C-Reactive Protein Is an Independent Predictor of Risk for the Development of Diabetes in the West of Scotland Coronary Prevention Study

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Accumulating evidence implicates inflammation as a potential pathway in the pathogenesis of type 2 diabetes. The objective of the present study was to assess the ability of C-reactive protein (CRP) to predict the development of diabetes in middle-aged men in the West of Scotland Coronary Prevention Study. Baseline plasma samples for CRP measurement were available for 5,245 men of whom 127 were classified as having a transition from normal glucose control to overt diabetes during the study, based on American Diabetes Association criteria. Baseline CRP was an important predictor of the development of diabetes in univariate analysis (hazard ratio [HR] for an increase of 1 SD = 1.55; 95% CI 1.32–1.82; $P < 0.0001$). In multivariate analysis, CRP remained a predictor of diabetes development (HR 1.30; 95% CI 1.07–1.58; $P = 0.0075$) independent of other clinically employed predictors, including baseline BMI and fasting triglyceride and glucose concentrations. Moreover, there was a graded increase in risk across CRP quintiles throughout the study, evident at even 1 year of follow-up. The highest quintile (CRP >4.18 mg/l) was associated with a greater than threefold risk of developing diabetes (HR 3.07; 95% CI 1.33–7.10) in a multivariate analysis at 5 years. Thus, CRP predicts the development of type 2 diabetes in middle-aged men independently of established risk factors. Because CRP, the most commonly used acute-phase protein in clinical practice, is very stable in serum, our observations have clinical potential in helping to better predict individuals destined to develop type 2 diabetes. They also add to the notion that low-grade inflammation is important in the pathogenesis of type 2 diabetes. *Diabetes* 51: 1596–1600, 2002

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ADA, American Diabetes Association; CRP, C-reactive protein; HR, hazard ratio; WCC, white cell count; WOSCOPS, West of Scotland Coronary Prevention Study.

C-reactive protein (CRP) is the prototypical, and most commonly used, acute-phase reactant marker of inflammation in the body. Increases in CRP concentration (even when within the clinically normal range) and of other inflammatory markers are independently predictive of future cardiovascular events (1,2). Cross-sectional studies have shown that elevated CRP levels correlate significantly with features of the metabolic (insulin resistance) syndrome, including indexes of adiposity, hyperinsulinemia and insulin sensitivity index, hypertriglyceridemia, and low HDL cholesterol (3–5).

Recently, data from the Women's Health Study identified elevated levels of CRP as a predictor of the development of diabetes in women (6), independent of BMI and insulin, although other established predictors such as fasting lipids and blood pressure were not considered. This finding is consistent with other studies (7,8) showing that other markers of inflammation (white cell count [WCC], serum albumin, and serum amyloid A) predict the development of diabetes.

The objective of the present study was to assess the ability of baseline serum CRP concentration to predict the development of type 2 diabetes in men, in conjunction with other established predictors such as plasma triglyceride, during the 5-year follow-up period of the West of Scotland Coronary Prevention Study (WOSCOPS).

RESEARCH DESIGN AND METHODS

Subjects. All subjects studied were participants in WOSCOPS; their characteristics are summarized in detail elsewhere (9,10). Our definition of transition to diabetes in WOSCOPS, based on the American Diabetes Association (ADA) definition of diabetes, which requires a fasting blood glucose level of ≥7.0 mmol/l, has been described in detail previously (7). This definition previously identified 139 individuals who developed diabetes during WOSCOPS from a total of 5,974 included in the analysis. For the present analysis of inflammatory markers, baseline plasma samples were available for only 5,245 of these individuals, of whom 127 developed diabetes. Baseline characteristics and their association with the risk of diabetes are similar in this subgroup and in the 5,974 subjects (7).

Laboratory methods. CRP was measured using a high-sensitivity, two-site enzyme-linked immunoassay (2). Measurement of other parameters has been described previously (7).

