Serum Monocyte Chemoattractant Protein-1 Concentrations Associate With Diabetes Status but Not Arterial Stiffness in Children With Type 1 Diabetes

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OBJECTIVE — The relationship between circulating markers of inflammation and arterial stiffness in children with type 1 diabetes is not well studied. We tested whether inflammatory monocyte chemoattractant protein (MCP)-1 concentrations correlate with arterial stiffness or type 1 diabetes status.

RESEARCH DESIGN AND METHODS — MCP-1 concentrations and radial tonometry data were available for 98 children with type 1 diabetes and 55 healthy control subjects. Arterial stiffness was calculated as augmentation index corrected for a heart rate of 75 (AI75). Correlation between MCP-1 and AI75 and differences in MCP-1 concentrations between case and control subjects were tested.

RESULTS — MCP-1 was significantly higher in children with type 1 diabetes than in control subjects ($P < 0.001$). However, there were no correlations between MCP-1 and AI75 in the overall sample or upon stratification by type 1 diabetes status (range $P = 0.28–0.66$).

CONCLUSIONS — Circulating MCP-1 was not associated with arterial stiffness but was significantly elevated in children with type 1 diabetes, indicating a proinflammatory state in children as young as 10 years. The clinical significance of MCP-1 elevation in type 1 diabetes needs further investigation.

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Type 1 diabetes is associated with endothelial inflammation and arterial stiffness. We previously demonstrated that arterial stiffness is apparent in type 1 diabetic children as young as 10 years when compared with matched control subjects (1) but noted poor correlation with both traditional cardiovascular disease (CVD) risk factors (A1C, LDL cholesterol, and family history) and novel serum CVD risk factors (interleukin-6, tumor necrosis factor, C-reactive protein, superoxide dismutase, and nitric oxide) (1,2). Notably, a genetic association with arterial stiffness was seen (3). We postulated that the lack of correlation between arterial stiffness and previously studied risk factors was likely representative of the low short-term absolute risk for macrovascular events in our young type 1 diabetic cohort. Given that the majority of CVD events in type 1 diabetic patients are clustered among those with concurrent diabetic nephropathy, we sought to determine if monocyte chemoattractant protein (MCP)-1, a serum marker with known correlation to CVD events and diabetic nephropathy, would correlate with arterial stiffness in children with type 1 diabetes (4). As MCP-1 is stimulated by chronic hyperglycemia and is responsible for induction of superoxide anion, cytokine production, and adhesion molecule expression (5), exploration of potential correlation with global vascular dysfunction in children with type 1 diabetes was warranted.

In this analysis, we sought to determine whether MCP-1 concentrations correlate with arterial stiffness as measured by radial artery tonometry and to validate previous associations between circulating MCP-1 concentrations and type 1 diabetes status in a case-control analysis.

RESEARCH DESIGN AND METHODS

— The study population and method for arterial stiffness measurement have been previously described (1). Briefly, children with type 1 diabetes of at least 1-year duration were recruited from the Florida Diabetes Camp. Control children were recruited from general pediatrics practices in Gainesville, Florida. Eligible children had no CVD and no history of antihypertensive or lipid-lowering medication use. Blood was collected, and augmentation index corrected for a heart rate of 75 (AI75) was measured by radial tonometry in children who fasted for at least 8 h as previously described (1). Serum lipids and cytokines, blood A1C, and plasma glucose were analyzed as previously reported (1). Serum MCP-1 concentrations were quantified by cytometric fluorescence detection (R&D Systems, Minneapolis, MN) and natural log (ln)-transformed before analyses. The study was approved by the institutional review board of the University of Florida, and children were enrolled after written consent and assent.

RESULTS

— AI75 measurements and MCP-1 concentrations were available for 98 children with type 1 diabetes and 55 healthy control subjects (Table 1). Both groups were well matched for age, heart rate, and total and LDL cholesterol. Control subjects had significantly higher BMI and triglycerides and lower HDL cholesterol. LnMCP-1 correlated with triglycerides in type 1 diabetic subjects ($r = 0.2$; $P = 0.04$) but showed no correlation with

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Table 1—*Comparisons of type 1 diabetic and control subjects and correlations with lnMCP-1*

