Effect of Intensive Glycemic Control on Levels of Markers of Inflammation in Type 1 Diabetes Mellitus in the Diabetes Control and Complications Trial

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Background—Type 1 diabetes mellitus is associated with an increased risk of cardiovascular disease (CVD) that is not fully explained by conventional risk factors. The Diabetes Control and Complications Trial (DCCT) showed that intensive diabetes therapy reduced levels of LDL cholesterol and triglycerides but increased the risk of major weight gain, which might adversely affect CVD risk. The present study examined the effect of intensive therapy on levels of several markers of inflammation that have been linked to risk of CVD.

Methods and Results—We measured levels of inflammatory biomarkers in stored baseline and 3-year follow-up serum specimens from a random sample of 385 participants in the DCCT, a multicenter trial in which 1441 subjects aged 13 to 39 years with type 1 diabetes mellitus were randomized to intensive or conventional diabetes treatment. The markers included high-sensitivity C-reactive protein (hsCRP), soluble intercellular adhesion molecule type 1 (sICAM-1), soluble vascular cell adhesion molecule type 1 (sVCAM-1), and the 55-kDa soluble tumor necrosis factor-α receptor 1 (sTNF-R1). We examined the effect of intensive therapy on the change in levels of the inflammatory markers. In unadjusted analyses, levels of hsCRP and sTNF-R1 increased in both treatment groups after 3 years of follow-up, with no significant difference between groups for hsCRP (P=0.53) but with a greater increase of sTNF-R1 in the intensive therapy group (P=0.002). In contrast, mean levels of sICAM-1 and sVCAM-1 decreased among participants assigned to intensive therapy, whereas they did not change among those in the conventional treatment group (P=0.03 for sICAM-1; P=0.02 for sVCAM-1). After adjustment for baseline levels and other factors, intensive therapy remained associated with a significant decrease in sICAM-1 (P=0.02) and an increase in sTNF-R1 (P=0.03). For hsCRP, there was a significant interaction between the top third of weight gain and treatment assignment (P=0.03). In subgroup analyses among subjects undergoing intensive therapy, hsCRP levels increased among those who gained the most weight, whereas it decreased among those in the bottom third of weight gain (P=0.0004).

Conclusions—Intensive therapy in patients with type 1 diabetes mellitus reduced levels of sICAM-1 and increased levels of sTNF-R1 and of hsCRP among those who gained weight. These data demonstrate that the effect of intensive therapy on inflammation is complex and, to the extent that hsCRP is a risk factor, suggest that the risk of atherosclerosis among diabetic patients may be influenced by the degree of weight gain while undergoing intensive therapy. (Circulation. 2005;111:2446-2453.)

Key Words: inflammation ■ epidemiology ■ cardiovascular diseases ■ diabetes mellitus ■ obesity

Cardiovascular disease (CVD) is a major cause of morbidity and the leading cause of mortality among people with type 1 diabetes mellitus. People with diabetes mellitus have a higher coincidence of a number of traditional CVD risk factors, including hyperlipidemia and hypertension.1–3 Moreover, chronic hyperglycemia is a risk factor for atherosclerosis in type 1 diabetes mellitus.4 However, neither traditional CVD risk factors nor hyperglycemia fully explains the risk for CVD. An additional factor that may play a role in the increased risk of CVD among diabetics is an increase in the overall level of systemic inflammatory activity.
Compelling evidence suggests that CVD is at least in part an inflammatory process. Moreover, prior research has shown increased levels of several markers of inflammation among people with diabetes, and these levels generally correlate with measures of glycemic control, such as glycosylated hemoglobin A1c (HbA1c). For example, HbA1c significantly correlates with levels of C-reactive protein (CRP), an acute-phase reactant that is associated with early atherosclerotic lesions and predicts future risk of CVD, including among subjects with type 1 diabetes mellitus. CRP also predicts onset of type 2 diabetes mellitus among those with low HbA1c and adds prognostic information on vascular risk among those with metabolic syndrome. Other markers of inflammation, including soluble intercellular adhesion molecule 1 (sICAM-1) and soluble tumor necrosis factor alpha- receptors (sTNF-R), predict risk of CVD in nondiabetic persons and are increased in type 2 diabetes mellitus.

