Inflammatory Markers Are Increased in Youth with Type 1 Diabetes: The SEARCH Case-Control Study

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Context: Increased inflammation may contribute to type 1 diabetes (T1D) complications.

Objective: The objective of the study was to investigate the association of inflammation with obesity, hyperglycemia and dyslipidemia in youth with T1D.

Design: This was a cross-sectional study of youth with and without T1D.

Setting: The study was conducted in Colorado and South Carolina.

Patients: SEARCH Case-Control participants with T1D [n = 553, mean age 15 yr (range 10–22), median duration 2.7 yr] and without diabetes [n = 215, mean age 15 yr (range 10–22)].

Intervention: This was an observational study.

Main Outcome Measures: IL-6, high-sensitivity C-reactive protein (hsCRP), fibrinogen, and leptin were measured.

Results: Inflammatory markers were evaluated by diabetes status, quartiles of glycated hemoglobin, and obesity using multiple linear regression analyses, adjusted for age, sex, study site, race/ethnicity, T1D duration, body mass index, and pubertal status. Compared with controls, youth with T1D had higher IL-6 and fibrinogen levels at all levels of glycemia and obesity, and hsCRP levels were significantly higher in youth with T1D in the top three quartiles of glycated hemoglobin (≥7.2%) and among normal-weight subjects. Leptin was lower in youth with poor glycemic control. Higher hsCRP and fibrinogen were correlated with higher total and LDL cholesterol, and apolipoprotein B in youth with T1D, whereas higher fibrinogen was correlated with higher LDL and apolipoprotein B in controls.

Conclusions: T1D is characterized by excess inflammation, independent of adiposity and glycemic control. Even T1D youth in good glycemic control had higher levels of IL-6 and fibrinogen than controls. Elevated inflammatory markers were associated with an atherogenic lipid profile, which may contribute to accelerated atherosclerosis in youth with T1D. **(*J Clin Endocrinol Metab* 95: 2868–2876, 2010)**

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Abbreviations: apo, Apolipoprotein; BMI, body mass index; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

The incidence of type 1 diabetes is increasing at 3–5% per year worldwide (1–3), and this increase cannot be accounted for by known genetic factors. A parallel increase in childhood obesity has occurred, and as a result, it is thought that obesity may be contributing to the increasing incidence of type 1 diabetes (4). Whereas the majority of adolescents with type 1 diabetes are not obese, overweight and obesity have increased in recent years among all youth, including those with type 1 diabetes (5, 6). Inflammation is a condition that is common to both obesity (7) and type 1 diabetes (8), and systemic inflammation is associated with the development of microvascular (9) and macrovascular (10) complications among persons with type 1 diabetes. However, the role of obesity compared with hyperglycemia in the development of inflammation among youth with type 1 diabetes is unclear.

Several acute-phase inflammatory markers have been reported to be increased in type 1 diabetes. IL-6 is a proinflammatory cytokine that is elevated in both type 1 and type 2 diabetes (11), and may be increased by hyperglycemia. High-sensitivity C-reactive protein (hsCRP) is an acute-phase protein that is associated with systemic inflammation and has been shown to be increased in individuals with coronary artery disease. In the Diabetes Incidence in Sweden Study, hsCRP was elevated in newly diagnosed youth and adults (aged 15–34 yr) with type 1 diabetes, and hsCRP levels were positively correlated with c-peptide levels (12). Fibrinogen is an acute phase protein which is related to CRP and is also synthesized in the liver (13). Fibrinogen may be increased in patients with type 1 diabetes (13) and is associated with a prothrombotic state and cardiovascular disease, particularly premature-onset coronary artery disease (14).

Leptin is a metabolic protein produced by adipose tissue, and both leptin levels and leptin receptor levels have been reported to be increased in individuals with type 1 diabetes (15, 16). Leptin regulates food intake via brain signaling of satiety and energy store levels and is paradoxically increased with obesity, with obese individuals appearing to be resistant to the effects of leptin (17). In addition to its role in regulating metabolism, leptin has been recognized more recently as a proinflammatory agent (18), and leptin levels have been shown to regulate inflammatory processes and immune cells (19).

