Cardiovascular Disease in U.S. Patients With Metabolic Syndrome, Diabetes, and Elevated C-Reactive Protein

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OBJECTIVE — C-reactive protein (CRP) independently predicts cardiovascular disease (CVD); whether it can stratify risk in those with metabolic syndrome and diabetes is not well documented. We evaluated whether elevated CRP levels modify the relationship of metabolic syndrome and diabetes with CVD in U.S. adults.

RESEARCH DESIGN AND METHODS — In a cross-sectional study of 3,873 subjects (weighted to 156 million) aged ≥18 years participating in the National Health and Nutrition Examination Survey 1999–2000, subjects were classified as having diabetes, metabolic syndrome according to modified National Cholesterol Education Program criteria, or neither condition by low (<1 mg/l), intermediate (1–3 mg/l), or high (>3 mg/l) CRP levels. Logistic regression examined the odds of CVD by disease condition and CRP group.

RESULTS — After adjusting for age, sex, smoking, and total cholesterol, compared with those with neither metabolic syndrome nor diabetes and low CRP levels, the odds of CVD were 1.99 (95% CI 1.10–3.59) for those with no disease and high CRP levels and 2.67 (1.30–5.48) for those with metabolic syndrome and intermediate CRP. Persons with metabolic syndrome but high CRP had an odds ratio (OR) of 3.33 (1.80–6.16), similar to those with diabetes and low CRP (3.21 [1.27–8.09]). The likelihood of CVD was highest in those with diabetes who had intermediate CRP levels (6.01 [2.54–14.20]) and in those with diabetes and high CRP (7.73 [3.99–14.95]).

CONCLUSIONS — In this cross-sectional analysis, CVD is more common in those with metabolic syndrome or diabetes who have elevated CRP. Stratification by CRP may add prognostic information in patients with metabolic syndrome or diabetes.

Diabetes Care **28:690–693, 2005**

It is well known that C-reactive protein (CRP), a sensitive circulating marker of inflammation, is independently associated with increased risk of cardiovascular disease (CVD) (1–5), with inflammation having a key role in the pathophysiology of atherosclerosis (6,7). Inflammation is also associated with metabolic syndrome and diabetes (8,9). Additionally, CRP is associated with insulin resistance (10,11). A recent statement from the Centers for Disease Control and Prevention and the American Heart Association considered the measurement of CRP for assessing the risk of CVD (12). We examined the relationship of preexisting CVD with metabolic syndrome and diabetes stratified by CRP levels in a population-representative sample of U.S. adults and whether CRP levels would help to further stratify the likelihood of CVD in patients with diabetes or metabolic syndrome.

RESEARCH DESIGN AND METHODS

In a cross-sectional study, we utilized data on 3,873 subjects (weighted to a U.S. population of 156 million) aged ≥18 years who were participants of the National Health and Nutrition Examination Survey (NHANES) 1999–2000, a multistage probability sample design survey. The study was approved by the institutional review board of the University of California, Irvine (IRB no. 2003-2884).

Serum triglyceride levels were measured enzymatically after hydrolyzation to glycerol on a Hitachi 704 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). HDL cholesterol was measured after the precipitation of other lipoproteins with a heparin-manganese chloride mixture on a Hitachi 704 analyzer. Plasma glucose concentration was measured using an enzymatic reaction (Cobas Mira Chemistry System; Roche Diagnostic Systems, Montclair, NJ). High-sensitivity CRP was analyzed by latex-enhanced nephelometry. These assays are performed on a Behring Nephelometer for quantitative CRP determination. The lowest detection limit of 0.1 mg/l allowed for three categories of CRP levels, which reflect the Centers for Disease Control/American Heart Association cut points of low CRP (<1 mg/l), intermediate CRP (1–3 mg/l), or high CRP (>3 mg/l) (12).

Assessment of metabolic syndrome, diabetes, and CVD

Metabolic syndrome was defined by modified National Cholesterol Education Program criteria (13) if three or more of the following were present: *1*) waist circumference >102 cm for men and >88 cm for women, *2*) triglyceride level ≥1.69 mmol/l (150 mg/dl) if fasting, *3*) HDL level <1.04 mmol/l (40 mg/dl) if male or

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Received for publication 5 October 2004 and accepted in revised form 21 November 2004.