In the Diabetes Control and Complications Trial (DCCT), intensive diabetes control was associated with a clear and sustained reduction in levels of HbA1c and of microvascular complications in type 1 diabetes mellitus; however, there was an increased risk of weight gain and obesity, accompanied by other cardiovascular risk factors, among those assigned to intensive diabetes therapy. Recently, higher body mass index has been linked with increased levels of inflammatory markers, particularly high-sensitivity CRP (hsCRP), including among subjects with type 2 diabetes mellitus. It was not proved conclusively whether intensive diabetes therapy reduces the risk of CVD. Nevertheless, long-term follow-up of the DCCT cohort has revealed a beneficial effect of previous intensive therapy on atherosclerosis as measured by carotid intima-media thickness. The present study was undertaken to examine the effect of intensive metabolic control on circulating levels of inflammatory molecules, including hsCRP, sICAM-1, soluble vascular cell adhesion molecule-1 (sVCAM-1), and the 55-kDa sTNF-R1, putative early markers of cardiovascular risk. The potential contribution of weight gain to the inflammatory molecules was also explored.

Methods

The DCCT was a multicenter trial of intensive versus conventional treatment of type 1 diabetes mellitus, designed to examine development and progression of microvascular complications. Subjects were 1441 individuals with type 1 diabetes mellitus between the ages of 13 and 39 years, recruited at 29 centers from 1983 through 1989. All DCCT participants had baseline HbA1c levels >3 SDs above the mean for nondiabetics. Subjects were recruited into 2 strata: (1) a primary prevention cohort with no retinopathy, diabetes duration of 1 to 5 years, and no evidence of microalbuminuria at baseline (albuminuria <28 µg/min [<40 mg/24 h]) or (2) a secondary intervention cohort with minimal to moderate nonproliferative retinopathy, diabetes duration between 1 and 15 years, and albuminuria ≤140 µg/min (200 mg/24 h). Subjects with baseline total cholesterol levels >3 SDs above the mean for sex and age, calculated LDL cholesterol levels >4.9 mmol/L (190 mg/dL), body weight >30% above ideal, major ECG abnormalities, a history of coronary heart disease, or symptoms of peripheral vascular disease were excluded. For the present study, we randomly selected a subgroup of 400 DCCT participants stratified by baseline retinopathy subgroup and randomized treatment assignment. This sample size was based on a calculation to achieve power of 85% to detect a difference of 0.15 SDs of the change in biomarker levels between treatment groups with a type 1 error rate of 0.05. None of the participants in the present study had hypertension or were taking hormone replacement therapy.

Intensive insulin therapy consisted of the administration of insulin 3 or more times per day by injection or external insulin pump therapy, guided by results of self-monitoring of blood glucose performed at least 4 times daily. Conventional therapy was with 1 to 2 daily injections of insulin, with daily self-monitoring of urine or blood glucose. Glycosylated hemoglobin levels fell rapidly in the intensive therapy group, reaching a nadir within 6 months, and average levels remained approximately 2 percentage points lower than in the conventional therapy group for the duration of the trial. After a mean follow-up of 6.5 years (range 3 to 9 years), the DCCT was stopped, having shown clinically and statistically highly significant reductions (range of 33% to >70%) in retinopathy, nephropathy, and neuropathy with intensive compared with conventional therapy.

DCCT Blood and Urine Collection and Storage

Fasting plasma and serum samples were obtained from DCCT participants at baseline and each annual visit. For stored plasma samples, blood was drawn into EDTA tubes with 500 U of Trasylol (aprotinin) per milliliter of whole blood, immediately placed on ice, and then centrifuged at 2000 rpm for 10 minutes. The plasma was then transferred to 1.8-ml cryotubes and immediately placed on dry ice. For stored serum samples, blood was drawn into a red-topped tube, allowed to clot for at least 20 minutes, and then spun in a centrifuge at room temperature for 10 minutes at 3000 rpm. Serum was then divided into 1.8-ml cryotubes and promptly frozen. Samples were maintained at −70°C at the DCCT Central Biochemistry Laboratory, Department of Laboratory Medicine and Pathology, University of Minnesota until preparation for the present study.

Laboratory Analysis

Baseline and 3-year serum samples were thawed and assayed for hsCRP with a latex-enhanced immunonephelometric assay on a BN II analyzer (Dade Behring). Serum levels of sICAM-1, sVCAM-1, and sTNF-R1 were measured by ELISAs (R&D Systems). All samples were handled in an identical and masked fashion, with baseline and 3-year specimens interspersed for analysis.