Differences in inflammatory markers between youth with type 1 diabetes and nondiabetic youth and associations between these markers of inflammation and body mass index (BMI) and level of glycated hemoglobin (HbA_{1c}) can shed light on the relative strength of association of obesity *vs.* hyperglycemia with inflammation in type 1 diabetes. This study investigated whether inflammation was associated with type 1 diabetes, independent of adiposity and hyperglycemia, and examined associations between inflammation and obesity, hyperglycemia, and dyslipidemia in youth with type 1 diabetes.

Materials and Methods

Study participants

The study population included 553 individuals with type 1 diabetes (50% male) and 215 nondiabetic individuals (40% male) who were participants in the SEARCH Case-Control (SEARCH-CC) study, an ancillary study to the multicenter SEARCH for Diabetes in Youth study. SEARCH participants who were residents of Colorado or South Carolina, aged 10–22 yr, and African-American, Hispanic, or non-Hispanic white were invited to participate in SEARCH-CC. Cases were identified using networks of health care providers and type 1 diabetes was defined based on provider diagnosis. Nondiabetic control youth, aged 10–22 yr and self-identified as African-American, Hispanic, or non-Hispanic white, were recruited from primary care offices in the same geographic areas. Primary care practices were chosen as the sampling frame for controls to closely represent the underlying population that gave rise to the type 1 diabetes cases. Additional details regarding sampling and recruitment for SEARCH-CC have been published (20, 21). Average glycemic control and lipids were similar in the SEARCH-CC study to those in the overall SEARCH study participants with type 1 diabetes who were 10–22 yr old (22).

All protocols were approved by the respective institutional review boards and written informed consent was obtained from participants aged 18 yr or older, and assent was obtained for participants younger than 18 yr.

Anthropometric measures

Height was measured in centimeters using a stadiometer. Weight was measured in kilograms using an electronic scale. Height and weight were measured and recorded twice. A third measurement was done if the first and second measures differed by more than 0.5 cm for height or more than 0.3 kg for weight. BMI was calculated using measured weight (kilograms) divided by measured height (meters) squared. Percentiles for BMI were determined specific to sex and month of age using algorithms prepared by the U.S. Centers for Disease Control and Prevention based on the 2000 CDC Growth Charts (23). This also allows each individual's deviation from the reference value to be calculated in terms of a normalized SD score (z-score). Weight categories of normal weight, overweight, and obesity were created based on the BMI z-score for youth under 18 yr and BMI for youth 18–22 yr. Youth were considered normal weight if their BMI z-score was under the 85th percentile or BMI was under 25 kg/m^2, overweight if their BMI z-score was 85th to less than 95th percentile or BMI was 25 to less than 30 kg/m^2, and obese if their BMI z-score was 95th percentile or greater or BMI was 30 kg/m^2 or greater. Waist circumference was measured according to the National Health and Nutrition Examination Survey protocol (24).

Pubertal status

Pubertal development was self-assessed using the technique described by Marshall and Tanner (25, 26). Participants were given a standardized series of drawings with explanatory text to

assess their own pubertal development. The Tanner staging was used to evaluate pubertal development and growth using scales ranging from 1 (prepubertal) to 5 (adult stage).

