C-Reactive Protein and Glycemic Control in Adults With Diabetes

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OBJECTIVE — Recent evidence suggests that poor glycemic control is significantly associated with the development of macrovascular complications of diabetes. Studies have indicated that C-reactive protein (CRP) is an important risk factor for cardiovascular disease. The purpose of this study was to determine the relation between CRP and HbA_{1c} in a large national sample of individuals with diabetes.

RESEARCH DESIGN AND METHODS — A nationally representative sample of noninstitutionalized U.S. adults aged 17 years and over with nongestational diabetes was derived from the National Health and Nutrition Examination Survey III (1988–1994) (n = 1,018). Respondents with diabetes were stratified by HbA_{1c} level. The main outcome measure was elevated (>0.30 mg/dl) CRP.

RESULTS — In unadjusted analyses, respondents with diabetes who had elevated HbA_{1c} levels (≥9.0%) had a significantly higher percent of elevated CRP than people with low (<7%) HbA_{1c} levels ($P < 0.001$). In adjusted regression analysis, after controlling for age, race, sex, smoking, length of time with diabetes, insulin, and BMI, HbA_{1c} was significantly associated with an increased likelihood of elevated CRP for HbA_{1c} >9.0% (OR 2.15, 95% CI 1.07–4.32) and for HbA_{1c} >11.0% (4.40, 1.87–10.38). Higher HbA_{1c} also predicted elevated CRP in the regression model when HbA_{1c} was analyzed as a continuous variable (1.20, 1.07–1.34).

CONCLUSIONS — In this study, the likelihood of elevated CRP concentrations increased with increasing HbA_{1c} levels. These findings suggest an association between glycemic control and systemic inflammation in people with established diabetes.

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C-reactive protein (CRP), a marker of systemic inflammation, is emerging as an independent risk factor for cardiovascular disease (1–3). High CRP levels have been linked to an increased risk of thrombotic events including myocardial infarction (3–5). Elevated CRP levels have also been linked to an increased risk of later development of diabetes (6,7). Furthermore, CRP levels are higher in people with diabetes compared with those without diabetes (8–10). Less is known about whether CRP in people with diabetes is related to level of glycemic control. Wu et al. (11) found that CRP is associated with HbA_{1c} levels; however, people with diabetes were excluded from the study. HbA_{1c} was 5.4% in people with low CRP and 5.5% in people with medium or high CRP ($P < 0.05$). Another study found an association between CRP and uncontrolled diabetes in 62 patients, but the study was limited by small a sample size (12).

To provide further insight into the role of inflammation in the development of cardiovascular disease in people with diabetes, we sought to elucidate the link between level of glycemic control and inflammation using a representative national sample. The purpose of the study was to investigate the relation between CRP and HbA_{1c} in adults with diabetes.

RESEARCH DESIGN AND METHODS

— A sample of respondents ≥17 years of age was derived from the National Health and Nutrition Examination Survey III (NHANES III), 1988–1994, a cross-sectional study of a nationally representative sample of noninstitutionalized U.S. residents. Respondents with diabetes were identified using the question, "Has your doctor ever told you that you have diabetes?" Respondents who answered positively to either of two questions regarding having diabetes "confined only to pregnancy" were excluded. Respondents with diabetes were not identified using laboratory data because blood was drawn on only one occasion and because people with diabetes may not have had elevated serum glucose at the time the blood was drawn. The respondents that had a usable sample of serum for analysis for CRP form the basis of this report.

People who had used anti-inflammatory drugs or cholesterol-lowering drugs within the previous 30 days were excluded from the analysis, due to the possible effects the drugs might have on CRP levels (13,14). The use of anti-inflammatory drugs was measured by questions regarding the use of prescription medications along with specific questions about the nonprescription use of aspirin and ibuprofen. Prescribed and over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids were classed as anti-inflammatory medications. The use of cholesterol-lowering drugs was measured by a specific question regarding whether any medication was used for the treatment of elevated cholesterol.