Statistical Analysis

We examined the change in levels of each biomarker from baseline to the 3-year follow-up visit and tested whether this was related to the randomization assignment using the Mann-Whitney U test. These relationships were also estimated with linear regression, with the natural logarithm of the 3-year follow-up levels of the biomarker as the dependent variable and treatment assignment, the natural log of baseline levels of the biomarker, and other factors as the independent variables. To enhance comparability of results among markers, we retained a common set of covariates for each marker of inflammation. These covariates included baseline levels of the marker, baseline HbA1c, age, sex, duration of diabetes, body mass index, and smoking status. For continuous variables, we subtracted the mean value from the measured value to obtain a distribution centered on the mean, to aid in interpretation of the models (particularly the intercepts). For each marker, we then fit an additional model in which we adjusted for the average HbA1c level over follow-up, to examine the relationships with glucose control per se. In further models, we considered interactions between baseline levels of the markers and randomized treatment assignment by including product terms in the models. Finally, for both hsCRP and sTNF-R1, molecules strongly correlated with body weight, we explored whether there was a relationship with weight gain or an interaction between weight gain and treatment assignment. For these analyses, we divided weight gain into approximate thirds based on the distribution of weight gain in the total DCCT population.
We performed regression diagnostics to identify unduly influential observations and repeated models that excluded these observations. Because exclusion of the most influential observations did not change interpretation of any findings, we present only the models for all participants. In a secondary analysis, we used the baseline to 3-year change in levels of the biomarkers as the independent variable for our models. Because the distributions of the changes in inflammatory markers were skewed, and log transformations were not possible because of negative values (because a participant’s marker level could have either decreased or increased), we obtained the normalized rank transformations of each of the markers and re-gressed covariates on these ranks to obtain probability values for the regression models. There were no substantial differences in this analysis compared with the findings presented.

Results

Of the 400 DCCT participants randomly selected for the present study, 385 had sufficient baseline and 3-year follow-up serum samples to measure at least 1 of the selected biomarkers; thus, any potential effect of dropouts on results is minimal and of no concern. In this subset of DCCT participants, there were no significant differences in levels of the inflammatory markers hsCRP, sICAM-1, sVCAM-1, or sTNF-R1 at baseline between subjects assigned to intensive versus conventional therapy (Table 1).

Median levels of hsCRP increased over time by 0.19 mg/L (23.9%) in the conventional treatment group and by 0.08 mg/L (9.3%) among those assigned to intensive therapy (Table 2). This difference was not statistically significant (P=0.53). In contrast, median levels of both sICAM-1 and sVCAM-1 increased from baseline to 3 years of follow-up by 4.9 ng/mL (1.7%) and 4.6 ng/mL (1.0%), respectively, among subjects assigned to conventional treatment but decreased by 2.5 mg/L (0.9%) and 9.5 mg/L (2.1%), respectively, among subjects assigned to intensive therapy. The differences in change in levels for intensive versus conventional therapy were statistically significant (each P=0.03). Levels of sTNF-R1 increased among subjects in both treatment arms of...
the DCCT but by a greater amount among subjects assigned to intensive therapy (6.0 pg/mL [0.6%] for conventional treatment versus 108.1 pg/mL [10.9%] for intensive therapy; \(P=0.002\)). Because baseline levels had a substantial impact on changes over time, as would be expected as more extreme levels regressed toward the mean, we reexamined associations with treatment assignment in models that adjusted for baseline levels of the markers, as well as for other potential predictors of change.

In analyses of hsCRP, after adjustment for baseline levels of hsCRP (\(P<0.0001\)), female sex (\(P<0.0001\)), and other factors, 3-year follow-up hsCRP levels were not significantly different among those assigned to intensive versus conventional control (\(P=0.98\); Table 3). In models for sICAM-1, both baseline sICAM-1 levels (\(P<0.0001\)) and current cigarette smoking at baseline (\(P<0.0001\)) were significant predictors of 3-year follow-up levels. After adjustment for these and other variables, intensive therapy was still associated with a significant decrease in sICAM-1 levels after 3 years of follow-up (\(P=0.02\); Table 3). For sVCAM-1, after adjustment for baseline levels (\(P<0.0001\)), age (\(P=0.0005\)), and other factors, the association of intensive therapy with change in sVCAM-1 was no longer significant (\(P=0.19\); Table 3). Lower baseline levels of sTNF-R1 (\(P<0.0001\)) and older age (\(P=0.01\)) were associated with an increase in sTNF-R1 at 3 years. After adjustment for these and other covariates, intensive diabetes control was associated with a significantly greater increase in sTNF-R1 levels than conventional therapy (\(P=0.03\); Table 3).