Statistical methods. Data are summarized as means ± SD for continuous variables and number of subjects (%) for categorical variables. Cox proportional hazards models, both univariate and multivariate, were fitted to identify predictors of transition to diabetes (11). Subjects' time to becoming diabetic was taken as the semiannual visit at which they first had at least two

TABLE 1
Baseline characteristics

	Diabetic subjects	Nondiabetic subjects
n	127	5,118
Age (years)	55.6 ± 5.7	55.3 ± 5.5
BMI (kg/m^2)	27.8 ± 3.7	25.9 ± 3.1
Alcohol (units/week)	11 ± 15	11 ± 13
Smoking (Y/N)	58 (46)	2,222 (43)
Pravastatin therapy	52 (41)	2,579 (50)
Systolic blood pressure (mmHg)	138 ± 17	135 ± 17
Diastolic blood pressure (mmHg)	85 ± 10	84 ± 10
Hypertension (Y/N)	34 (27)	793 (15)
Ln(triglyceride) [ln(mmol/l)]	0.78 ± 0.39	0.51 ± 0.40
Total cholesterol (mmol/l)	7.18 ± 0.61	7.02 ± 0.58
HDL cholesterol (mmol/l)	1.04 ± 0.20	1.14 ± 0.24
Total cholesterol–to–HDL cholesterol ratio	7.15 ± 1.48	6.41 ± 1.36
Glucose (mmol/l)	5.48 ± 0.70	4.69 ± 0.49
Ln(WCC) [ln(10^9 cells/l)]	1.94 ± 0.26	1.84 ± 0.27
Ln(sensitive CRP) [ln(mg/l)]	1.05 ± 0.90	0.53 ± 1.08

Data for continuous measurements are means ± SD, and for categorical measurements, *n* (%). Baseline characteristics of subjects who had at least two post-randomization measurements of glucose, were not self-reported diabetic patients at baseline and did not have a fasting glucose at baseline ≥7.0 mmol/l, and had baseline plasma available for CRP measurements. Ln, natural logarithm.

postrandomization glucose measurements ≥7.0 mmol/l and at least one postrandomization glucose measurement >2.0 mmol/l above baseline glucose, or the postrandomization visit at which they first indicated taking hypoglycemic drugs. Because of nonattendance at visits or end of study (with varying length of follow-up), subjects' time to becoming diabetic was censored at the last semiannual visit at which their glucose was measured. Lifestyle, lipids, and other coronary heart disease risk factors at baseline were considered. The multivariate model contained all the covariates, regardless of statistical significance, to allow the effect of each covariate in the presence of all other, possibly confounding, covariates to be assessed. Plasma triglyceride, sensitive CRP, and WCC were log transformed, and glucose was modeled after transformation into quintiles. Additionally, log sensitive CRP was modeled after transformation into quintiles for further multivariate and Kaplan-Meier analysis. Quintile limits were based on the distribution in those who did not develop diabetes.

RESULTS

Study subjects. In the WOSCOPS cohort, 5,974 participants had at least two postrandomization blood glucose measurements and were neither self-reported diabetic patients nor had elevated fasting blood glucose (≥7.0 mmol/l) at baseline. Of these, plasma samples for CRP measurement were available for 5,245 (87.8%), who make up the subjects of this study. During the follow-up period, 127 of the 5,245 subjects developed diabetes. The baseline characteristics of these men and those who did not develop diabetes are shown in Table 1.

Univariate predictors of diabetes. As shown in Table 2, BMI, HDL cholesterol, natural log triglyceride, total cholesterol, natural log WCC, baseline glucose, systolic blood pressure, and pravastatin therapy were all univariate predictors of the development of diabetes. Age, alcohol intake, and smoking status were not significant predictors. Baseline CRP was a strong significant predictor of the development of diabetes (hazard ratio [HR] 1.55; 95% CI 1.32–1.82; $P < 0.0001$). When baseline CRP levels were divided into quintiles, HRs increased continuously across the quintiles, with a greater than sixfold risk in the highest CRP quintile (HR 6.13; 95% CI 2.76–13.60) relative to the lowest quintile (Table 3).

Multivariate predictors of diabetes. In the multivariate Cox model, baseline BMI, natural log triglyceride, and baseline glucose remained significant predictors, but systolic blood pressure, total cholesterol, HDL cholesterol, and natural log WCC were no longer statistically significant (Table 2). Pravastatin treatment shows the same risk reduction as previously reported (HR 0.72) (7) but, probably because there are fewer cases, just fails to reach significance at the $P = 0.05$ level in the present analysis.