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Abbreviations: CRP, C-reactive protein; NHANES III, National Health and Nutrition Examination Survey III; NSAID, nonsteroidal anti-inflammatory drug.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Dependent variable: C-reactive protein

CRP was measured between 1988 and 1994 on an ongoing basis as part of the NHANES III physical and laboratory examination. Standard phlebotomy techniques were used to obtain specimens. Serum specimens were frozen to –20°C until analyzed for CRP (Behring Nephelometer Analyzer System; Behring Diagnostics, Somerville, NJ). The lower limit of detection was truncated at 0.30 mg/dl due to the limits of the diagnostic technique used. The value of 0.21 mg/dl was assigned to participants with CRP concentrations below the detection limit of 0.3. This lower limit of detection limited statistical analysis of CRP to elevated or nonelevated, because CRP was noncontinuous across the full range. Further details about the specific methods for laboratory procedures in the NHANES III are available elsewhere (15).

CRP level was evaluated as a dichotomous variable (elevated or not elevated). An elevated level of CRP was defined prospectively, using a cutoff (>0.30 mg/dl) based on previous studies of cardiovascular disease and NHANES III data (11,16).

Independent variable: HbA_{1c}

HbA_{1c} was measured in the NHANES III study by the Diabetes Diagnostic Laboratory at the University of Missouri using the Diamat Analyzer System (Bio-Rad Laboratories, Hercules, CA) (17). This ion-exchange high-performance liquid chromatography system measures HbA_{1c} and has demonstrated excellent, long-term precision (interassay correlation value 2.0). It was standardized to the reference method that was used for the Diabetes Control and Complications Trial. Further information regarding the specific methods used is available elsewhere (15).

Control variables

Demographic indicators (age, race, and sex) were included as control variables and categorized as in similar epidemiological studies, because CRP levels are known to vary according to these factors (17). In an effort to determine the independent relation between HbA_{1c} level and CRP, additional variables were included that have been shown to influence the level of CRP, including smoking and BMI (8,9,18). Smoking was coded three ways: current smoker, ex-smoker, and never smoker. BMI was calculated using the weight (in kilograms) divided by height (in meters squared) found in the examination file of the NHANES III and dichotomized at above or below 27 according to risk guidelines of the American Diabetes Association (19). Length of time with diabetes was included as a control variable to account for the greater likelihood of cardiovascular disease (and hence greater likelihood of elevated CRP) with a longer duration of diabetes. Fasting insulin levels were available on participants with diabetes and were included in the regression models as a possible confounding variable. Insulin was measured as a continuous variable in micromoles per milliliter.

Statistical analysis

All analyses were performed using SUDAAN to account for the complex sampling design of the NHANES III. Respondents were stratified into levels of glycemic control according to level of HbA_{1c} in 2% increments (HbA_{1c} <7.0, 7.0–8.9, 9.0–10.9, and >11.0%). We first performed descriptive statistics to compare the demographic characteristics of the HbA_{1c} groups using χ^2 and *t* tests. We then compared the percent of respondents with elevated CRP for each 2% increment of HbA_{1c} using χ^2.

Next, an adjusted model was constructed using elevated CRP as the response and HbA_{1c} (continuous) as the predictor, controlling for the following variables: age, race, sex, smoking, length of time with diabetes, and BMI. Standardized β, *P* values, odds ratios, and 95% CIs were obtained from the logistic regression output. Statistical significance was defined as $P \leq 0.05$.

RESULTS — A total of 1,614 adults answered yes to the question regarding diabetes in the NHANES III database. After excluding 152 for gestational diabetes and 444 who were taking excluded drugs, 1,018 adults with nongestational diabetes had CRP levels available and were included in this analysis. The demographic and general health characteristics of the participants are described overall and according to level of HbA_{1c} in Table 1. Mean percent elevated CRP values also are shown for each HbA_{1c} group.

The percent of participants with elevated CRP was compared at different levels of HbA_{1c}. For each level of HbA_{1c}, the percent of elevated CRP was as follows: <7, 48.9%; 7–8.9, 45.4%; 9–10.9, 60.7%; and ≥11, 70.6%. Overall, 51.5% of participants had elevated CRP. In unadjusted analyses, increasing HbA_{1c} was significantly associated with a higher percent of patients with elevated CRP levels ($P < 0.05$).

