	0.72
Insulin dose (units · kg^{-1} · day^{-1})	0.77 ± 0.17	0.88 ± 0.19	0.670
BMI (kg/m^2)	17.5 ± 0.5	17.6 ± 1.2	0.937
BMI *z* score	0.56 ± 0.22	0.47 ± 0.32	0.816
Mean SBP (mmHg)	100.3 ± 1.7	95.6 ± 3.2	0.198
Mean DBP (mmHg)	57.4 ± 1.9	59.9 ± 1.5	0.321
FPG (mg/dL)	169.9 ± 11.3	176.3 ± 12.7	0.709
2-week MBG (mg/dL)	174.8 ± 8.1	231.7 ± 12.8	0.001*
2-week blood glucose SD (mg/dL)	43.1 ± 3.6	66.6 ± 8.1	0.013†
Hypoglycemia rate/week (blood glucose <60 mg/dL)	1.7 ± 0.3	1.8 ± 0.3	0.817
HbA_{1c} (%)	7.4 ± 0.1	8.7 ± 0.3	0.0004‡
Triglycerides (mg/dL)	58.0 ± 5.6	66.2 ± 14.7	0.595
Cholesterol (mg/dL)	163.6 ± 6.8	176.1 ± 9.4	0.288
LDL cholesterol (mg/dL)	103.0 ± 7.9	112.4 ± 9.6	0.455
HDL cholesterol (mg/dL)	49.2 ± 2.9	50.4 ± 4.9	0.831
Cholesterol–to–HDL cholesterol	3.5 ± 0.3	3.8 ± 0.4	0.551
hs-CRP (mg/L)	2.5 ± 0.7	1.3 ± 0.40	0.163
Homocysteine (μmol/L)	4.4 ± 0.30	4.2 ± 0.40	0.690
RBC folate (ng/mL)	349.5 ± 11.8	353.3 ± 22.3	0.878
Fibrinogen (mg/dL)	333.1 ± 18.4	294.9 ± 10.9	0.097
FMD%	5.5 ± 0.9	9.1 ± 1.1	0.019†
c-IMT (mm)	0.48 ± 0.02	0.46 ± 0.02	0.497

Data are means ± SE. MBG, mean blood glucose. *$P < 0.01$; †$P < 0.02$; ‡$P < 0.001$.

Table 3—*Correlation between FMD% and subject characteristics*

	Spearman correlation	
FMD%	Correlation	*P*
Age at study	0.165	0.473
BMI *z* score	−0.131	0.571
Diabetes duration	0.022	0.924
FPG	0.271	0.233
2-week BGSD	0.50	0.021*
HbA_{1c}	0.470	0.033†
Triglycerides	−0.287	0.205
Cholesterol	−0.07	0.754
LDL cholesterol	−0.177	0.441
HDL cholesterol	0.351	0.119
Cholesterol–to–HDL cholesterol	−0.349	0.121
hs-CRP	−0.421	0.092
Homocysteine	−0.497	0.070
RBC folate	−0.044	0.871
Fibrinogen	−0.129	0.597
Mean c-IMT	0.159	0.491
Mean SBP	−0.084	0.738
Mean DBP	−0.148	0.558
Baseline brachial artery diameter	0.054	0.814

BGSD, blood glucose SD. *P = 0.021; †P = 0.033.

Table 4—*Correlation between c-IMT and subject characteristics*

	Spearman correlation	
Mean c-IMT	Correlation	*P*
Age at study	−0.138	0.549
BMI *z* score	−0.050	0.827
Diabetes duration	−0.160	0.487
FPG	0.162	0.473
2-week BGSD	0.111	0.631
HbA_{1c}	−0.138	0.549
Triglycerides	0.009	0.966
Cholesterol	−0.166	0.473
LDL cholesterol	−0.259	0.255
HDL cholesterol	−0.183	0.425
Cholesterol–to–HDL cholesterol	0.017	0.993
hs-CRP	−0.272	0.289
Homocysteine	−0.112	0.702
RBC folate	−0.117	0.664
Fibrinogen	−0.343	0.151
FMD%	0.159	0.490
Mean SBP	−0.133	0.596
Mean DBP	−0.271	0.277

BGSD, blood glucose SD.

were no significant correlations between c-IMT and BMI *z* score, diabetes duration, FPG, HbA_{1c}, plasma lipids, hs-CRP, homocysteine, RBC folate, fibrinogen, FMD%, and mean SBP and DBP.