N.D.W. has received grant/research support from Bristol-Myers Squibb.

Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey.

Table 1—*Baseline characteristics by disease condition*

	Total	Neither metabolic syndrome nor diabetes	Metabolic syndrome	Diabetes
Overall population (*n*)	3,873	2,704	704	465
Prevalent cardiovascular disease (%)	361 (9.3)	141 (5.2)	96 (13.6)	124 (26.7)
Baseline characteristics				
Male (%)	49.0	50.4	42.3*	52.0*†
Age (years)	44.1	40.8	51.1‡	58.2‡§
Waist circumference (cm)	94.3	89.3	108.1‡	108.7‡
Total serum cholesterol (mg/dl)	201.5	197.8	212.7‡	209.9‡‖
HDL cholesterol (mg/dl)	50.9	54.4	40.0‡	44.3‡†
LDL cholesterol (mg/dl)	124.5	123.6	129.0‡	122.0†‡
Triglycerides (mg/dl)	134.0	104.6	213.8‡	220.4†‡
Blood glucose (mg/dl)	100.1	92.6	100.3‡	174.6‡§
Current smoker	26.0%	27.3%	23.5%*	19.9%*
Systolic blood pressure (mmHg)	122.5	118.4	133.8‡	133.7‡
Diastolic blood pressure (mmHg)	72.4	71.3	77.4‡	71.2‡§
CRP (mg/l)	4.11	3.36	5.97‡	6.77†‡

*$P < 0.05$ compared with neither metabolic syndrome nor diabetes; †$P < 0.01$ comparing metabolic syndrome with diabetes; ‡$P < 0.0001$ compared with neither metabolic syndrome nor diabetes; §$P < 0.0001$ comparing metabolic syndrome with diabetes; ‖$P < 0.05$ comparing metabolic syndrome with diabetes.

<1.29 mmol/l (50 mg/dl) if female, *4*) blood pressure ≥130/85 mmHg or taking hypertension medication, and *5*) fasting glucose level ≥6.1 mmol/l (110 mg/dl) and <6.99 mmol/l (126 mg/dl). Those with a fasting glucose level of ≥6.99 mmol/l (126 mg/dl), with a nonfasting glucose level of ≥11.1 mmol/l (200 mg/dl), taking oral hypoglycemic medication or insulin, or with self-reported diabetes were considered to have diabetes. Those fitting the criteria for diabetes were analyzed as a separate group from those with metabolic syndrome (but who did not have diabetes). Because of missing data on risk factors, we classified persons as having neither diabetes nor metabolic syndrome if we could confirm the absence of three metabolic syndrome risk factors. Those reporting a prior myocardial infarction, stroke, or heart failure were classified as having CVD.

Statistical analyses

The χ^2 test of proportions, weighted to the U.S. population using NHANES 1999–2000 sample weights, was used to compare the prevalence of the individual baseline characteristics across clinical conditions. Multivariable logistic regressions, weighted to the U.S. population, were performed to examine the odds of CVD in those with metabolic syndrome or diabetes compared with those free of these conditions, stratified by the CRP levels as defined above. Analyses, completed using the SUDAAN PROC RLOGIST procedure (providing odds ratios [ORs] and 95% CIs), were adjusted for age, sex, total cholesterol, and cigarette smoking (risk factors not comprising the definition for metabolic syndrome). As a result, subjects were categorized into nine groups: *1*) no metabolic syndrome/diabetes and low CRP (referent), *2*) no metabolic syndrome/diabetes and intermediate CRP, *3*) no metabolic syndrome/diabetes and high CRP, *4*) metabolic syndrome and low CRP, *5*) metabolic syndrome and intermediate CRP, *6*) metabolic syndrome and high CRP, *7*) diabetes and low CRP, *8*) diabetes and intermediate CRP, and *9*) diabetes and high CRP. In a separate model, we examined the association of CRP with CVD, controlling for age, sex, total cholesterol, cigarette smoking, metabolic syndrome, and diabetes as covariates. Statistical procedures were done using SAS version 8.1 (SAS Institute, Cary, NC), and procedures using sample weights for projection to the U.S. population distribution utilized SUDAAN version 8.0.2 (Research Triangle Institute, Research Triangle Park, NC).