In further analyses, we included the average level of HbA\(_{1c}\) over follow-up in models to investigate the extent to which any observed effect of intensive control might be mediated through the degree of glucose control achieved. For hsCRP, adjustment for average levels of HbA\(_{1c}\) revealed a significant increase in hsCRP among those assigned to intensive control (\(P=0.04\)). In this model, the level of hsCRP after 3 years of follow-up was inversely associated with baseline HbA\(_{1c}\) levels (\(P=0.003\), but there was a direct association with average HbA\(_{1c}\) during follow-up (\(P=0.005\); Table 4). In contrast, for sICAM-1, sVCAM-1, and sTNF-R1, adjustment for average HbA\(_{1c}\) attenuated the effect of intensive control, which was not significant for any of these markers (Table 4). Additional adjustment for changes in cigarette smoking during follow-up did not change any of these findings (data not shown).

Finally, given the known tendency for subjects to gain weight after initiation of intensive therapy, the strong relationship between body mass index and hsCRP levels, and the observation that intensive control increased hsCRP levels after adjustment for average HbA\(_{1c}\) levels, we examined weight change and whether there might be an interaction between weight change and randomized treatment assignment that might provide some explanation for the lack of an overall effect of intensive therapy on change in levels of hsCRP. In this analysis, we identified a significant interaction between weight change and treatment assignment (\(P=0.03\); Table 5). In separate analyses in the 2 treatment groups, among subjects assigned to intensive therapy, there was a median increase of 0.54 mg/L (75%) in hsCRP levels at 3 years of follow-up among those in the top third of weight change (mean body mass index at 3 years of follow-up 27.0 kg/m\(^2\)) compared with a decrease of 0.24 mg/L (20%) among subjects in the lowest third of weight change (mean body mass index at 3 years of follow-up 22.8 kg/m\(^2\); \(P=0.0004\); Figure). In contrast, among those assigned to conventional control, there was no significant difference in the change in hsCRP according to weight change category (\(P=0.88\)). We also investigated potential effects of weight gain with regard to sTNF-R1 and found a significantly greater increase in sTNF-R1 levels among subjects who gained the most weight.
Inflammation in the DCCT Population, Adjusted for Average Levels of HbA1c Over Follow-Up

<table>
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<th>Parameter Estimate (SE)</th>
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<td>Log of baseline level of marker†</td>
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<td>&lt;0.0001</td>
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<td>Baseline HbA1c (%)††</td>
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<td>Average HbA1c (%)†‡</td>
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<tr>
<td>Duration of diabetes mellitus (mo)†</td>
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<td>-0.0007 (0.0009)</td>
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<td>Body mass index at baseline (kg/m²)†‡</td>
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<td>0.54</td>
<td>-0.01 (0.009)</td>
<td>0.16</td>
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<td>Current smoker at baseline</td>
<td>-0.02 (0.14)</td>
<td>0.87</td>
<td>0.12 (0.02)</td>
<td>&lt;0.0001</td>
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</table>

*A* values from regression on the natural log of the level of each marker at the 3-year follow-up visit, with adjustment for baseline levels and all other variables in the model.

†Each continuous variable was centered on the mean of its distribution and then divided by its SD, such that each estimate refers to the change per SD change in the variable.

‡Average of quarterly HbA1c measurements from baseline to 3 years of follow-up.