CONCLUSIONS—We observed significant increased levels of systemic vascular inflammation and impaired endothelial function, as measured by FMD, in type 1 diabetic preadolescent children compared with age-matched control siblings. However, there were no differences in c-IMT between the two groups. These data suggest that adverse changes in vascular homeostasis observed in preadolescent children with type 1 diabetes are evident during the earliest stages of their life, heralding future cardiovascular risk in this population.

Previous published data (5,7,8) clearly demonstrate that vascular homeostasis is disrupted in type 1 diabetes. Singh et al. (5) observed that FMD% was significantly impaired in a group of adolescents with a mean age of 15 years. Also, other studies (7,8) have demonstrated impaired endothelial function in children and adolescents with type 1 diabetes compared with age-matched healthy control subjects. We also found that circulating levels of hs-CRP were higher in preadolescents with type 1 diabetes relative to control subjects. These findings are consistent with previous work (11,18) that demonstrated increased systemic inflammation in adolescents with type 1 diabetes. Taken together, our data extend previous findings in type 1 diabetes adolescents to preadolescents and suggest that conditions for the early clinical manifestation of atherosclerosis are evident among very young children with type 1 diabetes.

Several studies (5,10–13) in children and adolescents with type 1 diabetes have consistently reported increased c-IMT compared with healthy control subjects. However, we did not observe any significant difference in c-IMT in preadolescent children with type 1 diabetes compared with control subjects. The average ages, duration of diabetes, and HbA_{1c} values in these studies were 11.8–15.0 years, 3.8–6.8 years, and 7.5–8.6%, respectively. These studies enrolled older populations with either a longer duration of type 1 diabetes and/or poorer glycemic control compared with our study cohort (5,12). The absence of a c-IMT difference between type 1 diabetic and control subjects in our study may be secondary to the significantly younger age and prepubertal status of our study population as well as differences in the time of exposure to type 1 diabetes and chronic glycemic control (19).

Interestingly, our data show a trend toward increased HDL cholesterol levels and significantly reduced cholesterol–to–HDL cholesterol ratios in preadolescent children with type 1 diabetes. These data are in line with two prior reports (8,10) in older children with type 1 diabetes. Although higher plasma HDL cholesterol levels are widely thought to be atheroprotective, in the setting of type 1 diabetes, HDL cholesterol may be dysfunctional in combating the adverse, proinflammatory, and proatherogenic effects of oxidized LDL cholesterol (20). The presence of dysfunctional HDL cholesterol would make type 1 diabetic subjects more vulnerable to oxidative vascular damage despite higher absolute levels. Additional work is necessary to elucidate whether this mechanism is at work in the development of endothelial dysfunction in children with type 1 diabetes.

In addition, we observed positive correlations between FMD% and HbA_{1c} and FMD% and glucose variability, as measured by blood glucose SD. One previous (9) study has reported a positive correlation between HbA_{1c} and reactive hyperemia. Although mechanistic links between glucose variability and glycemic control and endothelial function related to changes in oxidative stress levels have been suggested in diabetic subjects (21,22), we were not able to identify a correlation between either HbA_{1c} or glucose variability and FMD% when looking at diabetic and nondiabetic children separately. Therefore, the observed correlations between FMD% and glycemic control and variability may not represent a true physiological relationship. Mechanistic studies evaluating the relationship between short- and long-term glycemic control and endothelial function in children with type 1 diabetes are needed to better elucidate the biological plausibility of these findings.

Our study has several limitations. First, the small sample size of the cohort may have underpowered the study to detect alterations in some of the vascular biomarkers. Additional studies to corroborate our findings and extend them to other vascular biomarkers are necessary. In addition, we did not administer nitroglycerin to our preadolescents for assessment of smooth-muscle reactivity. Although differences in smooth-muscle reactivity between groups cannot be completely excluded, FMD% is a well-established measure of

endothelium-dependent vasodilatation (23). Balanced against these limitations, we report our novel findings of adverse vascular effects of type 1 diabetes in preadolescents.

In conclusion, our data suggest that vascular endothelial dysfunction and systemic inflammation are present in preadolescents with type 1 diabetes. Long-term prospective studies are needed to evaluate the progression of vascular changes in relation to duration of diabetes, glycemic control, and progression through the stages of puberty.

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G.S.B. researched data and wrote the manuscript. H.Z. wrote and reviewed the manuscript. M.E.W. researched data, oversaw the sonographic data acquisition, and edited the manuscript. E.D. researched data and performed sonographic vascular studies. R.G.H. helped design and perform the biostatistical analyses and contributed to the manuscript. M.D. researched data and performed biostatistical analyses. R.A. researched data and wrote and edited the manuscript.

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