TABLE 2
Univariate and multivariate analysis

	~1 SD change	Univariate hazard ratio (95% CI)	*P*	Multivariate hazard ratio (95% CI)	*P*
Age	5 years	1.03 (0.88–1.21)	0.68	1.00 (0.84–1.19)	1.00
BMI	3 kg/m^2	1.64 (1.43–1.88)	<0.0001	1.28 (1.10–1.49)	0.0012
Ln(WCC)	0.25 ln(10^9 cells/l)	1.41 (1.20–1.65)	<0.0001	1.14 (0.94–1.38)	0.19
Systolic blood pressure	20 mmHg	1.22 (1.00–1.48)	0.05	1.02 (0.83–1.25)	0.86
Ln(triglyceride)	0.5 ln(mmol/l)	2.25 (1.81–2.79)	<0.0001	1.42 (1.03–1.96)	0.031
Total cholesterol	0.5 mmol/l	1.26 (1.10–1.45)	0.0008	1.04 (0.87–1.24)	0.69
HDL cholesterol	0.25 mmol/l	0.60 (0.49–0.75)	<0.0001	0.84 (0.64–1.09)	0.18
Alcohol	10 units/week	1.02 (0.89–1.16)	0.83	0.95 (0.82–1.10)	0.48
Smoking	Y/N	1.13 (0.80–1.60)	0.5	0.95 (0.66–1.49)	0.97
Pravastatin therapy		0.70 (0.49–0.99)	0.045	0.72 (0.50–1.03)	0.070
Ln(CRP)	1 ln(mg/l)	1.55 (1.32–1.82)	<0.0001	1.30 (1.07–1.58)	0.0075
Glucose	mmol/l				
Quintile I: <4.3		Referent level		Referent level	
Quintile II: >4.3 to 4.5		0.98 (0.35–2.75)		0.90 (0.32–2.54)	
Quintile III: >4.5 to 4.7		0.42 (0.11–1.85)	<0.0001*	0.38 (0.10–1.42)	<0.0001*
Quintile IV: >4.7 to 5.0		1.53 (0.85–3.58)		1.31 (0.56–3.08)	
Quintile V: >5.0		11.9 (6.0–23.7)		8.78 (4.37–17.6)	

Univariate and multivariate hazard ratios with *P* values and approximate 95% CIs for baseline predictors of development of diabetes. The given hazard ratio for continuous covariates is for an approximate 1 SD change; for example, for log(triglyceride) the hazard ratio is for a 0.5 unit change in the logarithm of triglyceride (with triglyceride measured in millimoles per liter). For categorical variates, the hazard ratio is with or without the stated attribute, e.g., smoker or nonsmoker. Ln, natural logarithm. *P for the χ^2 test on four degrees of freedom for the equality of the five quintiles.

TABLE 3
Univariate and multivariate analysis of CRP quintiles

	Univariate	Multivariate	Multivariate*
P†	<0.0001	0.041	0.045
CRP (antilog) (mg/l)			
Quintile I: ≤0.66	Referent level	Referent level	Referent level
Quintile II: >0.66 to ≤1.28	2.30 (0.94–5.58)	1.76 (0.72–4.30)	1.35 (0.62–2.94)
Quintile III: >1.28 to ≤2.27	3.60 (1.56–8.28)	2.35 (1.01–5.46)	2.01 (0.98–4.13)
Quintile IV: >2.27 to ≤4.18	4.64 (2.05–10.5)	2.75 (1.19–6.36)	2.27 (1.11–4.64)
Quintile V: >4.18	6.13 (2.76–13.6)	3.07 (1.33–7.10)	2.46 (1.20–5.04)

Data are hazard ratios (95% CIs). Univariate and multivariate hazard ratios with P values and approximate 95% CIs for CRP quintiles as a predictor of development of diabetes. Multivariate analysis included all the covariates regardless of statistical significance on univariate analysis. *Analysis using definition of diabetes as two fasting blood glucose measurements ≥7.0 mmol/l; †P for the χ^2 test on four degrees of freedom for the equality of the five quintiles.

The natural log CRP level remained a significant predictor, with a multivariate HR of 1.30 (95% CI 1.07–1.58; P = 0.0075) (Table 2). When CRP quintiles were studied in a multivariate analysis (Table 3), there was a stepwise increase in risk across the quintiles, with the highest quintile associated with a greater than threefold risk of developing diabetes (HR 3.07; 95% CI 1.33–7.10) relative to the lowest. A Kaplan-Meier plot of time to development of diabetes in each CRP quintile confirms a graded risk across the quintiles (Fig. 1).