Discussion

Randomized clinical trials have not conclusively shown that intensive glycemic control reduces the risk of CVD among people with either type 1 or type 2 diabetes mellitus. Some epidemiological data suggest a stronger relationship with insulin resistance–related factors than with HbA1c. In the DCCT, intensive therapy was associated with a higher risk of overweight and obesity, which may adversely affect CVD risk. Several lines of evidence have come to light that suggest that inflammation is a key player in the development of CVD. A number of studies have found that several circulating molecules involved in inflammation, such as sICAM-1, hsCRP, and TNF-R1, predict risk of CVD, and some of these molecules, notably hsCRP and sTNF-R1, are highly influenced by body weight. The present data from the DCCT indicate that among subjects with type 1 diabetes mellitus, intensive glycemic control is associated with a significant reduction in levels of sICAM-1 but not with change in levels of hsCRP, the marker of inflammation most strongly and consistently predictive of CVD in epidemiological studies. Furthermore, the present analyses indicated that there was a significant rise in levels of hsCRP among intensively treated subjects who gained the most weight. There was also a significant rise in sTNF-R1 among intensively treated subjects, which appears to be explained by greater weight gain in the intensively treated group.

Although this is the largest study to date of these relationships among individuals with type 1 diabetes mellitus, several limitations deserve consideration. Given the uniqueness of the DCCT population, generalizability of these findings to individuals with type 2 diabetes mellitus and to ethnic minority groups is uncertain. The present analyses of weight change as a potential predictor of change may be controversial, because they include in the model a factor (weight gain) that is directly influenced by treatment assignment and is thus an intermediate variable. Multiple testing may have also resulted in an inflation of the type 1 error rate. However, we think that our analyses are informative because they provide a potentially relevant explanation for the overall lack of an effect of intensive therapy on hsCRP levels, in contrast to a significant increase after adjustment for average HbA1c during follow-up, and for the greater increase in sTNF-R1 among subjects undergoing intensive therapy. We were also limited to a single measure of the inflammatory markers at each time point, which may not accurately reflect the long-term or average levels of exposure that are likely to be most relevant to CVD. However, single measures have shown significant predictive value for CVD in prior prospective studies. Long-term follow-up of the DCCT cohort in the Epidemiology of Diabetes Interventions and Complications (EDIC) study presents the opportunity for future studies of the persistence of the observed changes in inflammatory biomarkers and their potential associations with CVD risk.

hsCRP has been strongly related to risk of CVD in a number of prospective studies and with early carotid atherosclerosis in young subjects with type 1 diabetes mellitus. Most studies have shown a positive correlation between hsCRP and HbA1c. In the present study, however, we found no overall difference in the change in levels of hsCRP comparing intensive and conventional therapy. There are few other data available, and none that we know of for type 1 diabetes mellitus or with comparable follow-up. A significant reduction in CRP was noted with an intensive insulin regimen in critically ill subjects. Moreover, CRP fell after 16 weeks of intensive therapy (data not shown).
of insulin treatment of 22 subjects with poorly controlled type 2 diabetes mellitus. In the present study of type 1 diabetes mellitus, we measured change in hsCRP after 3 years of intensive or conventional treatment and found no overall change in hsCRP. Interestingly, however, any potential benefit of improved glycemic control may have been limited by the weight gain in subjects assigned to intensive therapy.

By the end of the DCCT, the prevalence of obesity reached 33% among subjects assigned to intensive therapy versus 19% in the conventionally treated group. Subjects who gained the most weight with intensive therapy tended to experience metabolic changes similar to those seen in the insulin resistance syndrome. The present study adds to these findings by demonstrating an increase in hsCRP among intensively treated subjects who gained the most weight. This finding is consistent with the known direct relationship between body weight and hsCRP and with a large number of studies that show a relationship of CRP with the development of insulin resistance. Particularly in light of evidence that suggests a stronger relationship of insulin resistance–related factors than glycemia with CVD, if the increase in hsCRP levels associated with weight gain persists over time, this in conjunction with the other adverse metabolic changes that occur with excessive weight gain during intensive therapy may result in an increased risk of CVD.