RESULTS

Baseline characteristics

There were significant differences between disease groups in mean age, waist circumference, total cholesterol, HDL, LDL, triglycerides, blood glucose, blood pressure, CRP, and smoking (Table 1). Mean systolic and diastolic blood pressure, total cholesterol, and LDL were highest and HDL was lowest in those with metabolic syndrome compared with those with neither metabolic syndrome nor diabetes ($P < 0.001$). The remaining metabolic risk factors were highest in those with diabetes compared with those with neither metabolic syndrome nor diabetes ($P < 0.001$). In addition, those with diabetes had higher triglycerides ($P < 0.01$), blood glucose ($P < 0.001$), and CRP ($P < 0.01$) than those with metabolic syndrome and had lower total cholesterol ($P < 0.05$), HDL ($P < 0.01$), LDL ($P < 0.001$), and diastolic blood pressure ($P < 0.001$) compared with those with metabolic syndrome.

Multivariable model for odds of CVD in relation to disease category and CRP group

Adjusting for age, sex, smoking, and total cholesterol and CRP groups separately, increased odds of CVD were seen in those with metabolic syndrome (OR 1.78 [95% CI 1.20–2.64]) and in those with diabetes (3.85 [2.51–5.88]), compared with those with neither condition. Those with high CRP levels (>3 mg/l) had increased odds of CVD (1.46 [1.05–2.04]) compared with those with lower CRP levels (Table 2).

Risk of CVD for those with metabolic syndrome and diabetes, stratified by CRP

From multiple logistic regression, the adjusted OR for CVD for those with no disease and high CRP levels was 1.99 (95% CI 1.10–3.59; $P < 0.05$) compared with those with neither metabolic syndrome nor diabetes and low CRP levels (reference group) (Fig. 1). For individuals with metabolic syndrome and intermediate CRP, the likelihood of CVD was increased slightly (OR 2.67 [1.30–5.48]; $P < 0.05$). However, individuals with metabolic syndrome but high CRP had a greater OR (3.33 [1.80–6.16]; $P < 0.0001$), a magnitude similar to those with diabetes and low CRP (3.21 [1.27–8.09]; $P < 0.05$). Those with intermediate or high CRP levels and diabetes had the highest likelihood of CVD: 6.01 (2.54–14.20) and 7.73 (3.99–14.95), respectively (both $P < 0.001$). When we examined whether there were significant

Table 2—*Likelihood of cardiovascular disease by metabolic syndrome, diabetes, and CRP level*

	OR	95% CI	*P*
Age	1.07	1.06–1.08	<0.001
Female sex	0.57	0.41–0.80	<0.001
Smoking	1.22	0.81–1.83	0.34
Total cholesterol	0.99	0.99–1.00	0.02
Condition			
No disease	1.0		
Metabolic syndrome	1.71	1.15–2.55	0.01
Diabetes	3.77	2.47–5.75	<0.001
CRP			
Low (<1 mg/l)	1.0		
Intermediate (1–3 mg/l)	1.58	0.96–2.58	0.07
High (> 3 mg/l)	1.99	1.26–3.15	<0.001

Data are adjusted for age, sex, smoking, and total cholesterol.

differences between sex in the odds of CVD by disease/CRP groups, an interaction term of disease/CRP categories with sex was included in the logistic regression, indicating no significant difference in the associations with CVD among men and women (P = 0.78 for interaction term).