Laboratory methods

Laboratory samples were obtained under conditions of metabolic stability, defined as no episode of diabetic ketoacidosis within 1 month before the visit. Study participants were asked to come into the clinic after an overnight (10 h) fast. Specimens were processed at each site and shipped within 24 h to the Northwest Lipid Metabolism and Diabetes Research Laboratories in Seattle, WA, which serves as the study central laboratory, for analyses. HbA_{1c} was measured using ion-exchange high-performance chromatography. Measurements of total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride were performed enzymatically on a Hitachi 917 autoanalyzer (Roche Molecular Biochemicals Diagnostics, Indianapolis, IN). Low-density lipoprotein (LDL)-cholesterol levels were calculated by the Friedewald equation for individuals with triglyceride levels less than 400 mg/dl (27) and by Lipid Research Clinics Beta Quantification for those with triglyceride levels at least 400 mg/dl. Apolipoprotein (apo) B was measured by a nephelometric system (BNII; Behring Diagnostics, Deerfield, IL) calibrated with the World Health Organization international reference material for apoB (28). The lipoprotein cholesterol distribution was determined by cholesterol measurement of 38 fractions after nonequilibrium density gradient ultracentrifugation, and LDL relative flotation (rf) was determined as previously described (29). Serum IL-6 concentrations were determined by a capture sandwich immunoassay using a Bio-Plex suspension array system (Bio-Rad Laboratories, Hercules, CA) and commercially available reagents from Linco Research (St. Charles, MO). hsCRP and fibrinogen were assayed by a Dade Behring nephelometer (Deerfield, IL) using Behring reagents. Leptin levels were measured by use of commercially available RIA with sensitivity of 85.4 pg/ml.

Statistical analysis

The distribution of values for each variable was examined for normality and nonnormally distributed data were log transformed (IL-6, hsCRP, fibrinogen, leptin, triglycerides). Student's *t* test was used to assess differences in continuous variables, and χ^2 tests were used to determine differences in categorical variables. Correlations between inflammatory markers studied (IL-6, hsCRP, fibrinogen, leptin) and BMI, HbA_{1c}, blood pressure, and lipids were examined. Multivariate linear regression models were then fit to examine the determinants of inflammatory markers and test for differences by diabetes status and quartile of HbA_{1c} and weight category. In multivariate linear regression models, interaction terms were included for type 1 diabetes status and HbA_{1c} quartile, with all controls assigned to the first quartile of HbA_{1c} to compare each inflammatory marker by HbA_{1c} quartile in participants with type 1 diabetes to all control participants. Multivariate regression models were adjusted for study site (Colorado or South Carolina) to account for any differences in sample collection or other factors related to the site. To adjust for multiple comparisons, a simulated *P* value adjustment was made for comparisons of least square adjusted means (SAS proc GLM, adjustment simulated; SAS Institute, Cary, NC). For tests of linear trend, a *P* value of 0.0125 was considered statistically significant, using a Bonferroni adjustment for the four inflammatory markers.

Results

Characteristics of study participants are shown in Table 1. Unadjusted IL-6 and fibrinogen were significantly higher and leptin levels were significantly lower in participants with type 1 diabetes compared with controls. Participants with type 1 diabetes had higher total cholesterol, apoB, and HDL-cholesterol levels than the healthy controls. LDL-cholesterol levels were not significantly different between cases and controls, but denser LDL as reflected by lower LDL relative flotation, which is considered to be atherogenic, and higher levels of apoB were observed in the participants with type 1 diabetes. BMI and BMI z-score were significantly lower, and obesity was less prevalent, in participants with type 1 diabetes compared with controls.

Levels of inflammatory markers were further examined by diabetes status and race/ethnicity, after adjustment for age, sex, Tanner stage, study site, BMI, and HbA_{1c} (Fig. 1). Leptin levels were significantly higher among non-Hispanic white youth with type 1 diabetes compared with Hispanic youth with type 1 diabetes, whereas leptin levels were higher among Hispanic youth without diabetes compared with non-Hispanic white youth without diabetes. There was a significant interaction of race/ethnicity and group (type 1 diabetes *vs.* controls) on leptin levels ($P = 0.0006$). Due to these differences by race/ethnicity, all subsequent models were adjusted for race/ethnicity.