In common clinical practice, diabetes is diagnosed based on the findings of two fasting blood glucose measurements ≥7.0 mmol/l, and there is no requirement for a 2.0 mmol/l rise from baseline glucose measurements, since such results are often not available. To assess the applicability of our findings to the clinical setting, therefore, we reanalyzed our data using the sole criterion of two fasting blood glucose measurements ≥7.0 mmol/l as a definition for becoming diabetic; exclusions were as for the previous analysis. With this new definition of diabetes, an additional 24 men were identified as developing diabetes during the course of the study, giving a total of 151 cases. With this expanded number of cases, the quintiles of CRP in the nondiabetic group (now 5,094) remained the same. In univariate analysis, BMI, HDL cholesterol, triglyceride, cholesterol, WCC, baseline glucose, systolic blood pressure, and CRP remained significant predictors of the development of diabetes. In multivariate analysis, log CRP level remained a significant predictor (HR 1.27; 95% CI 1.07–1.52; P = 0.007), together with BMI (1.28; 1.12–1.47; P = 0.0005), natural log triglyceride (1.40; 1.05–1.88; P = 0.024), and baseline glucose (quintile 5 HR 11.1; 5.58–22.1; P < 0.0001). Finally, a stepwise increase in risk across the CRP quintiles was evident, with the highest quintile being associated with a 2.46-fold risk of developing diabetes (95% CI 1.20–5.04) relative to the lowest (Table 3).

DISCUSSION

We have shown, for the first time, that raised CRP is a predictor of the development of diabetes in middle-aged men independent of established risk factors, including fasting plasma triglyceride, BMI, and glucose. Indeed, in multivariate analysis, a 1-SD change in plasma CRP concentration in our cohort was associated with a hazard ratio similar to BMI, plasma glucose, and triglyceride concentration, factors known to predict diabetes. In addition, men in the top quintile of CRP (>4.18 mg/l) have a greater than threefold risk of developing diabetes compared with those in the lowest quintile (<0.66 mg/l) after adjustment for all other variables. These relationships were evident, but slightly attenuated, using a definition of transition to diabetes that excluded the requirement for a significant decline in glucose tolerance.

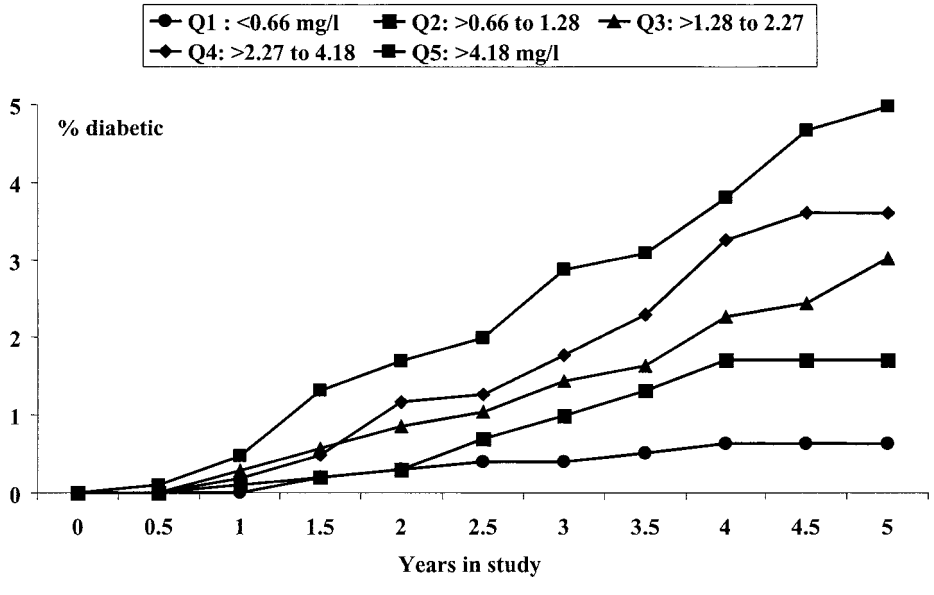

FIG. 1. Kaplan-Meier plot of time to diabetes by quintiles of $\log_e$ CRP. Quintiles limits are shown as the antilog, i.e., milligrams per liter of the logarithmic limits used in the statistical analysis. Subjects' time to becoming diabetic was taken as the semiannual visit at which they first had at least two postrandomization glucose measurements ≥7.0 mmol/l and at least one postrandomization glucose measurement >2.0 mmol/l above baseline glucose, or the postrandomization visit at which they first indicated taking hypoglycemic drugs.