CONCLUSIONS — We demonstrate that CRP levels may help to stratify odds of CVD in those in the U.S. population with metabolic syndrome or diabetes. In our large cross-sectional analysis, stratification by CRP showed that individuals with either metabolic syndrome or diabetes are more likely to have CVD if their CRP level is high. Those with neither metabolic syndrome nor diabetes but high CRP have a likelihood of CVD similar to that in those with metabolic syndrome who have intermediate CRP levels; those with metabolic syndrome and high CRP have a likelihood of CVD similar to that in those with diabetes and low CRP. Moreover, those with diabetes and high CRP are seven times more likely to have CVD than those with neither metabolic syndrome nor diabetes but low CRP. Although diabetes is defined as a coronary heart disease risk equivalent and warrants aggressive treatment (13,14), individuals with metabolic syndrome (but without diabetes) have a wide spectrum of risk (15). Our results demonstrate that those with metabolic syndrome and high CRP levels have at least as high a likelihood of CVD as those with diabetes and low CRP. Our report is unique in examining the relation of metabolic syndrome (without diabetes) and diabetes separately, stratified by CRP levels and in relation to CVD prevalence.

Our cross-sectional results in the U.S. population support findings from Rutter et al. (16), who recently demonstrated in the Framingham Heart Study that both CRP and metabolic syndrome (inclusive of diabetes) are independent predictors of new CVD events. Also, Ridker et al. (9) prospectively studied 14,710 women, showing those with CRP >3 mg/l without metabolic syndrome had nearly as great a CVD event incidence as those with the metabolic syndrome and CRP levels ≤3 mg/l and that those with metabolic syndrome who had CRP >3 mg/l had the worst prognosis. Further, Sattar et al. (17) reported that middle-aged men enrolled in the West of Scotland Coronary Prevention Study with metabolic syndrome and CRP <3 mg/l had risks of future coronary heart disease events identical to those with no metabolic syndrome and CRP >3 mg/l, similar to our findings in these groups. The increased risk of coronary heart disease in those with metabolic syndrome and CRP >3 mg/l was also similar to findings for this group. Our study provides additional data on the clinical significance of elevated CRP levels in the presence of metabolic syndrome (exclusive of those with diabetes) compared with diabetes in relation to CVD, demonstrating that the former have a likelihood of CVD similar to that with those with diabetes who have normal CRP levels. These findings support a recent review suggesting the addition of CRP as a criterion for the diagnosis of metabolic syndrome (18).

A strength of our study is our U.S. population sample, allowing generalization to the U.S. population. A limitation is the cross-sectional design, allowing us to only make projections to the odds of prevalent CVD. We cannot test whether CVD is the cause, rather than the consequence, of high CRP levels. Finally, it is possible that some of the increased risk seen in those with elevated CRP may be

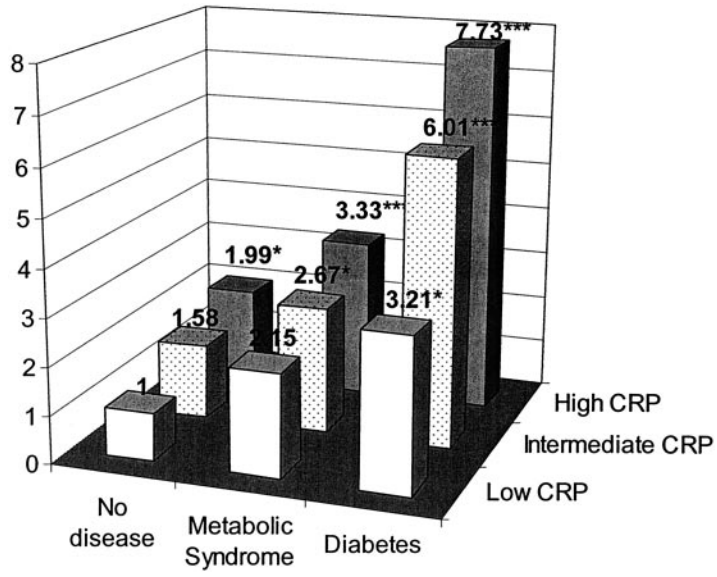

Figure 1—*Odds of CVD in those with metabolic syndrome or diabetes, stratified by CRP. Levels (low [<1 mg/l], intermediate [1–3 mg/l], and high [>3 mg/l]) from NHANES 1999–2000 data. *P < 0.05, ***P < 0.001.*