Youth were separated into normal weight, overweight, and obese categories based on their BMI z-score for youth under 18 yr and based on BMI for youth 18–22 yr old. Inflammatory markers were then examined by weight group (Table 2). IL-6 and fibrinogen levels were significantly higher in patients with type 1 diabetes as compared with youth without diabetes at all levels of weight, whereas hsCRP was increased only among normal-weight youth with type 1 diabetes compared with normal-weight controls. hsCRP, fibrinogen, and leptin all increased significantly across weight groups. Trends for all inflammatory markers by weight group were not different by diabetes status as tested using interactions for diabetes group by BMI group (all $P > 0.05$).

Levels of inflammatory markers in nondiabetic controls were compared with levels in participants with type 1 diabetes overall and by HbA_{1c} quartile (Table 3) in a single linear regression model, fitted with an interaction term by diabetes group. All nondiabetic youth were assigned to a single HbA_{1c} quartile (quartile 1) and were then compared with youth with type 1 diabetes in each quartile of HbA_{1c} as shown in Table 3. Levels of IL-6 and fibrinogen were higher in youth with type 1 diabetes compared with healthy controls regardless of HbA_{1c} level, and hsCRP levels were increased in the second and fourth

TABLE 1. Demographic and clinical characteristics of cases and controls in the study population

	Type 1 diabetes cases (n = 553)	Healthy controls (n = 215)	*P* value
Age at visit (yr)	14.9 ± 2.9	14.5 ± 3.3	0.18
Tanner stage 5 (%)	42	41	0.81
Race (%)			<0.0001
Caucasian	81	55	
African-American	10	29	
Hispanic	9	16	
Age at diabetes diagnosis (yr)	10.0 ± 3.9	N/A	N/A
Study site (n)			<0.0001
Colorado	304	106	
South Carolina	99	74	
Insulin dose (U/kg · d)	0.78 ± 0.02	N/A	N/A
HbA_{1c} (%)	8.4 ± 1.9	5.2 ± 0.3	<0.0001
BMI (kg/m^2)	22.0 ± 4.3	24.1 ± 7.0	<0.0001
BMI SD z-score	0.51 ± 0.91	0.78 ± 1.1	0.001
BMI category (%)			<0.0001
Normal weight	70	60	
Overweight	19	15	
Obese	11	25	
Waist circumference	77.9 ± 11.5	80.1 ± 15.9	0.06
Total cholesterol (mg/dl)	172 ± 36	163 ± 28	0.001
LDL cholesterol (mg/dl)	102 ± 28	98 ± 24	0.07
HDL cholesterol (mg/dl)	54 ± 12	48 ± 11	<0.0001
Triglycerides (mg/dl)	67 (50–92)	76 (56–107)	0.55
apoB (mg/dl)	79 ± 24	58 ± 16	<0.0001
LDL relative flotation	0.278 ± 0.021	0.283 ± 0.018	0.002
IL-6 (pg/ml)	8.8 (3.7)	3.3 (3.4)	<0.0001
CRP (mg/dl)	0.06 (4.1)	0.05 (5.4)	0.21
Fibrinogen (mg/dl)	355 (1.2)	286 (1.3)	<0.0001
Leptin (ng/dl)	5.4 (2.7)	7.8 (3.2)	<0.0001

N/A, Not applicable.

Presented are mean ± SD or geometric mean (SD). Conversion to SI units (millimoles per liter) are as follows: total cholesterol, LDL-cholesterol, and HDL-cholesterol, 0.0259; triglycerides, 0.0113; apoB (grams per liter), 0.01.

quartiles of HbA_{1c} in youth with type 1 diabetes compared with nondiabetic controls. No linear trend was apparent for leptin, and none of the other inflammatory markers (IL-6, hsCRP, and fibrinogen) differed by HbA_{1c} quartile in a test for linear trend, with $P < 0.0125$ considered significant. The only significant difference in leptin levels was found in the comparison of youth with type 1 diabetes in the highest HbA_{1c} quartile to nondiabetic controls.