The strengths of our study are, first, a rigorous assessment of development of diabetes over time based on the ADA criteria (7) using frequent laboratory assessment of fasting glucose. Second, we adjusted for fasting lipid measurements, including fasting plasma triglyceride, perturbances that signal an increased risk for diabetes to the clinician (12). Finally, we included other clinical cornerstones of the metabolic syndrome commonly identified with diabetes risk, such as blood pressure.

Thus our work complements the recent study by Pradhan et al. (6), who demonstrated a similar observation in women, in whom diabetes was initially identified by self-report and subsequently verified by a spectrum of criteria. Their study, while not including measures of plasma lipids or blood pressure, included fasting insulin and interleukin-6, which were not measured in the WOSCOPS cohort. Both of these studies, in turn, are consistent with the earlier observations of Schmidt et al. (8) in the Atherosclerosis Risk in Communities (ARIC) study, where several inflammatory markers such as orosomucoid were independent predictors of diabetes in adults. A more recently published study (13) demonstrates that CRP levels are associated with development of diabetes in the elderly. This study was based on fewer individuals ($n = 45$) developing diabetes and only assessed fasting glucose on one occasion after baseline at 3–4 years of follow-up. Thus, the ability of that study to test for a graded response was limited. Our analysis, identifying a larger number of cases with a more stringent definition of transition to diabetes, is a significant addition to these novel observations.

Our data in middle-aged men and data from the abovementioned studies (6,13) in women and the elderly indicate that CRP may be a useful predictor of diabetes. Because of its stability in plasma or serum, the availability of a recognized international standard, and the ease of measurement, CRP is of more utility than other markers of inflammation, such as the cytokines, for clinical practice and large-scale research studies.

Our finding also adds to the growing body of evidence implicating low-grade inflammation as a potential dynamic in the pathogenesis of type 2 diabetes. Potential mechanisms for this relationship may be direct or indirect. For example, cytokines such as tumor necrosis factor (TNF)-α may produce insulin resistance by influencing the function of the insulin receptor (14) or by stimulating adipocyte lipolysis (15,16). Alternatively, endothelial dysfunction may link inflammation to insulin resistance (4,17,18). It is also noteworthy that established mechanisms to lessen insulin resistance, such as weight loss and thiazolidinediones, as well as novel therapies (e.g., statins, ACE inhibitors), display significant anti-inflammatory effects (19–23). Finally, intracellular links between the inflammation cascade and insulin signaling have been reported in a recent study showing that salicylate prevents obesity and diet-induced insulin resistance (24).

The current analysis expands on our original description of predictors of diabetes in WOSCOPS (7) and, as a post hoc analysis, has similar limitations to its interpretation. The primary outcome in WOSCOPS was cardiovascular disease and not diabetes. It is well established that the prediabetic phase is atherogenic, and common risk factors such as BMI and triglycerides predict both cardiovascular disease and diabetes. Interestingly, of the 127 individuals who developed diabetes in WOSCOPS, only 17 experienced a cardiovascular event. Plasma CRP concentration, in addition to other inflammatory markers, has been demonstrated to predict cardiovascular events in this same population (2). However, because diabetes does not always lead to cardiovascular events and because the disease merits treatment in its own right, there is considerable importance in the ability to predict risk of diabetes.

An apparent J-shaped relationship between quintile of fasting glucose and risk of diabetes is observed in our data (Table 2). This is unexpected, but as can be seen from the confidence intervals, only the hazard ratio in quintile 5 (in which more than three-quarters of the cases arose) is significantly different from 1. The J-shaped pattern is therefore likely to be due to the very few cases of diabetes in the lower glucose quintiles.

In conclusion, we have shown for the first time that CRP concentration is a significant predictor of diabetes in middle-aged men independent of classic and clinically employed risk factors such as BMI, fasting triglyceride, and glucose. These data add support for the further evaluation of CRP as a potential predictor of diabetes development. They also add to the notion that low-grade inflammation is important in the pathogenesis of type 2 diabetes.

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