### Table 5: Effect of Intensive Therapy on Baseline to 3-Year Change in Levels of Markers of Inflammation, Adjusted for Average HbA1c During Follow-Up and Effects of Weight Change and/or Interactions*

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<tr>
<th>Variable</th>
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<th>Parameter Estimate (SE)</th>
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<td>Intercept</td>
<td>-0.39 (0.15) 0.01</td>
<td>6.97 (0.03) &lt;0.0001</td>
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<td>Intensive vs conventional therapy</td>
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<td>0.003 (0.03) 0.92</td>
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<tr>
<td>Log of baseline level of marker‡</td>
<td>0.56 (0.06) &lt;0.0001</td>
<td>0.13 (0.01) &lt;0.0001</td>
</tr>
<tr>
<td>Baseline HbA1c (%)‡</td>
<td>-0.31 (0.08) &lt;0.0001</td>
<td>0.02 (0.01) 0.12</td>
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<td>Average HbA1c during follow-up (%)‡§</td>
<td>0.34 (0.1) 0.0006</td>
<td>-0.02 (0.02) 0.38</td>
</tr>
<tr>
<td>Age (y)‡</td>
<td>0.08 (0.06) 0.14</td>
<td>0.03 (0.01) 0.005</td>
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<td>Sex (female)</td>
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<td>-0.01 (0.02) 0.52</td>
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<td>0.02 (0.01) 0.05</td>
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<td>Body mass index at baseline (kg/m²)‡</td>
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<td>Weight change‡</td>
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<td>Upper third</td>
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<tr>
<td>Interaction of weight change‡ and treatment</td>
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<tr>
<td>Upper third × treatment</td>
<td>0.62 (0.29) 0.03</td>
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*Models for sICAM-1 and sVCAM-1 are not presented because there were no significant interactions or effect of weight change. Interactions were only included if significant.

†P values from regression on the natural log of the level of each marker at the 3-year follow-up visit, with adjustment for baseline levels and all other variables in the model.

‡Each continuous variable was centered on the mean of its distribution and then divided by its SD, such that each estimate refers to the change per SD change in the variable.

§Average of quarterly HbA1c measurements from baseline to 3 years of follow-up.

Change in body mass index from baseline to the time of the 3-year follow-up visit, by thirds of the distribution among subjects assigned to conventional treatment.

Raised circulating levels of adhesion molecules are thought to indicate a state of endothelial activation with consequent induction of immunological activity. Levels of sICAM-1 but not sVCAM-1 predict future cardiovascular events. Although adhesion molecules have also been implicated in the pathogenesis of type 1 diabetes mellitus, there is little information about their relationship with metabolic control or their potential role in the pathogenesis of complications. Subjects with diabetes mellitus appear to have elevated levels of sICAM-1 and sVCAM-1. In a small study, sICAM-1 was significantly higher among diabetic subjects who later developed CVD than among those who did not. In the present study, levels of sICAM-1 fell significantly after the introduction of intensive therapy. Our analyses suggested that this decrease was mediated through reduction of glucose. Given the previously described association of sICAM-1 with future CVD, the fall in sICAM-1 with intensive therapy might exert a beneficial influence on future risk of CVD. However, this finding must be interpreted cautiously in light of the inconsistent effects of intensive therapy on other predictive markers, in particular hsCRP.

The presence of advanced glycosylation end products and glycated albumin in the diabetic milieu can enhance expression of tumor necrosis factor (TNF)-α. However, TNF-α...
has a short half-life, and high levels of its receptors can interfere with its detection, which limits its usefulness as a biomarker. Although less widely studied than other markers of inflammation, levels of TNF receptors are elevated in a variety of settings. In a cross-sectional study, higher levels of TNF receptors were associated with carotid atherosclerosis in subjects less than 70 years of age. In the present study, we observed a significantly greater increase in sTNF-R1 among subjects assigned to intensive therapy; however, after adjustment for weight gain during follow-up, the effect of intensive therapy was not significant. Rather, mean levels of sTNF-R1 increased to a greater extent among subjects who gained weight, regardless of type of therapy.

In summary, we examined the effect of intensive versus conventional therapy on 4 selected markers of inflammation in the DCCT. The effect of intensive control on levels of inflammatory markers was not uniform, which suggests a complex relationship between intensive diabetes therapy and inflammation. Levels of sICAM-1 were reduced, but there was an increase in sTNF-R1 among subjects with type 1 diabetes mellitus may be influenced by whether or not they gain weight while undergoing intensive therapy.

Acknowledgments
This study was supported by Juvenile Diabetes Research Foundation grant No. 1-2000-646 (Dr. Schaumberg), the Earle P. Charlton, Jr. Charitable Foundation (Dr. Nathan), and a contract with the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases.

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_Circulation_. 2005;111:2446-2453; originally published online May 2, 2005;
doi: 10.1161/01.CIR.0000165064.31505.3B
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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