Because some previous studies have reported differences in inflammation in recently diagnosed youth with type 1 diabetes, compared with those with longer disease duration, we examined whether inflammatory markers differed in youth with less than 1 yr duration of diabetes compared with those with type 1 diabetes for at least a year at the time of the examination. There were no significant differences between those with longer diabetes duration compared with those diagnosed within the past year for levels of IL-6 (6.4 *vs.* 7.6 pg/ml, $P = 0.36$), hsCRP (0.06 *vs.* 0.06 mg/dl, $P = 0.93$), fibrinogen (360 *vs.* 372 mg/dl, $P = 0.19$), or leptin (4.5 *vs.* 4.9 ng/dl, $P = 0.34$).

Because inflammation is associated with an increased risk of cardiovascular complications in adults with type 1 diabetes, we examined correlations of inflammatory markers and lipid levels using partial Pearson correlation coefficients, adjusted for age, Tanner stage, race/ethnicity, sex, HbA_{1c}, and BMI (Table 4). Among participants with type 1 diabetes, levels of IL-6 were inversely correlated with HDL-cholesterol, and hsCRP and fibrinogen were positively correlated with total cholesterol, LDL-cholesterol, and apoB, whereas the only significant correlation in controls was a positive correlation of fibrinogen with LDL-cholesterol and apoB and a negative correlation of hsCRP with HDL-cholesterol.

Discussion

In the present study, we found that youth with type 1 diabetes have increased systemic inflammation compared with youth without diabetes of similar age and Tanner stage, independent of race/ethnicity, sex, hyperglycemia, and obesity. Increased hsCRP, fibrinogen, and leptin were associated with being overweight or obese, and this relationship did not differ between youth with and without

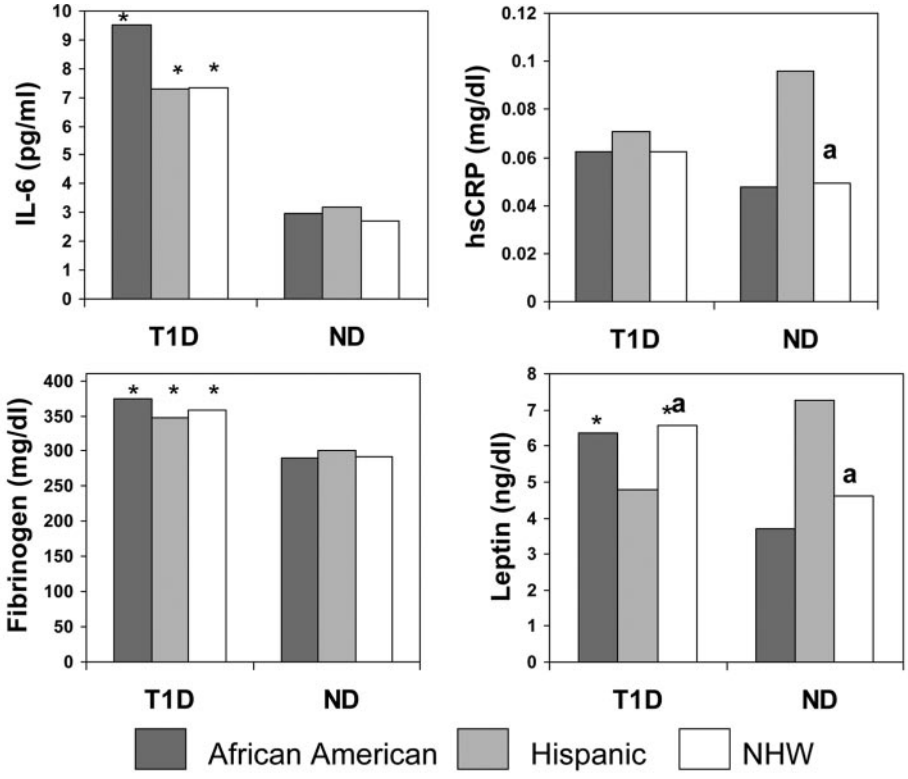

FIG. 1. Levels of inflammatory markers by case/control status and racial/ethnic group. T1D, Type 1 diabetes; NHW, non-Hispanic white.

