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.

Type 1 diabetes is associated with endothelial inflammation and arterial stiffess. 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...
Arterial stiffness and MCP-1 in type 1 diabetes

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/m²)             | 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 (0.35)                           |

Data are means ± SD, P, and r (P).
References

1. Haller MJ, Samyn M, Nichols WW, Brusko T, Wasserfall C, Schwartz RF, Atkinson M, Shuster JJ, Pierce GL, Silverstein JH. Radial artery tonometry demonstrates arterial stiffness in children with type 1 diabetes. *Diabetes Care* 27: 2911–2917, 2004

2. Haller MJ, Pierce GL, Braith RW, Silverstein JH. Serum superoxide dismutase activity and nitric oxide do not correlate with arterial stiffness in children with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 19:267–269, 2006

3. Zineh I, Beitelshees AL, Haller MJ. NOS3 polymorphisms are associated with arterial stiffness in children with type 1 diabetes. *Diabetes Care* 30:689–693, 2007

4. Tesch GH. MCP-1/CCL2: a new diagnostic marker and therapeutic target for progressive renal injury in diabetic nephropathy. *Am J Physiol Renal Physiol* 294: F697–F701, 2008

5. Conti P, Pang X, Boucher W, Letourneau R, Reale M, Barbacane RC, Thibault J, Theoharides TC. Impact of Rantes and MCP-1 chemokines on in vivo basophilic cell recruitment in rat skin injection model and their role in modifying the protein and mRNA levels for histidine decarboxylase. *Blood* 89:4120–4127, 1997

6. Chiarelli F, Cipollone F, Mohn A, Marini M, Iezzi A, Fazia M, Tumini S, De Cesare D, Pomilio M, Pierdomenico SD, Di Gioacchino M, Cucurullo F, Mezzetti A. Circulating monocyte chemoattractant protein-1 and early development of nephropathy in type 1 diabetes. *Diabetes Care* 25:1829–1834, 2002

7. Yang B, Houlberg K, Millward A, Demaine A. Polymorphisms of chemokine and chemokine receptor genes in type 1 diabetes mellitus and its complications. *Cytokine* 26:114–121, 2004

8. Kiyici S, Erturk E, Budak F, Ersoy C, Tunçel E, Duran C, Oral B, Sigirci D, Imamoglu S. Serum monocyte chemoattractant protein-1 and monocyte adhesion molecules in type 1 diabetic patients with nephropathy. *Arch Med Res* 37:998–1003, 2006

9. Lohmann T, Laue S, Nietzschmann U, Kapellen TM, Lehmann I, Schroeder S, Paschke R, Kiess W. Reduced expression of Th1-associated chemokine receptors on peripheral blood lymphocytes at diagnosis of type 1 diabetes. *Diabetes* 51:2474–2480, 2002

10. Stechova K, Bohmova K, Vrabelova Z, Sepa A, Stadlerova G, Zacharovova K, Faresjo M. High T-helper-1 cytokines but low T-helper-3 cytokines, inflammatory cytokines and chemokines in children with high risk of developing type 1 diabetes. *Diabetes Metab Res Rev* 23:462–471, 2007

11. McDermott DH, Yang Q, Kathiresan S, Cupples LA, Massaro JM, Keane JF Jr, Larson MG, Vasan RS, Hirschhorn JN, O’Donnell CJ, Murphy PM, Benjamin EJ. CCL2 polymorphisms are associated with serum monocyte chemoattractant protein-1 levels and myocardial infarction in the Framingham Heart Study. *Circulation* 112:1113–1120, 2005