Results of adjusted logistic regression analyses using HbA_{1c} as the predictor variable are shown in Table 2. After controlling for demographic variables, smoking, BMI, fasting insulin level, and length of time with diabetes, HbA_{1c} >9% and >11% remained a significant predictor of elevation of CRP (Table 2). We also evaluated HbA_{1c} in the same model using it as a continuous variable. Again we found that HbA_{1c} was a significant predictor of elevated CRP (1.20 OR, 95% CI 1.07–1.34), which means that for every 1.0% increase in HbA_{1c} there was a 20% increase in the likelihood of having an elevated CRP.

CONCLUSIONS — The present study demonstrated that a higher HbA_{1c} is significantly associated with a greater likelihood of higher CRP among adults with diabetes. The relation was significant in unadjusted comparisons of the percent of people with elevated CRP according to HbA_{1c} level and in logistic regression models to predict elevation of CRP after controlling for age, race, sex, smoking, BMI, insulin level, and length of time with diabetes.

Inflammatory markers such as CRP have been related to the development of insulin resistance and type 2 diabetes (6,7,11,20–22). Previous research has also established that CRP levels are higher in people with diabetes (8) and associated with HbA_{1c} in people without diabetes (11). The results of the current study go a step further with the finding that among people with established diabetes, at successively higher levels of HbA_{1c} the percent of people with CRP >0.30 mg/dl is significantly higher. The main implication of these findings is that inflammation may not only be implicated in the development of diabetes, but also in ongoing levels of hyperglycemia once diabetes is established.

Due to the cross-sectional design of the study, we cannot infer from these results a cause and effect relation, i.e., whether poor glycemic control leads to inflammation or whether inflammation leads to higher glucose levels (or whether

Table 1—*Demographic characteristics of adults with diabetes by HbA_{1c} (N = 1,018)*

	HbA_{1c} level				
	Total	<7%	7–8.9%	9–10.9%	≥11.0%	*P**
Age (years)						0.27
17–35	4.7	4.2	2.3	9.1	7.5	
36–50	21.1	20.2	15.7	26.6	35.3	
51–65	34.2	33.1	36.5	33.5	33.3	
66+	40.0	42.5	45.5	30.8	23.9	
Sex						0.30
Male	47.3	46.3	52.8	38.4	51.3	
Female	52.7	53.7	47.2	61.6	48.7	
Race						<0.01
White	74.4	74.1	79.6	70.5	64.6	
Black	14.8	15.1	10.4	16.3	26.6	
Mexican American	5.8	4.7	6.8	6.6	8.2	
Other	5.0	6.1	3.2	6.6	0.6	
Smoking						
Nonsmoker	38.8	44.6	34.1	33.3	36.1	0.38
Ex-smoker	41.0	37.1	46.6	42.8	37.3	
Smoker	20.2	18.3	19.3	23.9	26.6	
BMI (kg/m^2)						0.41
≥27	61.5	66.0	56.9	57.5	62.1	
<27	38.5	34.0	43.1	42.5	37.9	
Elevated CRP (mg/dl)						0.03
≥0.30	51.5	48.9	45.4	60.7	70.6	
<0.30	48.5	51.1	54.7	39.3	29.4	
Diabetes duration (years)						0.30
<5	44.2	45.3	43.1	42.7	46.1	
5–10	20.2	14.7	27.5	20.2	23.3	
>10	35.6	40.0	29.4	37.1	30.6	
Fasting insulin (μmol/ml)	12.3	11.3	25.4	35.6	38.8	<0.01†

*Data are % unless otherwise indicated. χ^2 analysis comparing HbA_{1c} groups; †ANOVA test used to test differences between groups.

a third factor influences both). Prospective studies are needed to evaluate that question. However, either direction of causality would have important implications. If poor glycemic control leads to inflammation, then better glycemic control should lower inflammation and therefore lower the risk of cardiovascular complications. If inflammation leads to poor glycemic control, then treatment of inflammation with NSAIDs or hydroxymethylglutaryl-CoA reductase inhibitors may help improve glycemic control. In light of recent findings of an association among inflammatory proteins, endothelial dysfunction, and insulin resistance (23–25), the results of the current study provide additional support for a relation between glycemic control and systemic inflammation in people with established diabetes.