type 1 diabetes. In fact, among normal-weight youth, increased inflammation (higher IL-6, hsCRP, and fibrinogen levels) was present in youth with type 1 diabetes compared with nondiabetic youth, suggesting that a mechanism other than obesity is responsible for the increased inflammation observed among youth with type 1 diabetes.

Alterations in inflammatory cytokines have previously been reported in children and adolescents with type 1 diabetes, but these reports have been inconsistent. A study in Turkey examined mediators of inflammation in a group of 35 children with type 1 diabetes (54% girls) with an average duration of diabetes of 3.9 yr and 30 nondiabetic children (47% girls) with a mean age of 12 and 11 yr, respectively (30). Consistent with our results, children with type 1 diabetes had increased total cholesterol and apoB and higher levels of hsCRP, although this did not reach significance in the Turkish study. Elevated IL-6 levels were reported in the Turkish study only among newly diagnosed patients with type 1 diabetes. Higher levels of hsCRP in children with both newly diagnosed and longer duration type 1 diabetes were also reported in a study that examined 69 children with type 1 diabetes compared with 74 age-matched nondiabetic children (31).

Acute hyperglycemia and worse glycemic control early in the course of type 1 diabetes have been associated with increased inflammation in children with type 1 diabetes,

TABLE 2. Geometric means of inflammatory markers by weight category, adjusted for age, Tanner stage, race, study site, and BMI

	IL-6 (pg/ml)		hsCRP (mg/dl)		Fibrinogen (mg/dl)		Leptin (ng/dl)	
	T1D	ND	T1D	ND	T1D	ND	T1D	ND
Normal weight	7.8[a]	3.2	0.049*	0.028	349[a]	268	3.5	3.7
Overweight	8.7[a]	2.6	0.105	0.083	393[a]	288	7.2	9.5
Obese	7.8[b]	2.9	0.189	0.207	403[a]	325	16.5	21.2
P for trend	0.55	0.61	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

T1D, Type 1 diabetes; ND, nondiabetic.

[a] $P < 0.001$ for comparison by diabetes status within weight group, adjusted for multiple comparisons (SAS simulation adjustment).

[b] $P < 0.05$ for comparison between those with and without diabetes within the weight category.

TABLE 3. Geometric means of inflammatory markers by diabetes status and HbA_{1c} quartile, adjusted for age, sex, race, Tanner stage, study site and BMI

	IL-6 (pg/ml)	hsCRP (mg/dl)	Fibrinogen (mg/dl)	Leptin (ng/dl)
Nondiabetic controls (n = 215)	3.0	0.047	280	5.7
T1D cases (n = 553)	7.9[a]	0.075[b]	366[a]	5.7
T1D glycemia by quartile				
Quartile 1 (n = 168): HbA_{1c} <7.2	8.2[a]	0.061	360[a]	6.7
Quartile 2 (n = 131): HbA_{1c} 7.2 to <8.3	7.6[a]	0.076[b]	359[a]	6.1
Quartile 3 (n = 116): HbA_{1c} 8.3 to <9.3	7.5[a]	0.074	363[a]	6.4
Quartile 4 (n = 138): HbA_{1c} ≥9.3	8.1[a]	0.092[a]	383[a]	4.2[b]
P value for linear trend	0.71	0.04	0.04	N/A

T1D, Type 1 diabetes; N/A, not applicable.

[a] $P < 0.001$ for comparison of T1D *vs.* control, adjusted for multiple comparisons (SAS simulation adjustment).