	Type 1 diabetic subjects	Control subjects	Comparison of type 1 diabetic and control subjects	LnMCP-1 correlation in type 1 diabetic subjects	LnMCP-1 correlation in control subjects
n	98	55			
MCP-1 (pg/ml)	337.9 ± 122.1	234.9 ± 106.8	<0.001	—	—
LnMCP-1 (pg/ml)	5.75 ± 0.39	5.36 ± 0.45	<0.001	—	—
Age (years)	12.9 ± 1.4	13.6 ± 2.3	0.084	−0.02 (0.84)	−0.06 (0.64)
BMI (kg/m^2)	22.0 ± 3.5	24.0 ± 5.4	0.003	0.11 (0.29)	0.10 (0.46)
A1C (%)	8.5 ± 1.2	5.27 ± 0.3	<0.001	−0.05 (0.60)	−0.004 (0.097)
Heart rate (bpm)	78.6 ± 11.8	76.5 ± 11.7	0.22	−0.03 (0.77)	0.05 (0.70)
Fasting glucose (mg/dl)	161.8 ± 70.4	85.1 ± 8.8	<0.001	0.06 (0.52)	0.10 (0.46)
Total cholesterol (mg/dl)	159.4 ± 32.3	158.7 ± 28.2	0.87	0.11 (0.29)	0.17 (0.22)
LDL cholesterol (mg/dl)	88.1 ± 26.6	88.4 ± 24.5	0.98	0.10 (0.36)	0.15 (0.28)
HDL cholesterol (mg/dl)	57.3 ± 11.3	51.6 ± 11.9	0.003	−0.17 (0.1)	−0.09 (0.51)
Triglycerides (mg/dl)	68.5 ± 61.2	94.9 ± 59.3	0.008	0.20 (0.04)	0.18 (0.55)

Data are means ± SD, *P*, and r_s (*P*).

age, heart rate, BMI, glucose, A1C, or other lipid parameters in control or type 1 diabetic subjects.

Overall in the study population (N = 153), there was no correlation between lnMCP-1 concentrations and AI75 (r = 0.04; P = 0.66). Furthermore, there were no significant correlations between lnMCP-1 concentrations and AI75 when children were stratified by type 1 diabetes status: type 1 diabetes r = −0.11, P = 0.28; children without type 1 diabetes r = −0.12, P = 0.38. AI75 did not differ across tertiles of lnMCP-1 in both children with and without type 1 diabetes. Among those with type 1 diabetes, AI75 values across lnMCP-1 tertiles were 6.38 ± 9.47, 1.89 ± 10.19, and 4.59 ± 12.45 (P = 0.20; P for trend = 0.32). Among children without type 1 diabetes, AI75 values across lnMCP-1 tertiles were 0.14 ± 5.91, −4.42 ± 10.72, and −5.03 ± 11.92 (P = 0.26; P for trend = 0.14).

Despite the lack of association between lnMCP-1 and AI75, lnMCP-1 concentrations differed between children with and without type 1 diabetes. LnMCP-1 concentrations were 5.75 ± 0.39 pg/ml and 5.36 ± 0.45 pg/ml in children with and without type 1 diabetes, respectively (P < 0.001).

CONCLUSIONS — Most studies of chemokines in adults with type 1 diabetes have concentrated on their correlation with microvascular disease (6–8). However, studies of chemokines in children with type 1 diabetes have largely been performed to examine the potential of chemokines to predict or explain developing or ongoing autoimmunity (9). Elevated MCP-1 concentrations have been previously documented in children with newly diagnosed type 1 diabetes when compared with children at increased risk of developing diabetes and control subjects (10).

In this study, we confirmed that serum MCP-1 concentrations are elevated in children with type 1 diabetes in comparison with matched control subjects. Nevertheless, MCP-1 levels failed to correlate with noninvasive measures of arterial stiffness, regardless of whether comparisons were made among type 1 diabetic subjects, control subjects, or the entire study population. Interestingly, MCP-1 levels in our type 1 diabetic population correlated with triglyceride levels. The observed correlation between serum MCP-1 and triglycerides in type 1 diabetic subjects provides support for the concept of MCP-1 as a marker or a potential mediator of CVD in the type 1 diabetic population. As we failed to reject the null hypothesis, additional analyses were not performed in order to avoid statistical bias for this focused study. A larger study designed to control for additional confounders (such as sleep apnea) and powered to evaluate the role of lipids, additional chemokines, acute glycemic changes, albuminuria, age, sex, pubertal status, duration of diabetes, and longitudinal A1C values would likely yield additional informative data on the role of MCP-1 in type 1 diabetes.

Given the strong associations between MCP-1 and CVD in large adult population studies, elevated MCP-1 levels likely reflect some component of overall lifetime macrovascular risk in type 1 diabetic patients (11). The low absolute risk of near-term CVD in children with high long-term risk may account for the lack of correlation between MCP-1 and arterial stiffness in this relatively young cohort. Because systemic cytokine concentrations may be influenced by multiple factors not solely related to arterial stiffness per se, such as acute stress, time of day, and metabolic status, serum MCP-1 concentrations at a single time point may imprecisely correlate with the specific arterial stiffness phenotype. Rather, MCP-1 concentrations could more plausibly provide a global index of inflammatory burden of disease, as was seen in the significant difference in MCP-1 by diabetes status in our analysis.

In summary, serum MCP-1 levels are higher in children with type 1 diabetes than in control subjects and correlate with triglycerides but not with arterial stiffness. Future efforts will be directed to explore the potential relationship between triglycerides and MCP-1 as we attempt to identify sensitive and specific serum markers predictive of long-term CVD risk in children with type 1 diabetes.

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No other potential conflicts of interest relevant to this article were reported.

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