Recent research evidence supports a link between hyperglycemia and inflammation. CRP is known to be higher in people with impaired glucose tolerance and frank diabetes (8,11). Furthermore, increased CRP has been found to be a risk factor for later development of diabetes (6,20,21). Festa et al. (22) found links between CRP and insulin resistance. Other studies have related hyperglycemia to inflammation by demonstrating simultaneous inflammation, endothelial dysfunction, and insulin resistance at the physiologic level (23,24). One of the several mechanisms proposed is oxidative stress on the endothelium, which promotes inflammation and is enhanced by hyperglycemia (26–28). Such evidence is consistent with the findings in the current study, which further documents the association between hyperglycemia and inflammation in adults with diabetes.

Limitations of this study include the fact that much of the data were by self-report, including the diagnosis of diabetes, use of anti-inflammatory medications, and smoking status. However, self-report questions have shown good agreement with other measures in previous studies and have proved useful (29,30). Furthermore, the CRP measure used is a different and older technique than the highly sensitive CRP assay developed more recently (2,5). However, the method used was also used and validated in the Diabetes Control and Complications Trial (16). In addition, the current study focused on elevated levels rather than the lower levels detectable by newer methods.

A further limitation of this study is that we were unable to control for the use of thiazolidinedione drugs that can affect CRP (31). However, such medications were not in common use at the time of the survey and were not included in the questions in the NHANES III about medication use.

The current study demonstrates that higher HbA_{1c} is significantly associated with elevation of CRP. These results imply a significant relation between inflamma-

Table 2—*Adjusted regression model to predict elevation of CRP (>0.30 mg/dl)*

Factor	Odds ratio	95% CI	β	SE β	*P*
HbA_{1c} (%)					
<7	1.00	1.00–1.00	0.00	0.00	
7–8.9	1.26	0.79–2.00	0.23	0.23	0.32
9–10.9	2.15	1.07–4.32	0.77	0.35	0.03
≥11	4.40	1.87–10.38	1.48	0.43	
Age (years)					
17–35	0.37	0.12–1.19	−0.98	0.58	0.09
36–50	0.64	0.32–1.30	−0.44	0.35	0.21
51–65	0.97	0.60–1.57	−0.03	0.24	0.90
66+	1.00	1.00–1.00	0.00	0.00	
BMI (kg/m^2)					
≥27	2.17	1.40–3.36	0.22	3.56	
<27	1.00	1.00–1.00	0.00	0.00	
Sex					
Male	1.00	1.00–1.00	0.00	0.00	
Female	2.04	1.25–3.34	0.71	0.24	0.01
Smoking					
Nonsmoker	1.00	1.00–1.00	0.00	0.00	
Ex-smoker	0.98	0.55–1.74	−0.02	0.29	0.94
Smoker	1.29	0.66–2.56	0.26	0.34	0.45
Race					
Non-Hispanic white	1.00	1.00–1.00	0.00	0.00	
Non-Hispanic black	1.43	0.90–2.28	0.36	0.23	0.12
Mexican American	1.20	0.74–1.95	0.19	0.24	0.44
Other	1.78	0.60–5.26	0.58	0.54	0.29
Diabetes duration (years)					
≤5	1.00	1.00–1.00	0.00	0.00	
6–10	0.58	0.34–1.00	−0.54	0.27	0.05
>10	0.71	0.40–1.24	−0.35	0.28	0.22
Insulin	1.01	1.00–1.02	0.01	0.01	0.25

tion and glycemic control in people with established diabetes. Prospective studies should be conducted to determine the direction of this association; such research would have important implications for the treatment of adults with diabetes.