mediated by increased levels of abdominal obesity or possibly differences in lipids or blood pressure. However, when we examined whether these factors differed within disease condition groups by CRP levels we found no consistent relationships, although waist circumference was higher in those with high versus low CRP who had metabolic syndrome, and in those with high CRP and diabetes. To test whether this could have partially explained the increased odds in these groups, we adjusted additionally for waist circumference in a separate logistic regression. This actually resulted in similar or higher odds of CVD for intermediate and high CRP groups, except for those with diabetes/intermediate CRP in whom the OR is reduced to 3.32 but remains significant ($P < 0.001$), indicating that our findings were not confounded by differences in abdominal obesity.

The Centers for Disease Control and Prevention and American Heart Association recently noted that screening of CRP levels may be appropriate among persons at intermediate risk for CVD (12). Our data lend support to the screening of CRP levels in persons with metabolic syndrome, many of whom are at intermediate risk; identification of those with elevated CRP levels may help identify a higher-risk subset of persons with metabolic syndrome who may warrant more intensified risk factor intervention as aggressive as that for those with diabetes (e.g., LDL goals of <100 mg/dl and blood pressure goals of <130/80 mmHg). However, clinical trials would be needed in these individuals to document whether there would be actual incremental benefit in prevention of CVD events from treatment to these lower levels.

Acknowledgments— This study was supported in part by a research grant from the Bristol-Myers Squibb Pharmaceutical Research Institute and was presented in part at the American College of Cardiology Scientific Sessions, New Orleans, LA, March 2004.

References

1. 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
2. Kuller LH, Tracy RP, Shaten J, Meilahn EN: Relation of C-reactive protein and coronary heart disease in the MRFIT nested case control study. *Am J Epidemiol* 144:537–547, 1996
3. Folsom AR, Aleksic N, Catellier D, Juneja HS, Wu KK: C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 144:233–238, 2002
4. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH: Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 98:731–733, 1998
5. Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, Hutchinson WL, Pepys MB: C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 99:237–242, 1999
6. Ridker PM: The pathogenesis of atherosclerosis and acute thrombosis: relevance to strategies of cardiovascular disease prevention. In *Prevention of Myocardial Infarction*. Manson JE, Ridker PM, Gaziano JM, Hennekens CH, Eds. New York, Oxford University Press, 1996, p. 32–54
7. Ridker PM: Inflammation, infection, and cardiovascular risk: how good is the clinical evidence? *Circulation* 97:1671–1674, 1998
8. Ford ES: The metabolic syndrome and C-reactive protein, fibrinogen, and leukocyte count: findings from the Third National Health and Nutrition Examination Survey. *Atherosclerosis* 168:351–358, 2003
9. Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events. *Circulation* 107:391–397, 2003
10. McLaughlin T, Abbasi F, Lamendola C, Liang L, Reaven G, Schaaf P, Reaven P: Differentiation between obesity and insulin resistance in the association with C-reactive protein. *Circulation* 106:2908–2912, 2002
11. Hak AE, Stehouwer CD, Bots ML, Polderman KH, Schalkwijk CG, Westendorp IC, Hofman A, Witteman JC: Associations of C-reactive protein with measures of obesity, insulin resistance and subclinical atherosclerosis in healthy, middle-aged women. *Arterioscler Thromb Vasc Biol* 19:1986–1991, 1999
12. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F, Centers for Disease Control and Prevention, American Heart Association: Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 107:499–511, 2003
13. The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
14. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
15. Wong ND, Pio JR, Franklin SS, L'Italien GJ, Kamath TV, Williams GR: Preventing coronary events by optimal control of blood pressure and lipids in patients with the metabolic syndrome. *Am J Cardiol* 91:1421–1426, 2003
16. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW: C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation* 110:380–385, 2004
17. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 108:414–419, 2003
18. Ridker PM, Wilson P, Grundy SM: Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation* 109:2818–2825, 2004