[b] $P < 0.05$ for comparison of T1D *vs.* control, adjusted for multiple comparisons (SAS simulation adjustment).

but it is less clear whether chronic hyperglycemia among children with longer duration of diabetes is associated with inflammation. In a study of 22 children with type 1 diabetes, acute hyperglycemia was associated with increased levels of IL-6, as well as IL-4 and IL-1α, and the increased inflammation persisted for at least 2 h after correction of hyperglycemia (32). In the present study, we found no association between IL-6 and HbA_{1c}. However, it is possible that acute hyperglycemic excursions may influence IL-6 levels more than overall glycemic control, perhaps explaining the lack of association between IL-6 and HbA_{1c} in our data.

The relationship we found between hsCRP and type 1 diabetes is more complex, with higher levels of hsCRP compared with controls only among youth with type 1 diabetes in the highest three quartiles of HbA_{1c}, and higher levels of hsCRP among normal-weight youth with type 1 diabetes compared with normal weight nondiabetic controls. Among persons 15 through 34 yr of age newly diagnosed with type 1 diabetes, hsCRP levels were reported in the high-normal range at diagnosis, and higher levels of hsCRP were associated with worsening glycemic control from 6 to 12 months after diagnosis (12). The median diabetes duration of participants in the present study was 32 months, and we found a positive association between higher levels of hsCRP and quartile of HbA_{1c}. These results suggest that hsCRP levels are associated with hyperglycemia and obesity but may also be increased in youth with type 1 diabetes independent of these factors.

In the present study, leptin levels were lower in youth with type 1 diabetes compared with nondiabetic controls in univariate analysis, but when examined by level of glycemic control, leptin levels were similar among youth with type 1 diabetes with HbA_{1c} in the lower three quartiles and significantly lower only among those with the highest HbA_{1c}. The leptin suppression we observed in the highest quartile of HbA_{1c} may be the result of poor glycemic con-

TABLE 4. Correlations between inflammatory markers and other variables of interest, adjusted for age, Tanner stage, sex, race, BMI, and HbA_{1c}

	IL-6	CRP	Fibrinogen	Leptin
Type 1 diabetes cases				
Total cholesterol (mg/dl)	−0.09	0.13[a]	0.25[a]	−0.08
LDL cholesterol (mg/dl)	−0.08	0.12[b]	0.23[a]	−0.07
HDL cholesterol (mg/dl)	−0.11[b]	0.03	0.02	0.06
Triglycerides (mg/dl)	0.02	0.05	0.13[b]	−0.12[b]
apoB (mg/dl)	−0.07	0.17[a]	0.31[a]	−0.14[a]
LDL density	0.002	−0.04	−0.08	0.19[a]
Nondiabetic controls				
Total cholesterol (mg/dl)	−0.14	0.01	0.14	0.07
LDL cholesterol (mg/dl)	−0.13	0.06	0.15[b]	0.09
HDL cholesterol (mg/dl)	−0.04	−0.16[b]	0.04	−0.14
Triglycerides (mg/dl)	−0.03	0.05	0.004	0.12
apoB (mg/dl)	−0.13	0.12	0.15[b]	0.09
LDL density	0.02	−0.05	0.02	−0.14

Conversion to SI units (millimoles per liter) are as follows: total cholesterol, LDL-cholesterol, and HDL-cholesterol, 0.0259; triglycerides, 0.0113; apoB (grams per liter), 0.01.

[a] $P < 0.001$.

[b] $P < 0.05$.

trol, or it may be a consequence of insufficient insulin levels. In a study of prepubertal children aged 3–10 yr with type 1 diabetes, newly diagnosed children had lower leptin levels than children with at least 2 yr duration of type 1 diabetes (33). In addition, higher leptin levels were observed among those with the highest HbA_{1c}, and leptin levels were positively correlated with insulin dose per kilogram body weight (33). These results suggest that leptin is lower in newly diagnosed patients with type 1 diabetes than in children with longer disease duration, perhaps related to differences in peripheral insulin levels and fat mass. In our cross-sectional study, we are unable to assess how changes in BMI affect the relationship of leptin and HbA_{1c}.