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References

1. Abdelmouttaleb I, Danchin N, Ilardo C, Aimone-Gastin I, Angioi M, Lozniewski A, Loubinoux J, Le Faou A, Gueant JL: C-reactive protein and coronary artery disease: additional evidence of the implication of an inflammatory process in acute coronary syndromes. *Am Heart J* 137: 346–351, 1999
2. Ridker PM, Rifai N, Lowenthal SP: Rapid reduction of C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. *Circulation* 103:1191–1193, 2001
3. Ridker PM, Glynn RJ, Hennekens CH: C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 97:2007–2011, 1998
4. Kervinen H, Palosuo T, Manninen V, Tenkanen L, Vaarala O, Manttari M: Joint effects of C-reactive protein and other risk factors on acute coronary events. *Am Heart J* 141:580–585, 2001
5. Ridker PM, Stampfer MJ, Rifai N: Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA* 285:2481–2485, 2001
6. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin-6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327–334, 2001
7. Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, Tracy RP: The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. *Diabetes* 50:2384–2389, 2001
8. Ford ES: Body mass index, diabetes, and C-reactive protein among U.S. Adults. *Diabetes Care* 22:1971–1977, 1999
9. Grau AJ, Buggle F, Becher H, Werle E, Hacke W: The association of leukocyte count, fibrinogen and C-reactive protein with vascular risk factors and ischemic vascular diseases. *Thromb Res* 82:245–255, 1996
10. Goldberg RB: Cardiovascular disease in diabetic patients. *Med Clin North Am* 84: 81–93, 2000
11. Wu T, Dorn JP, Donahue RP, Sempos CT, Trevisan M: Associations of serum C-reactive protein with fasting insulin, glucose, and glycosylated hemoglobin. *Am J Epidemiol* 155:65–71, 2002
12. Rodriguez-Moran M, Guerrero-Romero F: Increased levels of C-reactive protein in

noncontrolled type II diabetic subjects. *J Diabetes Complications* 13:211–215, 1999
13. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald: Long-term effects of pravastatin on plasma concentration of c-reactive protein. *Circulation* 100:230–235, 1999
14. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 336:973–979, 1997
15. Gunter EW, Lewis BG, Koncikowski SM: *Laboratory Procedures Used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994*. Atlanta, GA, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Environmental Health, 1996
16. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 347: 1557–1565, 2002
17. Wener MH, Daum PR, McQuillan GM: The influence of age, sex, and race on the upper reference limit of serum C-reactive protein concentration. *J Rheumatol* 27: 2351–2359, 2000
18. Tracy RP, Psaty BM, Macy E, Bovill EG, Cushman M, Cornell ES, Kuller LH: Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arterioscler Thromb Vasc Biol* 17: 2167–2176, 1997
19. American Diabetes Association: Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 25 (Suppl. 1):S33–S49, 2002
20. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, Offenbacher S, Azambuja MI, Tracy RP, Heiss G: Markers of inflammation and prediction of diabetes mellitus in adults (atherosclerosis risk in communities study): a cohort study. *Lancet* 353:1649–1652, 1999
21. Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM: Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 102:42–47, 2000
22. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM: Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the Insulin Resistance Atherosclerosis Study. *Diabetes* 51:1131–1137, 2002
23. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW: C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 19:972–978, 1999
24. Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S, Zeiher AM: Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. *Circulation* 102:1000–1006, 2000
25. Fröhlich M, Imhof A, Berg G, Hutchinson WL, Pepys MB, Boeing H, Muche R, Brenner H, Koenig W: Association between C-reactive protein and features of the metabolic syndrome: A population-based study. *Diabetes Care* 23:1835–1839, 2000
26. Mohanty P, Hamouda W, Garg R, Aljada A, Ghanim H, Dandona P: Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. *J Clin Endocrinol Metab* 85:2970–2973, 2000
27. Mohanty P, Ghanim H, Hamouda W, Aljada A, Garg R, Dandona P: Both lipid and protein intakes stimulate increased generation of reactive oxygen species by polymorphonuclear leukocytes and mononuclear cells. *Am J Clin Nutr* 75: 767–772, 2002
28. Dandona P, Aljada A: A rational approach to pathogenesis and treatment of type 2 diabetes mellitus, insulin resistance, inflammation, and atherosclerosis. *Am J Cardiol* 90 (Suppl. 5A):27G–33G, 2001
29. Wei M, Gaskill SP, Haffner SM, Stern MP: Effects of diabetes and level of glycemia on all-cause mortality: the San Antonio Heart Study. *Diabetes Care* 21:1167–1172, 1998
30. Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS 23). *BMJ* 316:823–828, 1998
31. Chu NV, Kong APS, Kim DD, Armstrong D, Baxi S, Deutsch R, Caulfield M, Mudaliar SR, Reitz R, Henry RR, Reaven PD: Differential effects of metformin and troglitazone on cardiovascular risk factors in patients with type 2 diabetes. *Diabetes Care* 25:542–549, 2002