However, in our study the leptin levels were lowest among patients with higher HbA_{1c}, even after adjusting for BMI. A possible explanation for the differing findings of these two studies is that insulin may be administered and closely monitored by parents of younger children, whereas adolescents with type 1 diabetes may have greater independence and administer insulin less consistently. Those youth with the poorest glycemic control in our study had an HbA_{1c} of 9.3 or higher, whereas the children in the study by Soliman *et al.* (33) had much better glycemic control, with an HbA_{1c} of 7.5, representing 2 SD above the mean. As a result, those youth with poor compliance and elevated HbA_{1c} in our study may have been skipping doses of insulin, and the lower levels of leptin may therefore be explained by hypoinsulinemia. In adults with type 2 diabetes who were not on insulin therapy, higher levels of HbA_{1c} were correlated with lower levels of leptin, even when adjusted for BMI (34). Because these study participants were not on insulin therapy and type 2 diabetes is a hyperinsulinemic state, the authors of this study concluded that very poor glycemic control may suppress leptin levels. Further study is needed to determine the relationship between leptin, HbA_{1c}, and insulin in youth with type 1 diabetes.

The increased inflammation in youth with type 1 diabetes observed in the present study is of concern because higher levels of hsCRP and fibrinogen were associated with increased total and LDL-cholesterol as well as increased apoB. In addition, higher levels of IL-6 were associated with lower levels of HDL-cholesterol. These results demonstrate that increased systemic inflammation in type 1 diabetes, independent of hyperglycemia and obesity, is associated with a more atherogenic lipid profile, putting these youth at higher risk for cardiovascular disease.

Several limitations to the present study should be considered when interpreting these findings. The definition of type 1 diabetes was based on the clinical diagnosis, and there may be some misclassification of diabetes type among these children. However, most children who had a clinical diagnosis of type 1 diabetes were positive for at least one autoantibody. In our study, Tanner stage was self-reported and may be less accurate than physician Tanner staging. In addition, it should be noted that even youth with type 1 diabetes who have excellent glycemic control have HbA_{1c} levels that exceed normal levels, so it is not possible to entirely adjust for the effects of hyperglycemia. As a result, the increased levels of IL-6 and fibrinogen in youth with type 1 diabetes may be explained by the increase in hyperglycemia, which occurs in diabetes, even though there was not an increase in levels with increasing levels of hyperglycemia. The strengths of this study include the large sample size compared with previous studies of inflammation in children with type 1 diabetes and the multiethnic sample for both cases and controls, which allows for comparisons by race/ethnicity.

In conclusion, our study has demonstrated that youth with type 1 diabetes have increased systemic inflammation compared with youth without diabetes, regardless of glycemic control and adiposity. hsCRP levels are increased among lean individuals with type 1 diabetes and in those in less than optimal glycemic control. Increased IL-6 and fibrinogen levels are present in youth with type 1 diabetes at all levels of glycemic control and obesity, and all three of these inflammatory markers are correlated with more atherogenic lipid profiles. As a result, it appears that having type 1 diabetes is a stronger correlate of inflammation than obesity, whereas overweight and obesity modestly increase levels of hsCRP and fibrinogen further in youth with type 1 diabetes. Increasing levels of hyperglycemia were not associated with increased inflammation. Furthermore, leptin levels appear to be decreased among youth with type 1 diabetes in poor control, perhaps reflecting poor compliance with their insulin regimen. Increased inflammation is associated with diabetes-related complications in persons with type 1 diabetes, including the development of retinopathy (35–37), nephropathy (9), and premature atherosclerosis (10). Further study is needed to determine methods for decreasing inflammation in youth with type 1 diabetes and investigate mechanisms through which systemic inflammation and inflammatory cytokines contribute to the development of chronic diabetic complications.

Acknowledgments

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